UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMERICAN ACADEMY OF PEDIATRICS, et al.,
Plaintiffs,
v.
ROBERT F. KENNEDY, JR., et al.,
Defendants,
and
CHILDREN'S HEALTH DEFENSE, ANDREA SHAW, SHANTICIA NELSON, DR. PAUL THOMAS, AND DR. KENNETH STOLLER
Intervenor-Defendants/Counterclaim Plaintiffs.
v.
AMERICAN ACADEMY OF PEDIATRICS, MASSACHUSETTS CHAPTER OF THE AMERICAN ACADEMY OF PEDIATRICS, and INFECTIOUS DISEASES SOCIETY OF AMERICA,
Counterclaim Defendants

Case No. 1:25-cv-11916 (BEM)

EMERGENCY MOTION OF CHILDREN'S HEALTH DEFENSE, ANDREA SHAW, SHANTICIA NELSON, DR. PAUL THOMAS, AND DR. KENNETH STOLLER TO INTERVENE AS DEFENDANTS AND COUNTERCLAIM PLAINTIFFS

Proposed Intervenor-Defendants Children's Health Defense ("CHD"), Andrea Shaw, Shanticia Nelson, Dr. Paul Thomas, and Dr. Kenneth Stoller (collectively, "Proposed Intervenors") respectfully and on an emergency basis move this Court for leave to intervene as defendants/counterclaim plaintiffs in this action pursuant to Fed. R. Civ. P. 24(a)(2), or in the alternative, Fed. R. Civ. P. 24(b)(1)(B), and to file the accompanying Proposed Answer to the Fourth Amended Complaint with Affirmative Defenses and Counterclaims, and their Opposition to Plaintiffs' Motion for a Preliminary Injunction.

In support of this Motion, Proposed Intervenors submit the following documents filed simultaneously herewith: (1) Memorandum of Law in Support of Emergency Motion to Intervene, (2) Declaration of Richard Jaffe, Esq. (with Exhibits A through E), (3) Proposed

Answer to the Fourth Amended Complaint with Affirmative Defenses and Counterclaims, (4) Proposed Order Granting Intervention, (5) Intervenors' Opposition to the Preliminary Injunction Motion, (6) Proposed Order Denying Preliminary Injunction.

CERTIFICATION OF EMERGENCY

Proposed Intervenors certify that this motion requires emergency consideration for the following reasons:

1. At its February 13, 2026, hearing, the Court granted Plaintiffs' Motion to File a Fourth Amended Complaint. At the same hearing, the Court heard argument on the first part of Plaintiffs' Preliminary Injunction Motion and took the motion under advisement. Per the clerk's notation, the Court ordered the defendants to file a supplemental opposition to Plaintiffs' supplemental declarations by 5:00 p.m. on February 18, 2026, and ordered counsel to file additional briefing regarding the legal consequence of the January guidance no later than the same date. The Court's ruling on the Preliminary Injunction motion appears to be imminent after it reviews the additional filings.

2. The ACIP meeting that Plaintiffs seek to enjoin is scheduled for February 25–26, 2026. Plaintiffs seek to restore the prior vaccination schedule before that meeting occurs. If the Court rules without hearing from Proposed Intervenors, it will do so on a record in which no party has presented: the Institute of Medicine's findings that the cumulative childhood immunization schedule has never been tested for safety; the families whose children died under the schedule Plaintiffs seek to restore; or the physicians who lost their licenses for questioning it.

3. This motion is filed contemporaneously with the deadline the Court set for the parties' supplemental submission. Proposed Intervenors have made every effort to file at the earliest

opportunity after learning the scope and posture of the Court's inquiry from the February 13 hearing. No party will be prejudiced by considering this motion now; all parties and the public will be prejudiced if the Court rules on an incomplete record.

4. Absent emergency consideration, the Court may restore a vaccination schedule under which the Shaw twins and Sa'Niya Carter died, that the IOM found has never been tested, and that two physicians lost their licenses for questioning—all without hearing from a single affected family or any physician who can speak to what the schedule does to children. A family whose child is injured under a judicially restored schedule cannot be unvaccinated. The harm is irreversible.

GROUNDS FOR INTERVENTION

5. Proposed Intervenors are entitled to intervene as of right under Fed. R. Civ. P. 24(a)(2). The motion is timely—it is filed before the Court has ruled on the preliminary injunction and before any existing party is prejudiced. Proposed Intervenors have direct, concrete interests in this action: their children died under the schedule Plaintiffs seek to restore; their medical licenses were revoked for practicing the individualized medicine the government's new SCDM policy now permits; and they are parties to a pending RICO action against AAP whose outcome will be directly affected by this Court's PI ruling. These interests will be impaired if the Court rules without their evidence. And no existing party adequately represents these interests.

6. The government's defense is procedural. In forty-five pages of opposition briefing, the government argues that the Secretary had the authority to revise the schedule. It does not argue the schedule needed revising. It does not present the IOM's findings. It does not challenge AAP's claim that the schedule was "rigorously tested." It does not identify a single child harmed. The government defends its right to act. It does not—and institutionally cannot—defend the

reasons for acting. The moment the government argues the prior schedule was substantively unsafe, it admits its own agencies endorsed an unsafe protocol for decades.

7. This case is readily distinguishable from the Court's denial of Jose Perez's motion to intervene. Mr. Perez was pro se, did not confer with opposing counsel, filed procedurally deficient papers, and asserted only diffuse constitutional interests indistinguishable from those of any citizen. Proposed Intervenors are represented by experienced federal litigation counsel who serves as counsel of record in three related federal proceedings. They assert concrete interests—dead children, revoked licenses, pending RICO litigation—that no existing party represents. They offer evidence the government has not and cannot present: the IOM reports, the state-by-state comparison, the enforcement architecture that Plaintiffs' own declarations unwittingly expose. Their Proposed Answer with Affirmative Defenses and Counterclaims is filed simultaneously with this Motion.

8. In the alternative, intervention is appropriate under Fed. R. Civ. P. 24(b)(1)(B). Proposed Intervenors' defenses and counterclaims share common questions of law and fact with the main action—principally, whether the childhood immunization schedule is evidence-based and safe. Intervention will not delay proceedings. Proposed Intervenors accept the Court's existing schedule and will not seek continuances.

EVIDENCE BEFORE THE COURT

9. Proposed Intervenors present evidence that transforms the factual landscape of this case and that bears directly on three of the four preliminary injunction factors:

The schedule has never been tested. The Institute of Medicine found in 2002 and again in 2013 that the cumulative childhood immunization schedule—the protocol as actually administered to American children, involving dozens of simultaneous and sequential

vaccinations—has never been tested for safety. Paragraph 34 of the Fourth Amended Complaint states that vaccine safety is "rigorously tested." The IOM said otherwise, twice. Neither Plaintiffs nor Defendants have cited these reports. They are attached to the Jaffe Declaration as Exhibits C and D.

Plaintiffs' alarm is pretextual. AAP calls the new schedule of 11 recommended vaccines "a very dark day for children." Massachusetts—where Plaintiffs chose to file—requires only 9 vaccines for grades K–6 and 10 for grades 7–12. California requires 10. AAP has never sued Massachusetts. AAP has never sued California. AAP has never called either state's schedule dangerous. If 11 is a "very dark day," then California's 10 and Massachusetts' 9 are darker still. Yet children in both states are healthy and vaccination rates exceed 95%.

Plaintiffs' own declarations are confessions. Every physician declaration filed in support of the preliminary injunction describes an enforcement infrastructure—HEDIS metrics tying reimbursement to compliance rates, combination vaccines that cannot be unbundled, "unbillable time" for informed consent counseling—that reveals a coercive system, not a public health program. What Plaintiffs characterize as harms from SCDM are the withdrawal symptoms of a system that never required the informed consent conversation in the first place.

The balance of irreparable harms weighs against restoration. Plaintiffs' Jane Does lost sleep, ground their teeth, and spent gasoline driving to pharmacies. Proposed Intervenors' families buried their children. The balance of irreparable harms weighs against restoration, not for it.

RELIEF REQUESTED

10. Proposed Intervenors respectfully request that this Court:

(a) Grant this Motion to Intervene and accept the accompanying Proposed Answer to the Fourth Amended Complaint with Affirmative Defenses and Counterclaims.

(b). Accept and consider Intervenors' Opposition paper to the Preliminary Injunction Motion.

(c) Consider the evidence presented in the Declaration of Richard Jaffe and its Exhibits before ruling on Plaintiffs' motion for a preliminary injunction; and

(d) Set an expedited briefing schedule for any opposition to this Motion, given the Court's stated need to decide the preliminary injunction on a tight timeline.

CERTIFICATION OF CONFERRAL

Pursuant to L.R., D. Mass. 7.1(a)(2), undersigned counsel certifies that he had a lengthy zoom call with Plaintiffs' counsel James Ho and his partner. Plaintiffs oppose this motion, and request to respond to the motion within the 14-day time set out in the local rules. Plaintiffs will file a notice of intent to respond. Movants have no objection, except if it forecloses the Court's consideration of the facts and arguments related herein in its decision on the first Part of the pending preliminary injunction motion. In that case, Movant request the Court order a preliminary response to allow for the Court to consider the facts and arguments set forth herein on the pending motion or grant oral argument at the Court's earliest convenience. I contacted the government's lead counsel yesterday afternoon, left a detailed voicemail but haven't heard back as of the time of filing.

ORAL ARGUMENT

Intervenors' counsel can appear for oral argument on this motion at the Court's earliest convenience, with five hours advance notice. However, given the obvious tight schedule for the

first part of this Preliminary Injunction hearing, we waive oral argument, unless the Court's schedule permits, it is determined that oral argument will assist in its deliberations, or as stated above, to serve as Plaintiffs' response to this motion within the time frame of the Court's impending decision.

Dated: February 18, 2026

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on the date indicated above, I caused the foregoing Emergency Motion to Intervene, Memorandum of Law in Support of Emergency Motion to Intervene, Intervenor-Defendants' Memorandum in Opposition to Plaintiffs' Motion for Preliminary Injunction, Proposed Answer to the Fourth Amended Complaint with Affirmative Defenses and Counterclaims, Declaration of Richard Jaffe with Exhibits A through E, Proposed Order

Granting Intervention, Proposed Order Denying Preliminary Injunction to be filed electronically through the Court's CM/ECF system, which will send notification of such filing to all counsel of record.

/s/ Robert N. Meltzer

Robert N. Meltzer

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Counterclaim Defendants.

Case No. 1:25-cv-11916 (BEM)

MEMORANDUM OF LAW IN SUPPORT OF EMERGENCY MOTION TO INTERVENE

INTRODUCTION

Proposed Intervenors Children's Health Defense ("CHD"), Andrea Shaw, Shanticia Nelson, Dr. Paul Thomas, and Dr. Kenneth Stoller seek to intervene in this action as defendants and counterclaim plaintiffs pursuant to Federal Rule of Civil Procedure 24(a)(2), or in the alternative, Rule 24(b)(1)(B). This memorandum sets forth the legal basis for intervention.

The Court is poised to rule on Plaintiffs' motion for a preliminary injunction that would restore a childhood vaccination schedule the Institute of Medicine twice found has never been tested for cumulative safety. No party in this case has presented the IOM's findings. No party has identified a child harmed under the schedule Plaintiffs seek to restore. No party has challenged AAP's foundational claim that the schedule was "rigorously tested." Proposed Intervenors present all three: the IOM reports, the families who buried their children under the prior schedule, and the physicians who lost their licenses for questioning it.

The First Circuit applies a four-part test to intervention as of right. *Geiger v. Foley Hoag LLP*, 521 F.3d 60, 64–65 (1st Cir. 2008). Each element of the four-part test is satisfied here.

ARGUMENT

I. PROPOSED INTERVENORS ARE ENTITLED TO INTERVENE AS OF RIGHT UNDER RULE 24(a)(2)

Federal Rule of Civil Procedure 24(a)(2) provides that a court must permit intervention by anyone who "claims an interest relating to the property or transaction that is the subject of the action, and is so situated that disposing of the action may as a practical matter impair or impede the movant's ability to protect its interest, unless existing parties adequately represent that interest." The First Circuit analyzes four factors: (1) timeliness; (2) whether the applicant claims an interest relating to the subject of the action; (3) whether disposition may impair or impede that interest; and (4) whether existing parties adequately represent it. *Geiger v. Foley Hoag LLP*, 521 F.3d 60, 64–65 (1st Cir. 2008).

A. The Motion Is Timely

Timeliness is assessed considering the totality of the circumstances, including "the length of time the applicant knew or should have known of its interest before making the motion, prejudice to the parties, prejudice to the applicant, and the existence of extraordinary circumstances." *Pub. Citizen v. Liggett Grp., Inc.*, 858 F.2d 775, 785 (1st Cir. 1988) (citing *Culbreath v. Dukakis*, 630 F.2d 15, 20–24 (1st Cir. 1980)).

This motion is timely. It was only after the Government filed its opposition papers to Plaintiffs' motion for a preliminary injunction late February 9, 2026, that intervenors realized how narrow its defense of the motion would be, as explained below. The Court has not yet ruled on the preliminary injunction motion. This motion is filed before any party is prejudiced and

contemporaneously with the deadline the Court set for supplemental briefing. Proposed Intervenors filed at the earliest opportunity after the February 13 hearing which granted Plaintiffs' Motion to File the Fourth Amended Complaint, and which hearing revealed the scope of the Court's inquiry.

Moreover, there is nothing unusual about intervention at the preliminary *i*njunction stage. Courts routinely permit intervention before a ruling on preliminary relief. *See, e.g., Food & Water Watch, Inc. v. United States Army Corps of Eng'rs*, 570 F. Supp. 2d 177 (D. Mass. 2008) (granting intervention while motion for preliminary injunction was pending and permitting intervenor to participate in PI briefing). The Court's bifurcation of the preliminary injunction hearing into two parts, with the oral argument on the second part scheduled weeks away in mid-March further suggests that this proposed intervention will not disrupt proceedings.

B. Proposed Intervenors Have Direct, Concrete Interests

The interest required for intervention must be "significantly protectable." *Donaldson v. United States*, 400 U.S. 517, 531 (1971).

Proposed Intervenors' interests are concrete, direct, and legally protectable:

Andrea Shaw and Shanticia Nelson. Mrs. Shaw's fraternal twins died eight days after receiving their 18-month vaccines. Ms. Nelson's daughter died twelve hours after receiving twelve antigens in a single catch-up visit. Both mothers reported concerns that were overridden by AAP's contraindications framework. They are plaintiffs in *Shaw v. American Academy of Pediatrics*, No. 1:26-cv-00171 (D.D.C.), a pending RICO action alleging that AAP made material misrepresentations about the safety of the schedule. If this Court restores the prior schedule, it judicially validates the protocol under which their children died and directly prejudices their pending RICO claims. Jaffe Decl. ¶¶ 5–6, 12–13.

Dr. Paul Thomas and Dr. Kenneth Stoller. Dr. Thomas published a vaccinated-versus-unvaccinated study—the very methodology the IOM recommended—and had his license suspended shortly thereafter. Dr. Stoller used genetic testing to identify at-risk children and had his license revoked for deviating from ACIP guidelines. If the prior schedule is restored, the individualized clinical approach for which both physicians lost their licenses will once again constitute professional misconduct. Jaffe Decl. ¶¶ 14–15.

Children's Health Defense. CHD publishes books, daily news, and educational programming on vaccine safety, competing directly with AAP in the market for vaccine-related health information. If the prior schedule is restored by judicial order, CHD's competing publications are delegitimized. CHD is also a plaintiff in both the *Shaw* and *Thomas* actions, whose outcomes will be directly affected by this Court's ruling. Jaffe Decl. ¶ 16.

C. Disposition Will Impair Intervenors' Interests

The impairment inquiry is practical, not technical. The question is whether "as a practical matter" disposition of the action may impair the applicant's ability to protect its interest. Fed. R. Civ. P. 24(a)(2). The First Circuit has recognized that impairment "need not be certain or inevitable; it is enough that disposition 'may' impair or impede the applicant's interest." Fed. R. Civ. P. 24(a)(2).

If the Court grants the preliminary injunction and restores the prior schedule:

- The schedule under which the Shaw twins and Sa'Niya Carter died will be reimposed by judicial order, directly harming the Shaw and Nelson families and prejudicing their pending RICO claims.

- The individualized clinical approach for which Dr. Thomas and Dr. Stoller lost their licenses will again constitute professional misconduct, impeding their efforts to restore their practices.
- CHD's publications questioning the schedule's safety will be contradicted by a federal court order restoring it, impairing CHD's competitive position in the market for vaccine-related health information; and
- The Court will have restored the schedule on a record that does not contain the IOM reports, the state-by-state comparison, or the enforcement infrastructure that Plaintiffs' own declarants described under oath—foreclosing the possibility of a fully informed judicial determination.

D. No Existing Party Adequately Represents Intervenors' Interests

The burden of showing inadequacy of representation is "minimal." *Trbovich v. United Mine Workers of Am.*, 404 U.S. 528, 538 n.10 (1972). The applicant "need show only that the representation 'may be' inadequate, not that it 'is' inadequate." *Id.* Where the interests of the proposed intervenor diverge from those of the existing parties, the burden is met. *Id.*

The government Defendants' interests necessarily diverge from those of Proposed Intervenors. The government's opposition briefing focuses, as one would expect, on the Secretary's legal authority. It does not address the interests Proposed Intervenors seek to protect. In forty-five pages, Defendants:

- Argue that the Secretary had the *authority* to revise the schedule but do not argue the schedule *needed* revising.
- Do not cite the IOM's 2002 or 2013 reports finding the cumulative schedule was never tested. (Exhibits C and D attached to the Jaffe Declaration).

- Do not challenge AAP's claim in Paragraph 34 of the Fourth Amended Complaint that vaccine safety is "rigorously tested".[1]
- Do not identify a single child harmed under the prior schedule; and
- Do not address the enforcement infrastructure—HEDIS metrics, combination vaccines, the Red Book contraindications framework—that Plaintiffs' own declarants described under oath.

This divergence is not a criticism of the government's litigation strategy. It reflects the reality that the government has distinct institutional interests. The government's own agencies endorsed the prior schedule for decades. Its FDA licensure decisions, CDC endorsements, and VICP adjudications all rest on the premise that the schedule was safe. The government is understandably not positioned to argue that the schedule it endorsed caused harm to specific children. Jaffe Decl. ¶¶ 9-10, 18-19.

The *Thomas v. Monarez* proceeding further illustrates the divergence. In that parallel federal case, the Department of Justice will soon be moving to dismiss the claims of two of the Proposed Intervenors, Drs. Thomas and Stoller. And will likely argue that they have no right to force it to reconsider the recommended status of ACIP schedule. The government has its own institutional position on these questions, and that position does not encompass the interests Proposed Intervenors seek to protect here. Jaffe Decl. ¶ 19.

II. THIS MOTION IS READILY DISTINGUISHABLE FROM THE COURT'S DENIAL OF THE PEREZ MOTION TO INTERVENE

[1] At the February 13 hearing, Defendants' counsel argued that the government seeks to restore trust in public health and increase vaccine uptake—a position that does not address the cumulative safety-testing deficiencies Intervenors raise here.

The Court previously denied Jose Perez's motion to intervene. That denial does not control here. Mr. Perez appeared pro se. He did not confer with opposing counsel. He filed procedurally deficient papers. He asserted diffuse constitutional interests indistinguishable from those of any citizen.

Proposed Intervenors are represented by experienced federal litigation counsel who serves as counsel of record in three related federal proceedings. They assert concrete, particularized interests that no other party shares: two families whose children died under the schedule Plaintiffs seek to restore, two physicians whose licenses were revoked for questioning it, and a nonprofit organization with a pending RICO action against AAP. They have conferred with all counsel of record. Their filings comply with all applicable rules. They present evidence—the IOM reports, the state-by-state comparison, the enforcement infrastructure—that no existing party has introduced.

III. IN THE ALTERNATIVE, PERMISSIVE INTERVENTION IS WARRANTED

Even if the Court determines that intervention as of right is not available, permissive intervention under Rule 24(b)(1)(B) is appropriate. Permissive intervention requires only that the applicant's claim or defense shares "a common question of law or fact" with the main action and that intervention will not "unduly delay or prejudice the adjudication of the original parties' rights." Fed. R. Civ. P. 24(b)(1)(B), (b)(3).

Both requirements are satisfied. Proposed Intervenors' defenses and counterclaims share the central question of this litigation: whether the childhood immunization schedule is evidence-based, safe as administered, and lawfully mandated. Their Proposed Answer with Affirmative Defenses and Counterclaims, filed simultaneously, addresses this question with evidence no existing party has introduced.

Intervention will cause no delay. Proposed Intervenors accept the Court's existing schedule, including the March 13 second hearing on the preliminary injunction. They will not seek continuances. Their opposition to the preliminary injunction is filed simultaneously with this motion. The Court's bifurcated hearing structure accommodates additional briefing without disrupting the proceedings.

IV. THE EVIDENCE INTERVENORS PRESENT BEARS DIRECTLY ON THE PRELIMINARY INJUNCTION

Even if the Court were to deny intervention, it should consider the evidence presented in the Declaration of Richard Jaffe and its Exhibits before ruling on the preliminary injunction. *See Fed. R. Civ. P. 24(a)(2) advisory committee's note to 1966 amendment* (intervention serves to protect "practical interests" and to ensure a "complete adjudication"). The Court has inherent authority to consider relevant evidence bearing on the PI factors regardless of whether formal intervention is granted.

The Jaffe Declaration and Exhibits present evidence that transforms the factual landscape of this case on three of the four preliminary injunction factors:

Likelihood of success. Plaintiffs' case rests on the premise that the prior schedule was "rigorously tested." The IOM's 2002 and 2013 reports (Exhibits C and D) establish that it was not. Plaintiffs' alarm about the new eleven-vaccine schedule is pretextual: Massachusetts requires only nine to ten vaccines, California requires ten, and AAP has never sued either state. Plaintiffs' own declarations describe not a public health program but a coercive enforcement infrastructure designed to eliminate clinical judgment.

Irreparable harm and balance of equities. Plaintiffs' individual declarants describe sleeplessness, tooth-grinding, and gasoline expenses. Proposed Intervenors describe dead children. The balance is not close.

Public interest. Shared clinical decision-making is the international norm in seventeen EU nations, the United Kingdom, and Japan—all of which achieve vaccination rates equal to or exceeding those of the United States. Exhibit E addresses the January guidance and demonstrates that the transition to SCDM will not reduce access to or insurance coverage for vaccines.

CONCLUSION

For the foregoing reasons, Proposed Intervenors respectfully request that this Court grant their Motion to Intervene, accept the accompanying Proposed Answer with Affirmative Defenses and Counterclaims, and consider the evidence presented in the Jaffe Declaration and its Exhibits before ruling on Plaintiffs' motion for a preliminary injunction.

Respectfully submitted,

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February 18, 2026

UNITED STATES DISTRICT COURT

DISTRICT OF MASSACHUSETTS

AMERICAN ACADEMY OF PEDIATRICS, et al.,

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and

CHILDREN'S HEALTH DEFENSE, ANDREA SHAW, SHANTICIA NELSON, DR. PAUL THOMAS, AND DR. KENNETH STOLLER

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AMERICAN ACADEMY OF PEDIATRICS, MASSACHUSETTS CHAPTER OF THE AMERICAN ACADEMY OF PEDIATRICS, and INFECTIOUS DISEASES SOCIETY OF AMERICA,

Counterclaim Defendants

PROPOSED ANSWER TO FOURTH AMENDED COMPLAINT, AFFIRMATIVE DEFENSES, AND COUNTERCLAIMS OF INTERVENOR-DEFENDANTS/COUNTERCLAIM PLAINTIFFS

Intervenor-Defendants/Counterclaim Plaintiffs Children's Health Defense ("CHD"), Andrea Shaw, Shanticia Nelson, Dr. Paul Thomas, and Dr. Kenneth Stoller (collectively, "Intervenors"), by and through undersigned counsel, respectfully submit this Answer to the Fourth Amended Complaint ("4AC") filed by Plaintiffs American Academy of Pediatrics, et al.

("Plaintiffs" or "AAP"), together with Affirmative Defenses and Counterclaims, and state as follows:

PRELIMINARY STATEMENT

1. None of the original parties to this case (or amici) speak for the children who have been injured or who have died from the vaccines which the Plaintiff trade and other public health organizations promote. The intervenors/counterclaim plaintiffs include two mothers who allowed their children to receive multiple vaccinations based on plaintiff American Academy of Pediatrics combination vaccine guidelines. Their decision and those guidelines resulted in the deaths of three children.

2. Plaintiffs are seven trade organizations representing physicians who administer and profit from vaccinating children, public health organizations, a trade group representing infectious disease specialists, and three unnamed pregnant women who wish to take the COVID-19 vaccine three years after the end of the pandemic and who are alleged to have experienced difficulty accessing this vaccine.

3. Defendants are government officials defending executive prerogative. In forty-five pages of opposition briefing, Defendants never argue that restoring the prior schedule would harm anyone. Defendants defend the Secretary's right to change the schedule. They do not argue the schedule should be changed, because doing so would constitute an admission against the government's own prior conduct in endorsing the schedule for decades.

4. Intervenors fill the gap that neither side can fill. Children's Health Defense is a nonprofit organization that publishes books on vaccine safety and children's health, produces daily news content through The Defender, operates a streaming platform (CHD.TV), and

conducts educational seminars and events—all addressing vaccine safety and informed consent. CHD's mission is directly impeded by the relief Plaintiffs seek. Perhaps most importantly, CHD's media give a voice to families like Intervenor Andrea Shaw who lost her fraternal twins eight days after their 18-month vaccinations, and Intervenor Shanticia Nelson who lost her daughter twelve hours after a single catch-up vaccination visit during which twelve antigens were administered. As described below, according to Plaintiff AAP's vaccine guidelines, it was perfectly appropriate to give Intervenor Nelson's infant daughter six shots and 12 antigens in a single visit shortly after her first birthday. A healthy adult Marine officer candidate would never have been given more than five immunizations at one time.

5. Dr. Paul Thomas and Dr. Kenneth Stoller lost their medical licenses for questioning the schedule's safety. If the prior schedule is restored, the clinical approach of prioritizing their patients' health and right to informed consent—the approach for which both physicians lost their licenses—will once again constitute professional misconduct.

6. What Intervenors bring to this case is what no existing party will provide: the evidence that the childhood immunization schedule Plaintiffs want restored was never cumulatively tested for safety, despite the Institute of Medicine's repeated requests for such studies; that Plaintiffs' own foundational safety claims are unsupported by empirical evidence; and that restoring the prior schedule would cause concrete, irreparable harm to Intervenors and the families they represent.

7. The factual allegations in this Answer are drawn from the Complaint filed in *Shaw v. American Academy of Pediatrics*, No. 1:26-cv-00171 (D.D.C.), in which CHD and individual plaintiffs have brought claims under the Racketeer Influenced and Corrupt

Organizations Act against AAP for the same pattern of conduct described herein, and *Thomas v. Monarez*, No. 1:25-cv-02685 (D.D.C.), wherein the relief requested is that all childhood vaccines be moved from Category A, "Recommended" to Category B, "shared clinical decision-making," primarily on the grounds that it is arbitrary and capricious for the CDC to recommend a combination vaccine schedule where the incontrovertible fact is that the schedule itself has never been safety tested or shown to provide more benefit than harm.

ANSWER TO FOURTH AMENDED COMPLAINT

Introduction (¶¶ 1–23)

8. Intervenors admit that this action challenges certain actions taken by the Department of Health and Human Services and the Centers for Disease Control and Prevention regarding the Advisory Committee on Immunization Practices and the childhood immunization schedule. Intervenors deny that such actions are unlawful.

9. Intervenors admit the procedural history described in ¶¶ 2–7 to the extent it is consistent with the Court's docket. To the extent these paragraphs characterize the challenged actions as unlawful, arbitrary, or capricious, Intervenors deny those characterizations.

10. Intervenors admit that the Court has entered certain orders as described in ¶ 8. Intervenors deny that these orders establish the merits of Plaintiffs' claims.

11. Intervenors admit that AAP describes itself as "the nation's premier professional organization for pediatric medicine" with approximately 67,000 members. Intervenors further state that AAP generates $115–125 million in annual revenue; that AAP's commercial publications include the Red Book, sold for $175, which AAP markets as "the authoritative guide" to pediatric infectious disease; and that AAP's financial

interests are directly tied to the vaccination schedule through administration fees, quality bonuses, and pay-for-performance metrics tied to schedule compliance. AAP's characterization of itself as a purely scientific organization omits these material financial interests.

12. Intervenors admit that ACP is a professional organization as described in ¶ 10. Intervenors deny that ACP's organizational interests in this litigation are representative of the public interest.

13. Intervenors admit the general descriptions of APHA, IDSA, SMFM, MPHA, and MCAAP in ¶¶ 11–15. Intervenors note that these are trade and professional organizations representing the interests of their physician and public health professional members—not the interests of the families and children who receive vaccines, families of children who have been injured or who have died from these vaccines.

14. Intervenors do not have the knowledge or information to admit or deny the allegations concerning Plaintiffs Jane Does 1, 2, and 3, but deny that these Plaintiffs' alleged difficulties obtaining the vaccine constitute irreparable harm sufficient to justify the extraordinary remedy of a preliminary injunction. Intervenors further state that Intervenor Andrea Shaw's fraternal twins died eight days after receiving their 18-month vaccines, and Intervenor Shanticia Nelson's daughter died twelve hours after a catch-up visit in which twelve antigens were administered. The Court must weigh both sides of this equation: three individuals who allegedly had difficulty finding a pharmacy against families who buried their children who received multiple doses of vaccines per the schedule promoted by AAP and endorsed by the other Plaintiff organizations.

15. Intervenors admit the general descriptions of the Defendants as government officials and agencies in ¶¶ 19–23. For the reasons set forth in this pleading, Intervenors deny that the Defendants can adequately represent the interests of Intervenors and the families similarly situated to the individual Intervenors. Defendants' institutional interests in defending executive authority are distinct from Intervenors' interests in protecting the health and safety of their children.

Factual Allegations: The ACIP Process (¶¶ 24–36)

16. Intervenors admit the general historical description of ACIP's creation and procedural framework in ¶¶ 24–33. Intervenors note that nothing in this history addresses whether the cumulative childhood immunization schedule—the protocol as actually administered to American children—has ever been tested for safety. The GRADE framework, the EtR framework, and the Work Group process described in these paragraphs all evaluate individual vaccines in isolation. None evaluates the cumulative effect of administering multiple vaccines simultaneously or in rapid sequence to infants and children, which is the protocol Plaintiffs seek to restore.

17. Response to ¶ 34: Denied as materially misleading. Paragraph 34 is the load-bearing factual allegation of Plaintiffs' entire case. It states: "The safety of a vaccine is rigorously tested before receiving FDA authorization. Work Groups of the ACIP thoroughly examine the safety data before the ACIP votes on a vaccine's recommended use. The safety of a vaccine is continually monitored after listed on a CDC schedule."

18. This paragraph conflates two fundamentally different propositions: (a) that individual vaccines undergo pre-licensure testing, and (b) that the cumulative childhood immunization schedule—the protocol as actually administered to American children,

involving dozens of simultaneous and sequential vaccinations—has been tested for safety. Proposition (a) is generally true, though many individual vaccines were licensed without true saline placebo controls. Proposition (b) is false.

19. In 2002, the Institute of Medicine found that no study had ever compared health outcomes between children who received the full schedule and those who did not, and recommended such studies be conducted using existing data in the Vaccine Safety Datalink ("VSD"). IOM, *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* (2002), at 14–15, 107–08. The IOM specifically identified the VSD—a database containing health records for millions of children—as the tool for conducting these studies without withholding vaccines from anyone.

20. In 2013, the IOM returned to this issue and found that the recommended studies had not been conducted. The IOM concluded that "studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted." IOM, *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies* (2013), at 6.

21. As of this filing, twenty-four years after the IOM's first recommendation, no cumulative schedule safety study has been conducted. The VSD data exists. The filing cabinet remains unopened.

22. Plaintiff AAP's foremost vaccine expert, Dr. Paul A. Offit, was lead author of the foundational article published in AAP's journal *Pediatrics* claiming that infants could "theoretically" respond to 10,000 vaccines at once. Offit PA, et al., "Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?" *Pediatrics* 2002;109(1):124–129. This was a theoretical calculation about B-cell epitope

capacity that answered an immunological question no parent was asking, while ignoring the toxicological and clinical safety questions parents were asking—including cumulative aluminum dose, mercury toxicokinetics, synergistic adjuvant effects, neuroinflammation, and autoimmune activation. The 10,000 vaccines claim has never been empirically validated. It substituted theory for testing and has been deployed for twenty-four years to block the studies the IOM recommended, and the theoretical basis for why children like Intervenors Shaw and Nelson receive so many vaccines at one time.

23. Paragraph 34's claim that vaccine safety is "rigorously tested" is the equivalent of claiming that because each ingredient in a recipe has been individually tasted, the finished dish has been tested. It has not. The IOM said so twice. AAP knows this because its own committee members participated in the IOM reviews.

24. Intervenors admit the general description of the CDC Director's role in approving ACIP recommendations in ¶ 35. Intervenors deny any implication that this process has resulted in a cumulatively tested immunization schedule.

25. Intervenors admit that individual vaccines undergo clinical trials before licensure as described in ¶ 36, but deny that all such trials span years. Intervenors deny that this testing establishes the safety of the cumulative schedule as administered, or that it is safe to receive the dozen antigens which Intervenor Nelson's daughter received in one "well-child" visit. A child receiving the full schedule by age two receives vaccines targeting up to 14 diseases, involving multiple simultaneous injections at single well-child visits. No clinical trial has ever tested this cumulative protocol.

The Challenged Actions (¶¶ 37–70)

26. Intervenors admit that on January 5, 2026, Acting CDC Director Jim O'Neill signed a decision memorandum revising the childhood immunization schedule as described in ¶¶ 37–46. Intervenors deny that this action was arbitrary, capricious, or unsupported by evidence. The HHS scientific assessment found that the United States was "a global outlier" in recommended vaccine doses, yet "does not have higher vaccination rates" than peer nations relying on recommendation-only models. Seventeen EU member states, the United Kingdom, and Japan use such models while maintaining vaccination rates exceeding 90%.

27. Intervenors admit that the Secretary issued directives regarding COVID-19 vaccine recommendations as described in ¶¶ 47–53. Intervenors deny that these directives were arbitrary or unsupported. Intervenors further state that the COVID-19 vaccine was recommended for pregnant women despite pregnant women being excluded from the Pfizer and Moderna pivotal trials. The recommendation was made based on theoretical benefit and observational data, not randomized controlled trials in the target population.

28. Intervenors lack knowledge or information sufficient to form a belief about whether specific ACIP appointments comply with the ACIP Charter's requirements as alleged in ¶¶ 54–61 and therefore deny the same. Intervenors note, however, that Plaintiffs' characterization of new ACIP members as "anti-vaccine" (¶ 78) is belied by the members' actual voting records. At the September 2025 meeting, ACIP members voted in favor of COVID-19 SCDM, thimerosal-free flu vaccines, and Hepatitis B SCDM—all votes that accepted the vaccines while introducing individualized clinical judgment. Voting for informed consent is not "anti-vaccine."

29. Response to ¶¶ 62–70 (The Assessment): Intervenors deny that the HHS Assessment was scientifically unsound. Plaintiffs' primary criticism is the Denmark comparison (¶¶ 62–69). Plaintiffs themselves cite Martin Kulldorff's contribution to the IOM 2013 report to argue that country comparisons are "very difficult to do well" (¶ 69 n.34). But this citation opens a door Plaintiffs cannot close: the very IOM report Plaintiffs cite concluded that "studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted." IOM 2013 at 6. Plaintiffs invoke the IOM's methodological caution about country comparisons while ignoring the IOM's central finding that the schedule they want restored has never been tested.

30. Moreover, Plaintiffs' characterization of the new schedule as "dangerous" is contradicted by their own silence about state schedules that are less comprehensive. California law requires vaccines for only 10 diseases for school entry. Cal. Health & Safety Code § 120335(b)(1)–(10). California eliminated all personal belief exemptions in 2015, creating the strictest vaccine mandate in the nation. The new CDC schedule recommends 11 vaccines—one more than California mandates. Massachusetts, where Plaintiffs chose to file this action, requires vaccines for only 9 diseases for grades K–6 and 10 for grades 7–12.

31. If recommending 11 vaccines is "dangerous," "a very dark day for children," and will cause "more disease, more infection, more hospitalizations," then California's 10-disease mandate and Massachusetts' 9-disease mandate are even more dangerous. Yet AAP has never called California's schedule dangerous, never sued Massachusetts, never told Massachusetts parents to "ignore everything" from the Massachusetts Department of

Public Health. The only variable that changes between a "safe" 10-disease state mandate and a "dangerous" 11-disease federal recommendation is revenue: under SCDM, physicians must discuss rather than simply administer, the bundled well-child visit becomes less efficient, and pay-for-performance metrics become harder to achieve.

ACIP Member Allegations (¶¶ 71–83)

32. Intervenors deny the characterization of ACIP members as unqualified or "anti-vaxxer" in ¶¶ 71–78. Plaintiffs' standard for "qualification" appears to be agreement with AAP's position that the cumulative schedule has been rigorously tested—a standard that excludes anyone who has read the IOM reports.

33. Intervenors lack knowledge or information sufficient to form a belief about the specific procedural requirements for ACIP member appointments as alleged in ¶¶ 79–83 and therefore deny the same. Intervenors note that Plaintiffs' characterization of the Secretary's statement—"we need to stop trusting the experts"—omits the broader point that scientific questions should be resolved by evidence, not authority. This is the position the IOM took when it recommended that the cumulative schedule be studied rather than assumed safe.

Three ACIP Meetings (¶¶ 84–100)

34. Intervenors admit that ACIP held three meetings in 2025 at which members and presenters made various statements about vaccine safety. Intervenors deny that all such statements were "false or misleading." Plaintiffs' "correction" regarding Hepatitis B trials (¶ 85) states that "there have been more than 15 studies of Hep B vaccines, including randomized control studies." This is partially responsive to the individual vaccine

question (ignoring fundamental flaws with a number of HepB vaccine studies) but completely ignores the cumulative schedule question. No study has ever tested the safety of administering the Hepatitis B birth dose in combination with the other vaccines an infant receives in the first months of life.

35. The United Kingdom, Canada, and seventeen EU member states delay the Hepatitis B birth dose without infection surges or increased liver cancers, directly contradicting AAP President Susan Kressly's claim that the ACIP Hepatitis B decision would cause "99,000 preventable hepatitis B infections" and "devastating results." Kressly's projections derive from unpublished models, not observed outcomes from the many industrialized nations that have implemented exactly the policy ACIP adopted.

Counts I–IV (¶¶ 101–183)

36. Intervenors deny that the January 5 Action alleged in Count I (¶¶ 101–115) was arbitrary, capricious, or contrary to law. The Action moved six vaccines from universal recommendation to shared clinical decision-making—a framework that preserves access to all vaccines, as well as insurance coverage, while introducing individualized physician-patient discussion. This is not the elimination of vaccines. It is the introduction of informed consent.

37. Intervenors lack knowledge or information sufficient to form a belief about the FACA compliance of ACIP appointments alleged in Count II (¶¶ 116–133) and therefore deny the same. Intervenors deny, however, that seeking candidates outside the traditional AAP-industry nomination pipeline constitutes "inappropriate influence." (Supp. Ex. A, Zuckerman Decl.) To the contrary, FACA's "fair balance" requirement, 5 U.S.C. App. § 5(b)(2), exists precisely to prevent the kind of single-viewpoint advisory committee that

AAP maintained for decades — a committee whose members were drawn from AAP's own liaison network, shared AAP's foundational assumption that the schedule was "rigorously tested," and never recommended the studies the IOM identified as necessary. The Zuckerman declaration does not describe corruption of the appointment process. It describes the end of a captured appointment process.

38. Intervenors deny that the three challenged ACIP votes alleged in Count III (¶¶ 134–154) were arbitrary, capricious, or contrary to law. The Hepatitis B vote aligned with practices in the UK and Canada. The COVID-19 SCDM vote recognized limitations in the evidence base. The thimerosal vote reflected decades of concern about mercury exposure in infant vaccines.

39. Intervenors deny that the Secretarial Directive alleged in Count IV (¶¶ 155–183) was arbitrary, capricious, or contrary to law. The Directive removed the routine COVID-19 recommendation for children—a population which faced minimal COVID-19 mortality risk.

Standing and Harm Allegations

40. Intervenors deny that ACIP deliberations constitute "misinformation" as alleged in ¶ 119. AAP's own foundational safety claim—that the cumulative schedule has been rigorously tested—is contradicted by the IOM's findings. AAP cannot credibly accuse others of spreading misinformation when its own published claims misrepresent the state of scientific evidence.

41. Intervenors do not have knowledge or information to admit or deny whether Jane Does 1, 2, and 3 experienced the difficulties described in ¶¶ 121–123. Jane Doe 1's claimed injuries include losing sleep and headaches from difficulty finding a COVID-19 vaccine.

Jane Doe 2's claimed injuries include stress-induced tooth-grinding and gasoline expenses from driving to pharmacies. Jane Doe 3's son had an anxiety attack about a rescheduled appointment. These claimed injuries, even if true, must be weighed against the injuries of Intervenors: Andrea Shaw buried twin sons. Shanticia Nelson buried a daughter. Sleeplessness against death. Tooth-grinding against a coroner's report. Gasoline expenses against three funerals.

The Physician Declarations: Confessions Dressed as Complaints

42. Every declaration Plaintiffs filed in support of their motion is a confession dressed as a complaint. The physician who cannot bill for a counseling session is admitting she never had the conversation before. The practice that must discard $847 combination vaccines is admitting it stocked products designed to make the full schedule administratively mandatory. The specialist who cannot meet quality benchmarks under SCDM is admitting her compensation was tied to administering vaccines without individualized clinical discussion. The infectious disease expert who protests the abandonment of the GRADE framework is admitting that the framework was designed to evaluate individual vaccines in isolation — making it structurally incapable of asking the cumulative safety question the IOM told everyone to ask twenty-four years ago. These declarants are not describing injuries inflicted by the government; they are describing dependencies created by the prior system — and their disruption is the strongest evidence that the system operated exactly as Intervenors' Counterclaims allege.

43. Fifty-Three Form Letters. Before examining the substance of these confessions, the Court should know how they were assembled. Plaintiffs filed fifty-three declarations in support

of their preliminary injunction motion. They are substantially identical. The final paragraphs of nearly every physician declaration contain the same language—verbatim—about "compounding" harms, the GRADE and EtR frameworks, and clinical practice being pushed "toward a breaking point absent immediate injunctive relief." Several declarations contain the same copy-paste error: "follow established the GRADE" rather than "follow the established GRADE." The declarants practice in different states, treat different populations, and work in different clinical settings. They use the same sentences, down to the same typographical errors. These are not independent accounts of irreparable harm. They are a form letter with a signature line. Stripped of the boilerplate, the fifty-three declarations reduce to the confessions described below.

44. The "Unbillable Time" Confession. Several physician declarants complain that SCDM requires 10–20 minutes of counseling per vaccine conversation, time that current reimbursement codes do not cover. (Ex. 46, Srinivas Decl.; Ex. 38, Wheeler Decl.) This is an admission that under the prior schedule, these conversations were not happening. The prior framework treated vaccination as a ministerial act — check the box, administer the dose, bill the visit — not as a medical decision requiring physician judgment and true informed patient consent. The "unbillable time" these physicians now face is the time required for informed consent. If informed consent is too expensive to provide, the problem is not SCDM. The problem is a reimbursement structure built on the assumption that consent was unnecessary. Plaintiffs ask this Court to restore that assumption. Intervenors ask the Court to recognize it for what it is: compelled speech enforced through economic architecture.

45. The Combination Vaccine Confession. Plaintiffs' declarants report that the schedule change renders existing combination vaccine inventory — products like VAXELIS and PEDIARIX, valued at up to $847 per dose — unusable, because these products bundle multiple antigens that cannot be administered separately. (Ex. 43, Bornstein Decl.; Ex. 31, Berman Decl.) This is not a harm caused by the challenged actions. It is a harm caused by product architecture that was designed to make the full schedule administratively mandatory. A hexavalent vaccine cannot be unbundled. A physician who stocks VAXELIS must administer all six antigens or none. The product does not permit clinical judgment about individual components. When Plaintiffs complain about "wasted" inventory, they are describing a supply chain engineered to prevent exactly the kind of individualized assessment SCDM introduces. The waste is a feature of an assembly line approach to vaccines which abnegates the rule of individual clinical judgment and informed consent.

46. The Quality Metric Confession. Physician declarants report that SCDM makes it impossible to meet HEDIS vaccination quality measures and pay-for-performance targets tied to schedule compliance rates. (Ex. 46, Srinivas Decl.) This admission maps the compensation-side enforcement mechanism that complements the medical-board-side enforcement alleged in Intervenors' Counterclaims. Under the prior system, physicians were financially rewarded for achieving target vaccination rates — rates defined by AAP's schedule, adopted by insurers, and measured by metrics that treated any deviation as a quality failure. A physician who spent twenty minutes discussing vaccine risks with a concerned parent and ultimately respected the parent's decision to defer one vaccine was penalized twice: once in unbillable time, once in a missed quality target. The

performance metric did not measure quality of care. It measured compliance with AAP's protocol. When these physicians complain that SCDM disrupts their quality scores, they are admitting that the scores measured obedience, not medicine focused on the individual patient.

47. The VFC and Pharmacy Access Confession. Plaintiffs and their amici argue that moving vaccines to SCDM will disconnect them from the Vaccines for Children program and from pharmacy administration, because pharmacies stock only "routine" vaccines and VFC funds only CDC-recommended vaccines. (Ex. 31, Berman Decl.; Ex. 27, Kressly Decl.) This argument maps the supply-chain enforcement mechanism. VFC conditions federal funding on following the CDC schedule. Pharmacies stock what VFC covers. Practices order what pharmacies stock. Parents receive what practices order. No actor in this chain exercises independent clinical judgment — each follows the signal from the level above, and the signal originates with AAP's recommendations, laundered through CDC adoption, and funded by federal appropriation. When Plaintiffs complain that SCDM disrupts this pipeline, they are not describing a public health harm. They are describing a vertically integrated distribution system in which every participant's financial incentive points in the same direction: administer the full schedule, do not ask questions, do not deviate.

48. The GRADE Framework Confession. Plaintiffs' physician declarants — including specialists in infectious disease and pediatric medicine — protest that the reconstituted ACIP abandoned the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) and EtR (Evidence-to-Recommendations) frameworks that governed prior ACIP deliberations. (Ex. 36, Pavia Decl.; Ex. 30, Boyce Decl.; Ex. 35, Goldman

Decl.) GRADE is a systematic methodology for evaluating individual interventions against individual clinical endpoints using randomized controlled trial data. It is a rigorous tool — for the question it was designed to answer. But the IOM did not ask ACIP to evaluate individual vaccines. The IOM asked ACIP to evaluate the cumulative schedule — the protocol as actually administered. GRADE has no methodology for this question. It cannot evaluate a protocol that was never tested as a protocol. It evaluates components, not systems. When these declarants insist that GRADE must govern ACIP deliberations, they are insisting on a framework that is structurally incapable of asking the question the IOM identified as the central unresolved safety issue in American pediatric medicine. GRADE suppresses the cumulative safety question by design — because the question falls outside its analytical architecture. The declarants' protest that GRADE was abandoned is an admission that the tool used to foreclose the IOM's recommendation was finally set aside.

49. The Predetermined Outcome Confession. Even the conversations these physicians claim to be having under SCDM are not informed consent. They are scripted advocacy for a predetermined outcome. Dr. Boyce describes his SCDM practice as "briefly discussing the benefits of a vaccine that I recommend the patient receive and risks of not being vaccinated." ECF No. 185-30, ¶ 10. Not risks of the vaccine—risks of declining it. Dr. Andreae states under oath that "there is only one medically reasonable option consistent with the standard of care, and that would be to vaccinate all children." ECF No. 185-32, ¶ 14. Dr. Shaw describes pediatricians as "foot soldiers who can rely on the researched recommendations and findings of the ACIP." ECF No. 185-33, ¶ 8. The answer to every parental question is the same: vaccinate. Every concern is misinformation to be corrected.

Every hesitation is an obstacle to the only acceptable outcome. The physician who told Andrea Shaw to disregard her family history of adverse reactions was following this framework. The clinic staff who told Shanticia Nelson it was safe to vaccinate her sick daughter were following this framework. AAP's contraindications list is so narrow that virtually no child qualifies for an exception—and family history of adverse reactions is expressly classified as a "misperceived contraindication" to be overridden, not respected. These declarations do not describe physicians prepared to exercise individualized clinical judgment. They describe a coordinated network of practitioners dependent on a framework that never tested the cumulative safety of the schedule they were paid to enforce.

50. Intervenors are grateful for the candor of Plaintiffs' declarants. Their declarations, intended to demonstrate irreparable harm, instead constitute the most detailed evidentiary record ever assembled of the enforcement mechanisms through which AAP's untested schedule was maintained for two decades. No discovery could have produced what Plaintiffs volunteered.

51. Intervenors admit that several Northeastern states formed a cooperative to issue joint vaccine recommendations as described in ¶ 124. Intervenors note that this cooperative's adoption of AAP's schedule, under the Brentwood delegation mechanism documented by the Association of State and Territorial Health Officials, transforms AAP's private recommendations into state-enforceable standards—the very state action that gives rise to the compelled speech and listener's rights injuries alleged in Intervenors' Counterclaims.

52. Intervenors deny that the challenged actions "injected mistrust" into the physician-patient relationship as alleged in ¶ 125. The SCDM framework enhances that relationship by

requiring physicians to engage in genuine informed consent. The prior schedule—which Plaintiffs seek to restore—is what injected mistrust: physicians were compelled to deliver safety assurances that the IOM had found to be unsupported, and families who questioned those assurances were dismissed, ostracized, or expelled from practices.

Proposed Remedy

53. Intervenors oppose the Proposed Order's request to restore the prior schedule. Restoring the prior schedule would reimpose on American children a cumulative vaccination protocol that the IOM found has never been tested for safety. It would subject Intervenor Shaw's and Intervenor Nelson's surviving family members to the same protocol under which their children died. It would compel physicians who have adopted SCDM conversations to return to AAP's compelled script.

54. Intervenors oppose the Proposed Order's request to block all ACIP meetings as unconstitutional. The First Amendment protects the government's right to seek and receive information. FACA requires that advisory committees meet publicly. An order blocking all ACIP meetings would prevent HHS from deliberating on vaccine policy entirely.

55. Intervenors further note that AAP's request for judicial restoration of the prior schedule is belied by AAP's own conduct. After the January 5 schedule change, AAP did not merely file this lawsuit. AAP published its own competing immunization schedule — the "AAP Harmonized Schedule" — directing its 67,000 member pediatricians to follow AAP's version rather than the CDC's. AAP cannot simultaneously argue in this Court that only the federal government has authority to set the immunization schedule and then publish a private competing schedule instructing physicians to ignore the government's version. If

the schedule is a federal prerogative, AAP has no business publishing a competing one. If private organizations may set their own schedules, the government's decision to change its schedule is an exercise of the same prerogative AAP claims for itself. AAP's Harmonized Schedule is not a scientific document. It is a commercial product distributed through the same channels — the Red Book, HealthyChildren.org, state chapter networks — that Intervenors' Counterclaims identify as the distribution infrastructure of the enterprise.

AFFIRMATIVE DEFENSES

First Affirmative Defense: Unclean Hands

56. Plaintiffs seek equitable relief to restore a schedule they promoted through material misrepresentations. AAP represented the cumulative childhood immunization schedule as "rigorously tested" and safe when no cumulative safety study exists. AAP's foundational expert published the 10,000 vaccines claim as a substitute for empirical testing. AAP blocked the studies the IOM recommended. AAP's Committee on Infectious Diseases published a clinical report claiming the IOM "strongly affirmed" the schedule's safety while omitting the IOM's central finding that the cumulative schedule had never been studied. A court of equity should not restore a protocol promoted through misrepresentation.

Second Affirmative Defense: No Irreparable Harm / Self-Inflicted Harm

57. Plaintiffs' claimed harms are self-inflicted consequences of their own decision to maintain recommendations inconsistent with the evolving scientific evidence. AAP has never sued California (10 diseases), Massachusetts (9–10 diseases), or any state whose

schedule is less comprehensive than the new CDC schedule (11 diseases). Plaintiffs' resource diversion is the result of their own decision to publish a competing schedule and oppose federal health policy, not of any unlawful government action.

Third Affirmative Defense: Overbreadth of Requested Relief

58. The relief Plaintiffs seek is grossly overbroad. Paragraph 3 of the Proposed Order would block all future ACIP meetings—an unprecedented prior restraint on government deliberation that violates the First Amendment and FACA's public meeting requirements. Paragraph 1 would restore a schedule that no court has ever been asked to mandate by judicial decree.

Fourth Affirmative Defense: Failure to Join Indispensable Parties

59. If the Court is being asked to restore a vaccination schedule that affects millions of American children, the families on the receiving end of that schedule are indispensable parties under Federal Rule of Civil Procedure 19. Prior to this intervention, the Court was being asked to adjudicate the propriety of the childhood immunization schedule without hearing from a single family affected by it.

COUNTERCLAIMS

Intervenor-Defendants/Counterclaim Plaintiffs Children's Health Defense, Andrea Shaw, Shanticia Nelson, Dr. Paul Thomas, and Dr. Kenneth Stoller (collectively, "Counterclaim Plaintiffs"), assert the following Counterclaims against Counterclaim Defendants American Academy of Pediatrics, Massachusetts Chapter of the American Academy of Pediatrics, and Infectious Diseases Society of America (collectively, "Counterclaim Defendants"):

PARTIES TO THE COUNTERCLAIMS

Counterclaim Plaintiffs

60. Counterclaim Plaintiff Children's Health Defense ("CHD") is a nonprofit organization headquartered in Franklin Lakes, New Jersey. CHD publishes books on vaccine safety and children's health, produces daily news content through The Defender, operates a streaming platform (CHD.TV), and conducts educational seminars and live events. CHD competes directly with AAP in the market for vaccine-related health information directed at healthcare providers and families. CHD sues on its own behalf and in its associational capacity on behalf of its members whose children are subject to the childhood immunization schedule.

61. Counterclaim Plaintiff Andrea Shaw is the mother of fraternal twins Dallas and Tyson Shaw, who both died on May 1, 2025, eight days after receiving their 18-month vaccines. Mrs. Shaw had warned the pediatrician about a family history of adverse vaccine reactions. The pediatrician dismissed the warning consistent with AAP's contraindications framework, which classifies family history as a "misperceived contraindication." Shaw Compl. ¶¶ 16–21.

62. Counterclaim Plaintiff Shanticia Nelson is the mother of Sa'Niya Carter, who died on March 27, 2025, less than twelve hours after receiving six injections containing twelve antigens in a single catch-up visit. Sa'Niya was ill at the time. Ms. Nelson expressed concern. Clinic staff told her it was safe per AAP guidelines. The coroner found a swollen brain consistent with encephalitis—a recognized DTaP Table Injury—but listed the cause of death as Sudden Unexplained Death in Childhood. Shaw Compl. ¶¶ 22–27.

63. Counterclaim Plaintiff Dr. Paul Thomas is a board-certified pediatrician in Oregon. Dr. Thomas published a peer-reviewed vaccinated-versus-unvaccinated study—the type of

comparative analysis the IOM recommended in 2002. His medical license was suspended shortly after publication. Thomas Compl. ¶¶ 12–13.

64. Counterclaim Plaintiff Dr. Kenneth Stoller is a physician who used genetic testing to identify children at heightened risk of adverse vaccine reactions and adjusted their vaccination protocols accordingly. His license was revoked for deviating from ACIP guidelines. Thomas Compl. ¶¶ 21–30. If the prior schedule is restored, the clinical approach for which both Dr. Thomas and Dr. Stoller lost their licenses will once again constitute professional misconduct.

Counterclaim Defendants

65. Counterclaim Defendant American Academy of Pediatrics ("AAP") is a nonprofit corporation headquartered in Itasca, Illinois, with an office in the District of Columbia. AAP generates $115–125 million in annual revenue and represents approximately 67,000 pediatricians. AAP publishes the Red Book ($175/copy), which it markets as "the authoritative guide" to pediatric infectious diseases. AAP operates HealthyChildren.org, a consumer-facing health information portal.

66. Counterclaim Defendant Massachusetts Chapter of the American Academy of Pediatrics ("MCAAP") represents over 1,600 pediatricians in Massachusetts and is the conduit through which AAP's national guidelines become the operative standard of care in this judicial district.

67. Counterclaim Defendant Infectious Diseases Society of America ("IDSA") represents over 13,000 infectious disease specialists. IDSA members serve on ACIP and its Work Groups and co-develop the recommendations that form the basis of the childhood immunization schedule.

FACTUAL ALLEGATIONS COMMON TO ALL COUNTERCLAIMS

A. The Foundational Fraud: Theory Substituted for Testing

68. The childhood vaccine schedule expanded from 11 doses targeting four diseases in 1983 to over 72 doses targeting 18 diseases. This expansion dramatically accelerated after the National Childhood Vaccine Injury Act of 1986 granted manufacturers immunity from liability.

69. In January 2002, AAP published in its journal *Pediatrics* an article by Paul A. Offit, M.D., FAAP, a member of AAP's Committee on Infectious Diseases, claiming that infants could "theoretically" respond to 10,000 vaccines at once. Offit PA, et al., "Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?" *Pediatrics* 2002;109(1):124–129.

70. Parents were asking a toxicological question: Is it safe to inject my infant with multiple vaccines containing aluminum adjuvants, thimerosal, formaldehyde, polysorbate 80, residual DNA fragments, and other components? Offit answered a different question—an immunological one about whether the immune system could theoretically generate antibody responses. His calculation said nothing about cumulative aluminum dose, mercury toxicokinetics, synergistic adjuvant effects, neuroinflammation, autoimmune activation, or any clinical safety endpoint.

71. The misdirection created a framework that foreclosed the safety question. Under Offit's paradigm, concerns about cumulative vaccine load became anti-science. Questioning the schedule was no longer a scientific inquiry to be resolved by evidence—it was a failure to understand basic immunology. The contraindication framework, already narrow before 2002, became locked in for 72+ doses.

72. AAP distributed this paradigm through its 67,000-member network. Pediatricians learned to cite the 10,000 vaccines figure when parents expressed concern. The Red Book incorporated it. HealthyChildren.org repeated it. Board certification and continuing medical education reinforced it.

B. The IOM Recommendations: Open the Filing Cabinet

73. One month after Offit's article, the IOM found that no study had compared health outcomes between vaccinated and unvaccinated children and recommended such studies. IOM, *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* (2002), at 14–15, 107–08. The IOM specifically told CDC to use the VSD—a database containing health records for millions of children—to conduct these studies without withholding vaccines from anyone.

74. In 2013, the IOM returned and found the filing cabinet remained unopened: "studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted." IOM, *The Childhood Immunization Schedule and Safety* (2013), at 6.

75. When pressed to explain why, Offit argued it would be "unethical" to conduct placebo-controlled trials withholding vaccines from children—an objection to a recommendation the IOM never made. By conflating database analysis with randomized trials, Offit made an easy study sound impossible and an ethical study sound unethical. Twenty-four years later, the filing cabinet remains unopened.

C. The Suppressed Studies Show the Harm

76. Independent researchers worldwide have conducted comparative analyses consistently finding concerning health outcomes associated with the cumulative vaccine schedule.

These include Jablonowski & Hooker (2025), analyzing Louisiana infant deaths, finding 68% higher mortality for infants vaccinated at two months and 112% higher mortality for female infants.

77. Military medicine has recognized what AAP denies. The U.S. Marine Corps limits healthy adults selected for physical resilience to five vaccines in one sitting. Infants face no limit whatsoever—because the Offit paradigm declares their immune systems can theoretically handle 10,000.

D. The Financial Architecture

78. Vaccine manufacturers have systematically acquired companies developing treatments for conditions listed as adverse events in their own vaccine package inserts (or developed drugs through their R&D processes). Pfizer acquired Anacor (pediatric eczema, $5.2B). Sanofi acquired Principia Biopharma (immune thrombocytopenia, $3.7B). GSK acquired Human Genome Sciences (lupus, $3.6B). Merck acquired Pandion Therapeutics (IBD, $1.85B). These acquisitions create a closed-loop revenue system.

79. AAP ensures this revenue continues. Vaccine administration is essential revenue for pediatric practices: administration fees, performance bonuses, bundled well-child visits. Major insurers enforce the schedule through incentive programs. AAP acknowledges these financial dependencies while publicly denying that pediatricians profit from vaccines.

E. The Enforcement Mechanisms: How the Schedule Was Maintained

80. The childhood immunization schedule was not maintained by scientific consensus. It was maintained by an interlocking set of enforcement mechanisms — intellectual, financial,

logistical, and professional — each of which Plaintiffs' own declarants have now described under oath.

81. The intellectual enforcement mechanism was the GRADE framework. GRADE evaluates individual interventions against individual endpoints using randomized controlled trial data. It has no methodology for evaluating a cumulative protocol. Because GRADE governed all ACIP deliberations for two decades (Ex. 36, Pavia Decl.; Ex. 30, Boyce Decl.; Ex. 35, Goldman Decl.), the IOM's recommendation to study the cumulative schedule could never enter the analytical framework. The question was not suppressed by fiat. It was suppressed by architecture: GRADE made the question unaskable within the only institution authorized to ask it.

82. The financial enforcement mechanism was the quality metric system. HEDIS vaccination measures and pay-for-performance targets rewarded physicians for achieving schedule compliance rates and penalized deviation. (Ex. 46, Srinivas Decl.) A physician who engaged in genuine informed consent — spending twenty minutes discussing risks and ultimately respecting a parent's decision to defer — was penalized twice: unbillable time and a missed quality target. The metrics measured compliance, not care.

83. The logistical enforcement mechanism was the VFC/pharmacy supply chain. VFC conditioned federal funding on following the CDC schedule. Pharmacies stocked what VFC covered. Practices ordered what pharmacies stocked. Parents received what practices ordered. (Ex. 31, Berman Decl.; Ex. 27, Kressly Decl.) No actor exercised independent clinical judgment. Each followed the signal from the level above, and the signal originated with AAP's recommendations.

84. The product enforcement mechanism was the combination vaccine. Products like VAXELIS and PEDIARIX bundle multiple antigens into a single injection that cannot be unbundled. (Ex. 43, Bornstein Decl.) A physician who stocks a hexavalent vaccine must administer all six antigens or none. The product architecture eliminated clinical discretion at the point of care. When the schedule changed and the bundles could no longer be administered as designed, the "waste" was not caused by the government. It was caused by products designed to prevent the very flexibility the new schedule introduced.

85. The professional enforcement mechanism was the medical board disciplinary system. Physicians who deviated from the schedule — whether by recommending alternative schedules, expressing concerns about cumulative safety, or supporting parental choice — faced investigation, suspension, or license revocation. Dr. Paul Thomas, a board-certified pediatrician in Oregon and a Counterclaim Plaintiff herein, had his medical license suspended by the Oregon Medical Board after publishing a peer-reviewed study comparing health outcomes between vaccinated and unvaccinated children in his practice — a study that attempted to answer the very question the IOM recommended. Dr. Kenneth Stoller, also a Counterclaim Plaintiff herein, faced medical board discipline for exercising the individualized clinical judgment that SCDM now requires. These are not hypothetical risks. They are documented consequences, inflicted on physicians who tried to do what the IOM said needed doing, by a system that punished the question rather than answer it.

86. These mechanisms operated in concert. GRADE prevented the question from being asked. Quality metrics prevented the answer from being sought. VFC prevented the supply chain from accommodating alternatives. Combination products prevented clinical

discretion at the point of care. Medical boards punished anyone who tried to exercise it anyway. The result was a system that appeared to reflect scientific consensus but in fact reflected structural coercion — a distinction that Plaintiffs' own declarations have now made visible.

F. AAP as Distribution Network: The Red Book as Rulebook

87. AAP controls pediatric medicine. Its Red Book defines the standard of care. Through the *Brentwood* delegation mechanism, AAP's recommendations have been adopted by at least 28 states as regulatory standards. The Association of State and Territorial Health Officials documented approximately 600 statutes across 49 states that automatically incorporate ACIP recommendations—recommendations that AAP historically co-developed. This transforms AAP's private guidelines into state action under *Brentwood Academy v. Tennessee Secondary School Athletic Ass'n*, 531 U.S. 288 (2001).

88. Physicians who deviate face medical board discipline, loss of hospital privileges, exclusion from insurance networks, and professional destruction. The message is clear: follow AAP's script or lose your livelihood.

G. The Families

89. Andrea Shaw's fraternal twins Dallas and Tyson both died on May 1, 2025, eight days after receiving their 18-month vaccines, including Hepatitis A, influenza, and DTaP. Mrs. Shaw and her mother-in-law had warned the pediatrician about a family history of adverse reactions to the flu vaccine. The pediatrician dismissed these concerns consistent with AAP's Red Book, which classifies family history of adverse vaccine reactions as a "misperceived contraindication." The emergency room diagnosis was "post-

immunization reaction." A homicide investigation was opened targeting the mother. Shaw Compl. ¶¶ 16–21.

90. Shanticia Nelson's daughter Sa'Niya Carter died on March 27, 2025, less than twelve hours after receiving six injections containing twelve antigens in a single catch-up visit. Sa'Niya was ill at the time. Ms. Nelson expressed concern. Clinic staff told her it was safe per AAP guidelines. Sa'Niya experienced seizures and cardiac arrest. The coroner found a swollen brain consistent with encephalitis—a recognized DTaP Table Injury under the National Childhood Vaccine Injury Act. The death certificate listed the cause as Sudden Unexplained Death in Childhood. Shaw Compl. ¶¶ 22–27.

91. These families trusted the protocol. They followed the recommendations. They did everything AAP told them to do. Their children died under the schedule Plaintiffs seek to restore.

H. The California/Massachusetts Comparison

92. AAP filed this action in the District of Massachusetts, asking the Court to restore a schedule recommending vaccines for 18 diseases. Massachusetts requires only 9 diseases for grades K–6. California requires only 10, with the strictest mandate in the nation. The new CDC schedule recommends 11.

93. AAP has never sued California. AAP has never called Massachusetts' schedule dangerous. If recommending fewer vaccines than 18 were dangerous, California and Massachusetts would be in crisis. They are not. Vaccination rates exceed 95% in both states. AAP's alarm is pretextual. The concern is not public health—it is revenue.

COUNTERCLAIM I

DECLARATORY JUDGMENT — CUMULATIVE CHILDHOOD SCHEDULE SAFETY
(Against AAP, MCAAP, IDSA)

94. Counterclaim Plaintiffs reallege and incorporate by reference the preceding paragraphs.

95. An actual controversy exists between the parties within the meaning of 28 U.S.C. §§ 2201–2202. AAP alleges in Paragraph 34 of its Fourth Amended Complaint that vaccine safety is "rigorously tested." Counterclaim Plaintiffs contend this representation is materially misleading because the cumulative childhood immunization schedule has never been tested for safety.

96. The IOM found in 2002 that no study had compared health outcomes between children receiving the full schedule and those who did not, and recommended such studies. In 2013, the IOM found these studies had not been conducted. As of this filing, no such study has been produced.

97. Counterclaim Plaintiffs seek a declaration that: (a) no study has established the cumulative safety of the childhood immunization schedule as administered; (b) the IOM recommended such studies in 2002 and 2013; and (c) those studies have not been conducted.

COUNTERCLAIM II

FALSE ADVERTISING UNDER THE LANHAM ACT, 15 U.S.C. § 1125(a)
(Against AAP)

98. Counterclaim Plaintiffs reallege and incorporate by reference the preceding paragraphs.

99. AAP has made and continues to make false or misleading representations of fact in commercial advertising and promotion, in violation of Section 43(a) of the Lanham Act, 15 U.S.C. § 1125(a). These include: (a) that the childhood immunization schedule is

"fully tested and proven safe"; (b) that infants can "theoretically respond to 10,000 vaccines at once"; and (c) that "Vaccines are not associated with autism or developmental delay," when the IOM found evidence "inadequate to accept or reject a causal relationship."

100. These representations appear in commercial products: the Red Book ($175), HealthyChildren.org, CME programs, and annual conferences generating pharmaceutical exhibitor revenue. They constitute commercial advertising and promotion.

101. CHD is a direct market competitor, publishing books on vaccine safety, producing The Defender, operating CHD.TV, and conducting educational seminars—all in the same market for vaccine-related health information. AAP's false representations suppress demand for CHD's competing content and damage CHD's credibility. CHD has standing under *Lexmark Int'l, Inc. v. Static Control Components, Inc.*, 572 U.S. 118 (2014).

102. Most recently, following the January 5, 2026 schedule change, AAP published the "AAP Harmonized Schedule" as a commercial alternative to the new CDC schedule, directing its 67,000 members to follow AAP's version and distributing it through the Red Book, HealthyChildren.org, and state chapter networks. The Harmonized Schedule repeats the same unqualified safety representations that underlie the prior schedule — representations the IOM found unsupported — and constitutes the most recent act of false advertising in the pattern of commercial misrepresentation alleged herein.

103. Counterclaim Plaintiffs seek injunctive relief under 15 U.S.C. § 1116: AAP must either produce the cumulative safety study or cease making unqualified safety claims in its commercial publications, and provide corrective disclosure in the Red Book and on HealthyChildren.org.

COUNTERCLAIM III

42 U.S.C. § 1983 — COMPELLED SPEECH (FIRST AMENDMENT)
(Against AAP, MCAAP)

104. Counterclaim Plaintiffs reallege and incorporate by reference the preceding paragraphs.

105. Through the *Brentwood* delegation mechanism, AAP's recommendations have been adopted by at least 28 states as the operative standard of care. This transforms AAP's private guidelines into state action under *Brentwood Academy v. Tennessee Secondary School Athletic Ass'n*, 531 U.S. 288 (2001).

106. Physicians who deviate face state-imposed consequences: medical board investigation, suspension, or revocation; loss of hospital privileges; exclusion from insurance networks; and professional destruction.

107. Under *National Institute of Family and Life Advocates v. Becerra*, 138 S. Ct. 2361 (2018), the government cannot compel professionals to deliver a misleading state-scripted message. Counterclaim Plaintiffs Dr. Thomas and Dr. Stoller were compelled to deliver AAP's safety assurances—that the schedule is "rigorously tested," that infants can handle 10,000 vaccines—or face professional consequences. These assurances are unsupported. Both lost their licenses for refusing to deliver them.

108. Counterclaim Plaintiffs seek a declaration that AAP's guidelines, as enforced through state action, compel physician speech in violation of the First Amendment, and an injunction prohibiting such enforcement.

COUNTERCLAIM IV

42 U.S.C. § 1983 — LISTENER'S RIGHTS (FIRST AMENDMENT)
(Against AAP, MCAAP)

109. Counterclaim Plaintiffs reallege and incorporate by reference the preceding paragraphs.

110. Under *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council*, 425 U.S. 748 (1976), the First Amendment protects the right to receive information. Counterclaim Plaintiffs Andrea Shaw, Shanticia Nelson, and CHD's community members have a constitutional right to receive truthful medical information about the vaccines administered to their children.

111. AAP's monopoly on the pediatric information channel—67,000 members who deliver AAP's message or face professional destruction—deprives families of the honest disclosure required for informed consent. Andrea Shaw's and Shanticia Nelson's children were vaccinated based on safety assurances that omitted material facts: that the cumulative schedule had never been tested, that the IOM recommended studies were never conducted, and that AAP's expert substituted theory for evidence.

112. Counterclaim Plaintiffs seek a declaration that AAP's control of medical communication, as enforced through state action, violates the First Amendment rights of families to receive truthful information, and an injunction requiring that physicians be permitted to disclose the IOM findings and the limitations of the evidence without professional penalty.

PRAYER FOR RELIEF

WHEREFORE, Intervenors/Counterclaim Plaintiffs respectfully request that the Court:

A. Deny the Plaintiffs' claims for relief in their entirety.

B. Declare that no study has established the cumulative safety of the childhood immunization schedule as administered to American children, and that the Institute of

Medicine recommended such studies in 2002 and 2013 and they have not been conducted;

C. Enjoin AAP from representing in commercial publications that the cumulative childhood immunization schedule has been "rigorously tested" or "proven safe" unless and until such testing has been conducted, or require corrective disclosure;

D. Enjoin the enforcement of AAP guidelines through state action insofar as such enforcement compels physicians to deliver unqualified safety assurances about a schedule that has never been cumulatively tested;

E. Declare that families have a First Amendment right to receive truthful information about the limitations of the cumulative safety evidence and that AAP's control of the medical information channel violates that right;

F. Award Counterclaim Plaintiffs their reasonable attorneys' fees and costs pursuant to 15 U.S.C. § 1117 and 42 U.S.C. § 1988; and

G. Grant such other and further relief as the Court deems just and proper.

Dated February 18, 2026

Respectfully submitted,

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Counterclaim Plaintiffs
(pro hac vice pending)
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Local Counsel for Proposed Intervenor-Defendants/Counterclaim Plaintiffs

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMERICAN ACADEMY OF PEDIATRICS, et al.,
Plaintiffs,

v. Case No. 1:25-cv-11916 (BEM)

ROBERT F. KENNEDY, JR., et al.,
Defendants,

and

CHILDREN'S HEALTH DEFENSE, ANDREA SHAW, SHANTICIA NELSON, DR. PAUL THOMAS, AND DR. KENNETH STOLLER

Intervenor-Defendants/Counterclaim Plaintiffs.

AMERICAN ACADEMY OF PEDIATRICS, MASSACHUSETTS CHAPTER OF THE AMERICAN ACADEMY OF PEDIATRICS, and INFECTIOUS DISEASES SOCIETY OF AMERICA,

Counterclaim Defendants

[PROPOSED] ORDER GRANTING MOTION TO INTERVENE

Upon consideration of the Emergency Motion to Intervene filed by Children's Health Defense, Andrea Shaw, Shanticia Nelson, Dr. Paul Thomas, and Dr. Kenneth Stoller (collectively, "Proposed Intervenors"), the Memorandum of Law in Support, the Declaration of Richard Jaffe with Exhibits A through E, and any opposition thereto, and for good cause shown, it is hereby

ORDERED that the Emergency Motion to Intervene is GRANTED; and it is further

ORDERED that the Proposed Answer to the Fourth Amended Complaint with Affirmative Defenses and Counterclaims filed by Intervenors is accepted for filing; and it is further

ORDERED that Intervenor-Defendants' Memorandum in Opposition to Plaintiffs' Motion for Preliminary Injunction is accepted for filing and shall be considered by the Court in ruling on the pending preliminary injunction motion; and it is further

ORDERED that the Declaration of Richard Jaffe and its Exhibits A through E shall be considered by the Court in connection with the pending preliminary injunction motion; and it is further

ORDERED that Intervenor-Defendants may participate in all remaining proceedings in this action, including the hearing currently scheduled for March 13, 2026, subject to the Court's existing schedule and any further orders of the Court.

SO ORDERED.

Dated: _____

_____

HONORABLE BRIAN E. MURPHY

United States District Judge

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

AMERICAN ACADEMY OF PEDIATRICS, et al.,

Plaintiffs,

v. Case No. 1:25-cv-11916 (BEM)

ROBERT F. KENNEDY, JR., et al.,

Defendants,

and

CHILDREN'S HEALTH DEFENSE, et al.,

Intervenor-Defendants/Counterclaim Plaintiffs

v.

AMERICAN ACADEMY OF PEDIATRICS, et al.,

Counterclaim Defendants

DECLARATION OF RICHARD JAFFE
IN SUPPORT OF MOTION TO INTERVENE

I, Richard Jaffe, declare as follows:

1. I am counsel of record for all Proposed Intervenors in this matter. I submit this declaration in support of their Motion to Intervene.

2. I have filed three federal cases which are directly related to this proceeding. In April 2025, I filed *Cardenas v. Monarez* in the Central District of California (8:25-cv-00867). *Cardenas* sought to move the COVID-19 vaccine for children from Category A, recommended to Category B, shared clinical decision-making. On May 27, 2025, Secretary of Health and Human Services, Robert F. Kennedy, Jr. announced the removal of the COVID-19 shot from the schedule for children and pregnant women. On or about August 11, 2025, I voluntarily dismissed the *Cardenas* Complaint, in light of the Secretary's action.

3. I then filed *Thomas v. Monarez* in the District of Columbia (1:25-CV-02685, D.D.C.)—the mirror image of some of the relief requested in this case. *Thomas* seeks to move all remaining childhood recommended vaccines to shared clinical decision-making primarily because the childhood immunization schedule has never been cumulatively tested for safety, despite that the Institute of Medicine advised such studies in 2002 and again in 2013. A schedule never proven safe let alone proven to confer a net benefit — should not be imposed as a universal mandate. The CDC will be moving to dismiss *Thomas* by Friday, February 20, 2026, a motion we intend to oppose.

4. I am also the 'some California antivax lawyer who filed a RICO suit against AAP' to whom Plaintiffs' counsel reportedly referred to at last Friday's hearing.

5. Specifically, on January 21, 2026, I filed *Shaw v. American Academy of Pediatrics* (1:26-cv-00171, D.D.C) in the District of Columbia on behalf of Andrea Shaw, Shanticia Nelson, Children's Health Defense, Dr. Paul Thomas, and Dr. Kenneth Stoller — all of whom are Proposed Intervenors in this proceeding.

6. The *Shaw* complaint alleges that AAP has for decades claimed the childhood immunization schedule is "rigorously tested" and "thoroughly studied" while knowing that the Institute of Medicine twice found the opposite — that the cumulative safety of the schedule has never been tested. AAP blocked the studies the IOM recommended, enforced schedule compliance through its control of the Red Book, the contraindications framework, and state medical board standards, and destroyed the careers of physicians who questioned the schedule's safety. The families who relied on AAP's safety assurances lost their children. The physicians who challenged those assurances lost their

licenses. The *Thomas* and *Shaw* complaints are attached hereto as Exhibits A and B respectively.

7. I believe that information about the testing of the schedule and how other industrial countries employ the SCDM model (upon which the CDC's recent moves are based) as related in these two complaints are highly relevant to the Court's consideration of the pending preliminary injunction motion.

I. WHY THIS COURT NEEDS TO HEAR FROM PROPOSED INTERVENORS BEFORE IT RULES ON THE PENDING PRELIMINARY INJUNCTION MOTION

8. Plaintiffs argue that the government's moving six immunizations to shared clinical decision-making (and moving the Covid shot off the schedule), recommending immunization against 11 diseases, will cause irreparable harm to children. Not only is this new schedule consistent with similar high resource nations (like Denmark), it surpasses the recommendations of many states. For example, Massachusetts only requires immunization against 9 diseases for K- 6th grade and 10 diseases for older children. California also requires ten. Plaintiffs have not sued Massachusetts or California or any other state that requires fewer immunizations than the CDC recommends. Instead, they have sued to force the federal government to recommend more vaccines than required by the state in which this Court sits.

9. On the evening of February 9, 2026, the government filed its opposition to Plaintiffs' preliminary injunction motion. In forty-five pages, the government argues that the Secretary had the *authority* to revise the schedule. It does not argue that the schedule *needed* revising. The government does not make the arguments presented by the proposed intervenors. It does not present the Institute of Medicine's findings. It does not

challenge AAP's claim that the schedule was "rigorously tested." It does not identify a single child harmed under the prior schedule. The government defends its right to act. It does not appear to defend the reasons for acting.

10. It cannot. The moment the government argues the prior schedule was substantively unsafe, it admits its own agencies endorsed an unsafe protocol for decades. The government will never make the case these Intervenors make: that the schedule was untested, that children were harmed, and that AAP and other members of the enterprise are responsible.

11. Neither Plaintiffs nor Defendants have identified these children or any child harmed under the schedule Plaintiffs seek to restore.

II. THE PROPOSED INTERVENORS[1]

12. Andrea Shaw's fraternal twins Dallas and Tyson both died on May 1, 2025, eight days after receiving their 18-month vaccines. Mrs. Shaw had warned the pediatrician about a family history of adverse vaccine reactions. The pediatrician dismissed the warning consistent with AAP's contraindications framework. Shaw Complaint ¶¶ 16–21.

13. Shanticia Nelson's daughter Sa'Niya Carter died on March 27, 2025, less than twelve hours after receiving six injections containing twelve antigens in a single catch-up visit. Sa'Niya was ill at the time. Ms. Nelson expressed concern. Clinic staff told her it was safe per AAP guidelines. Shaw Complaint ¶¶ 22–27.

14. Dr. Paul Thomas published the vaccinated-versus-unvaccinated study the IOM had recommended. His license was suspended shortly thereafter. Dr. Kenneth Stoller used

[1] The information about the proposed intervenors is taken from the attached Thomas and Shaw Complaints.

genetic testing to identify at-risk children. His license was revoked for deviating from ACIP guidelines. Thomas Complaint ¶¶ 12–13, 21–30.

15. If this Court restores the prior schedule, the individualized clinical approach for which both physicians lost their licenses will once again constitute professional misconduct.

16. Children's Health Defense publishes books, daily news, and educational programming on vaccine safety. CHD competes directly with AAP in the market for vaccine-related health information. If the prior schedule is restored, CHD's competing publications are delegitimized by judicial order.

III. THE GOVERNMENT DOES NOT ADEQUATELY REPRESENT INTERVENORS' INTERESTS

17. Under Federal Rule of Civil Procedure 24(a)(2), a proposed intervenor need show only that representation of its interests by existing parties "may be" inadequate. *Trbovich v. United Mine Workers of Am.*, 404 U.S. 528, 538 n.10 (1972). The government's own filings in this case and in *Thomas v. Monarez* satisfy this minimal burden.

18. The government's opposition to the preliminary injunction confirms the inadequacy as discussed above. In addition, the government does not mention the claim that children can tolerate 10,000 vaccine antigens.

19. The *Thomas v. Monarez* motion to dismiss removes any remaining ambiguity. In *Thomas*, the Department of Justice likely will argue the undersigned's clients, including proposed intervenors Drs. Thomas and Stoller have no actionable claim against the government challenging the CDC's vaccine schedule, or the need for conducting the IOM-recommended cumulative safety studies. Thus, the government is not merely failing

to assert Intervenors' interests in this proceeding; It is actively litigating against those interests in a parallel federal proceeding.[2]

IV. THE INSTITUTE OF MEDICINE REPORTS

20. Attached hereto as Exhibit C is the Institute of Medicine report, *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* (2002). At pages 14–15 and 107–108, the IOM found that no study had compared health outcomes between children receiving the full immunization schedule and those who did not, and recommended that such studies be conducted using the Vaccine Safety Datalink.

21. Attached hereto as Exhibit D is the Institute of Medicine report, *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies* (2013). At page 6, the IOM found that "studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted."

22. Neither Plaintiffs nor Defendants have cited these reports in their respective filings. The Court should review them prior to issuing its preliminary injunction ruling.

V. EVIDENCE NO PARTY HAS PRESENTED

23. Shared clinical decision-making is not a radical experiment. It is the international norm. Seventeen European Union nations, the United Kingdom, and Japan have no mandatory childhood vaccination requirements. They use voluntary recommendation programs — the functional equivalent of SCDM — and achieve coverage rates that equal or exceed

[2] For the Court's information, Defendant Robert F. Kennedy, Jr. was a co-founder and chairman of proposed Intervenor Children's Health Defense but severed all connection to the organization in December 2024. Prior to his current position, Mr. Kennedy worked with undersigned counsel on various litigation matters, all of which have either been resolved, or Mr. Kennedy has been removed from those cases which are still pending.

those of the United States: Sweden 97%, Denmark 95%, Japan 98%. Thomas Compl. ¶¶ 54–59. SCDM does not mean no vaccination. It means what most of the developed world already does: recommend rather than require.

24. Neither the CDC's catch-up schedule nor AAP's Red Book imposes any upper limit on the number of vaccines that may be administered simultaneously. Sa'Niya Carter received six injections containing at least twelve antigens in a single catch-up visit. She died twelve hours later. Shaw Compl. ¶ 22 n.7. (Marine candidates selected for physical resilience have been limited to five vaccines in one sitting. Shaw Complaint. Page 24, ¶¶ 79-80). Infants with immature immune systems face no limit despite the fact that the cumulative safety of simultaneous vaccine loading has never been studied. The catch-up protocol that killed Sa'Niya Carter is part of the schedule Plaintiffs seek to restore.

25. The 1986 National Childhood Vaccine Injury Act requires the Secretary of Health and Human Services to submit biennial reports to Congress on efforts to improve vaccine safety, including adverse event data and research progress. 42 U.S.C. § 300aa-27(c). HHS disbanded the task force responsible for these reports in 1998 and has not submitted a single report in twenty-seven years. Thomas Compl. ¶¶ 66–69. During that twenty-seven-year silence, the childhood immunization schedule grew from eleven recommended diseases to eighteen. Plaintiffs ask this Court to restore a schedule that expanded without the congressional safety oversight that the 1986 Act required.

26. The United States has the most aggressive vaccination schedule in the developed world and the sickest children. Over fifty percent of American children have at least one chronic health condition. The autism rate has risen from 1 in 150 to 1 in 31. The Department of Defense reports that seventy-one percent of American youth are unfit for

military service. Thomas Compl. ¶¶ 47–53. Correlation is not causation. But correlation is reason for the cumulative safety studies the IOM recommended twenty-four years ago — studies that have never been conducted.

27. Plaintiffs' own declarations, filed in support of their preliminary injunction motion, describe the infrastructure that enforces schedule compliance. These sworn statements are central to both the pending motion and Intervenors' Proposed Answer with Counterclaims, filed herewith.

28. Multiple declarants describe HEDIS — the Healthcare Effectiveness Data and Information Set — quality metrics that tie insurer reimbursement and physician performance ratings to childhood vaccination rates. HEDIS is administered by the National Committee for Quality Assurance and used by virtually every major health plan in the United States. Physicians who fall below schedule-compliance thresholds face reduced reimbursement, lower quality scores, and exclusion from insurance networks. This is not a clinical standard. It is a financial enforcement mechanism that punishes the exercise of clinical judgment.

29. Declarants describe combination vaccines — such as Pediarix, which bundles DTaP, hepatitis B, and polio in a single injection — that make it physically impossible to administer one component without the others. When HHS moved hepatitis B to SCDM, the combination product became unusable for the remaining components. Plaintiffs characterize this as harm. It is the consequence of product design that eliminated physician choice by bundling antigens that serve different clinical purposes into a single needle.

30. AAP's own Red Book classifies family history of adverse vaccine reactions as a "misperceived contraindication" — meaning a factor that providers and parents may believe warrants caution but that AAP's framework directs them to disregard. Andrea Shaw and her mother-in-law warned the pediatrician about a family history of adverse reactions to the flu vaccine. The pediatrician dismissed these concerns, consistent with this framework. Both twins died eight days later. Shaw Compl. ¶ 16 n.6. The contraindications framework is not neutral. It is designed to override parental caution and clinical judgment alike.

31. These declarations and the enforcement infrastructure they describe are addressed in detail in Intervenors' Proposed Answer with Affirmative Defenses and Counterclaims. What Plaintiffs describe as harms from SCDM are the withdrawal symptoms of a coercive system.

32. Plaintiffs have filed fifty-three declarations in support of their preliminary injunction motion. The final paragraphs of nearly every physician declaration contain the same language—verbatim—about "compounding" harms, the GRADE and EtR frameworks, and clinical practice being pushed "toward a breaking point absent immediate injunctive relief." Several declarations contain the same copy-paste error: "follow established the GRADE" rather than "follow the established GRADE." The declarants practice in different states, treat different populations, and work in different clinical settings, yet they use the same sentences, down to the same typographical errors. Intervenors' Opposition to the Preliminary Injunction addresses these declarations in detail.

33. After the February 13, 2026 hearing, the Court directed counsel to file additional briefing regarding the legal consequence of the January guidance. I have written on this very

topic, demonstrating that the move to shared clinical decision-making will have no effect on access to or insurance coverage for the vaccines. That analysis is attached hereto as Exhibit E.

VI. CONCLUSION

34. If this Court grants the preliminary injunction and restores the prior schedule without hearing from these Intervenors, it will reimpose on American children a vaccination protocol that the Institute of Medicine found has never been tested for safety — over the objection of the families who buried their children under that protocol.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

Executed on February 18, 2026.

_____

RICHARD JAFFE

TABLE OF EXHIBITS

EXHIBIT A

UNITED STATES DISTRICT COURT
DISTRICT OF COLUMBIA

PAUL THOMAS, M.D, 3515 SW 108th Ave Beaverton, OR 97005 KENNETH P. STOLLER, M.D., 2410 Northview St. Boseman, MT 59715, and STAND FOR HEALTH FREEDOM, a Not-For-Profit Organization, 3940 W. 96th St, Indianapolis, IN 46268 Plaintiffs, v. SUSAN P. MONAREZ, in her official capacity as Director of the CENTERS FOR DISEASE CONTROL AND PREVENTION, Defendant.	Civil Action No. 1:25-cv-02685

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF

I. INTRODUCTION

1. This lawsuit challenges the Centers for Disease Control and Prevention's recommended childhood immunization schedule,[1] a 72+ dose regimen that represents the most aggressive vaccination program in the world. While some states make minor modifications to their required vaccination lists, most incorporate ACIP's recommended vaccines directly into statute or regulation and uniformly adopt ACIP's narrow contraindications and precautions list

[1] CDC, ACIP Vaccine Recommendations and Schedules, https://www.cdc.gov/acip/vaccine-recommendations/index.html.

for medical exemptions, thereby enforcing adherence to the recommended schedule as a practical matter.[2]

2. ACIP's vaccine framework is only based on an evaluation of short-term individual vaccine risks. **The CDC has never studied the combined effects and the accumulating dangers of administering all of the vaccines on the CDC's recommended childhood vaccination schedule**.

3. For over two decades, the Institute of Medicine has urged the CDC to study the cumulative effects of the pediatric vaccine schedule. First in 2002 (*see* Institute of Medicine, *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* (2002), https://www.ncbi.nlm.nih.gov/books/NBK220493/ (hereinafter "IOM 2002") and then again in 2013 (*see* Institute of Medicine, *The Childhood Immunization Schedule and Safety* (2013), https://doi.org/10.17226/13563 (hereinafter "IOM 2013"). These calls have remained unanswered to this day.

4. ACIP organizes its vaccine recommendations into two categories: "Category A" recommendations apply universally to all children in an age group, while "Category B" involves shared clinical decision-making between physician and family based on individual circumstances. However, almost all childhood vaccines carry the Category A designation.[3]

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[2] "While ACIP recommendations are just that, recommendations and not requirements, they have a far-reaching impact on vaccine policy with nearly 600 statutes and regulations across 49 states, three territories, and Washington, D.C., referencing ACIP. These laws often direct the use or consideration of ACIP recommendations in developing or implementing state or territorial vaccine policy. If the ACIP recommendations change, then any state or territorial policy that depends on them will be altered as well."Association of State and Territorial Health Officials (ASTHO), Impact of ACIP Recommendations on State Law (2025) https://www.astho.org/topic/resource/impact-of-acip-recommendations-on-state-law.

[3] Only COVID-19 vaccines and MenB vaccines for adolescents fall under Category B.

5. The rigidity of the universal Category A recommendations is enforced through ACIP's narrow contraindications and precautions framework, which excludes many documented risk factors and prevents physicians from exercising individualized medical judgment. ACIP propagates an unscientific, one-size-fits-all model that denies individualized risk assessment while refusing to acknowledge that some children suffer serious harm from continued vaccination. Meanwhile, physicians who attempt to protect vulnerable patients face career destruction.

6. Government reports confirm this crisis. The White House's Make America Healthy Again Commission Report (May 22, 2025) documents exploding rates of chronic illness in children and systematic retaliation against dissenting physicians.[4]

7. When Plaintiff Dr. Paul Thomas published a study finding vaccinated children had significantly higher rates of chronic illness, which is exactly the research IOM recommended, his license was suspended within five days. When Plaintiff Dr. Kenneth Stoller used genetic markers to identify at-risk children, California's Medical Board declared only CDC guidelines could be followed, and revoked his medical license. The message is clear: conform or face professional banishment.

8. The refusal to test the schedule is particularly striking given that vaccine advocates like Paul Offit claim children can theoretically tolerate 10,000 vaccine antigens, yet the CDC won't study whether the 72+ doses it actually recommends are safe in combination.[5]

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[4] https://www.whitehouse.gov/wp-content/uploads/2025/05/MAHA-Report-The-White-House.pdf (hereinafter "MAHA Report").

[5] Paul A. Offit et al., "Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?" *Pediatrics* 109, no. 1 (January 2002): 124-129, https://pubmed.ncbi.nlm.nih.gov/11773551/.

9. Unable to defend their position scientifically, the medical establishment now seeks total control. On July 28, 2025, the American Academy of Pediatrics demanded elimination of all religious and philosophical exemptions,[6] forcing 100% compliance despite already achieving herd immunity thresholds.

10. Finally, and consistent with the deliberate ignorance manifest in the CDC's vaccine policies, there is no record of any biennial vaccine safety report made by HHS to Congress concerning the safety of vaccines, which violates its statutory duty. (*See* Factual Background, section F, page 17 below.) This silence reveals an agency that does not want to know if its program causes more harm than good.

11. Accordingly, Plaintiffs seek judicial intervention to restore scientific integrity and medical freedom. Specifically: (1) a declaration that CDC's framework is arbitrary and capricious and (2) only then may CDC return vaccines to Category A if the evidence supports it. Seventeen EU nations, the UK, and Japan already use this voluntary model while maintaining over 90% vaccination rates. (*See* Factual Background Section D, page 14 below.) Choice and science can coexist.

II. THE PARTIES

A. Plaintiffs

12. Plaintiff Paul Thomas, M.D., is an individual residing in Oregon. He was a board-certified pediatrician who founded and operated Integrative Pediatrics, serving over 10,000 patients until his medical license was suspended. Dr. Thomas developed individualized vaccine

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[6] https://www.cidrap.umn.edu/childhood-vaccines/aap-calls-end-nonmedical-vaccine-exemptions-school-attendance.

protocols based on each patient's medical history and published peer-reviewed research comparing vaccinated and unvaccinated children—the exact study the Institute of Medicine had urged CDC to conduct. He lost his license for practicing and advocating this evidence-based approach.

13. Plaintiff Kenneth P. Stoller, M.D., is an individual residing in Montana. He was a licensed physician specializing in integrative medicine with four decades of pediatric experience until his license was revoked. Dr. Stoller pioneered the use of genetic testing to identify children at risk for vaccine injury and issued medical exemptions based on these findings. The Medical Board revoked his license for deviating from CDC's one-size-fits-all guidelines.

14. Stand for Health Freedom ("SHF") is a national 501(c)(4) not-for-profit organization headquartered in Indiana. It operates through 41 state chapter leaders and a nationwide network of close to one million supporters, and is dedicated to protecting informed consent, parental rights, and medical freedom for families.

B. Defendant

15. Defendant Susan P. Monarez is the Director of the Centers for Disease Control and Prevention. She is sued in her official capacity only. The Centers for Disease Control and Prevention is a federal agency within the United States Department of Health and Human Services, and is headquartered in Atlanta, Georgia. The CDC establishes national vaccination guidelines and contraindication criteria that states adopt as binding standards.

III. JURISDICTION AND VENUE

16. This Court has subject matter jurisdiction under 28 U.S.C. § 1331 (federal question) as this action arises under the Constitution and laws of the United States, including the

Administrative Procedure Act, 5 U.S.C. § 701 et seq., and the First and Fifth Amendments to the United States Constitution.

17. This Court has authority to grant declaratory and injunctive relief under 28 U.S.C. §§ 2201-2202 (Declaratory Judgment Act) and 5 U.S.C. § 702 (APA judicial review).

18. Venue is proper in this District under 28 U.S.C. § 1391(e)(1) because defendant is an officer of the United States sued in her official capacity. The CDC is an agency within the Department of Health and Human Services, which maintains its headquarters in Washington, D.C.

IV. STANDING

19. Although ACIP recommendations are nominally "advisory," this characterization is a legal fiction. The widespread statutory incorporation of ACIP guidance into state law transforms these federal recommendations into binding national mandates. Once ACIP adopts a vaccine recommendation or narrows its contraindications list, that standard is effectively enforced in almost every jurisdiction in the United States. This makes ACIP the de facto rulemaking body for childhood vaccination policy nationwide—despite the absence of notice-and-comment rulemaking or cumulative safety testing.[7]

[7] "References to ACIP recommendations appear in several different areas of vaccine policy including state and territorial laws related to: School immunizations. Mandatory insurance coverage. Provider scope of practice to dispense or administer vaccines. Required vaccine information. Mandatory and voluntary immunizations for health care workers and patients. Standing orders and protocols for dispensing or administering vaccines. Notifications for recommended or overdue immunizations. Vaccine purchasing determinations." Association of State and Territorial Health Officials (ASTHO), Impact of ACIP Recommendations on State Law (June 23, 2025), https://www.astho.org/topic/resource/impact-of-acip-recommendations-on-state-law.

20. Article III standing requires: (1) injury in fact that is concrete and particularized; (2) causal connection between the injury and challenged conduct; and (3) likelihood that a favorable decision will redress the injury. *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560-61 (1992).

21. Dr. Thomas suffered concrete injury when his medical license was suspended and his 14-year practice destroyed. This occurred after he published peer-reviewed research comparing health outcomes between vaccinated and unvaccinated children, the very type of study the Institute of Medicine had urged CDC to conduct.

22. Dr. Thomas's retrospective analysis of over 3,000 patients found vaccinated children had significantly higher rates of asthma (OR 4.49), allergic rhinitis (OR 30.1), and ADHD (OR 3.33).[8]

23. Five days after publication, Oregon's Medical Board emergency-suspended Dr. Thomas's medical license, citing "serious concerns regarding the safety and welfare of his patients." The Board's action targeted his individualized vaccine protocols—protocols that deviated from CDC guidelines and that produced the data showing higher chronic illness rates in vaccinated children. The timing strongly suggests retaliation for publishing unwelcome findings.

24. Eight months later, the journal retracted the study without prior notice or opportunity for the authors to respond—departing from standard editorial practice. The retraction cited concerns about study design, not data integrity.

25. This injury is directly traceable to CDC's contraindications framework. Dr. Thomas's individualized approach, which allowed parents to make informed choices based on

[8] Lyons-Weiler & Thomas, *Relative Incidence of Office Visits*, Int'l J. Envtl. Res. Pub. Health (2020). https://doi.org/10.3390/ijerph17228674.

risk factors, violated the one-size-fits-all standard that medical boards enforce. When his research documented better health outcomes from this individualized approach, it provided evidence that contradicted CDC's universal recommendations, leading to his license suspension.

26. Judicial relief would redress Dr. Thomas's injury. If childhood vaccines were reclassified to Category B, the individualized protocols that formed the basis for his discipline would become permissible medical practice, which could lead to his obtaining a new medical license.

27. Between 2016-2019, Dr. Stoller issued medical exemptions based on genetic predispositions and documented family histories of adverse reactions. He relied on emerging peer-reviewed research showing certain children face heightened risks.

28. California's Medical Board revoked his license, explicitly ruling that "the standard of care for medical exemptions, as set forth in the ACIP guidelines adopted by CDPH, requires that exemptions be based on recognized contraindications or precautions." [9] Genetic predispositions and family history are not ACIP-recognized contraindications. The revocation of Dr. Stoller's medical license constitutes concrete injury.

29. Dr. Stoller's injury flows directly from CDC's narrow framework. Despite scientific evidence that some children are genetically vulnerable, the CDC's guidelines prohibit individualized risk assessment. The Board's decision confirms that only CDC criteria—not clinical judgment or emerging science—determine acceptable medical practice.

[9] *In re Stoller*, Cal. Med. Bd. Decision at 32 (Apr. 12, 2021) https://search.dca.ca.gov/details/8002/A/41183/82248c0e93cb87387b066f703eae8d73.

30. Reclassifying vaccines to Category B shared decision-making would eliminate the rigid standard used to revoke Dr. Stoller's license, which could lead to the reinstatement of his medical license.

31. As indicated above, Plaintiff Stand for Health Freedom ("SHF") is a national 501(c)(4) grassroots advocacy organization headquartered in Indiana, operating through 41 state chapter leaders and a nationwide network of supporters.

32. SHF has suffered concrete organizational injury as a direct result of the CDC's refusal to conduct safety studies on the cumulative childhood vaccine schedule. This refusal has allowed CDC to maintain universal Category A recommendations that states adopt as school-entry mandates. In response, SHF has been forced to divert substantial resources from its normal mission to address the consequences of these policies, including: developing educational materials to counter vaccine safety misinformation, hosting webinars presenting scientific evidence excluded from CDC's process, coordinating legislative advocacy for informed consent laws, and supporting families facing school exclusion. These diversions constitute cognizable organizational injury.

33. SHF's injuries are fairly traceable to CDC's conduct. The CDC's untested schedule drives state mandates and creates the coercive environment SHF must combat. But for CDC's refusal to test the schedule and its issuance of blanket recommendations without safety data, SHF would not need to divert resources to advocacy and crisis response. A favorable decision requiring CDC to conduct safety testing and reclassify vaccines to Category B would eliminate the need for SHF's extraordinary resource diversions, allowing it to return to its core mission.

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V. FACTUAL BACKGROUND

A. The CDC's Contraindications Framework: Rigid Categories Without Scientific Basis

34. The CDC's childhood vaccination policy operates through ACIP, established in 1964. Though statutorily advisory, ACIP's recommendations become binding through state adoption. The framework's rigidity appears in CDC's contraindications tables, which limit valid contraindications to: (1) severe allergic reaction (anaphylaxis) after a previous dose; (2) severe combined immunodeficiency (for live vaccines); and (3) a handful of other rare conditions.

35. Individual vaccines undergo limited FDA clinical trials before approval, typically monitoring adverse events for days or weeks.[10] **Neither the FDA nor the CDC has ever required or conducted safety testing of the cumulative childhood schedule,** now at least 72 doses.

36. This framework excludes documented injuries that do not fit narrow diagnostic categories. A child who suffers seizures, developmental regression, or autoimmune disease after vaccination typically will not qualify for exemption unless the reaction was immediate anaphylaxis or the exact same reaction occurs with subsequent doses.[11]

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[10] 21 C.F.R. § 600.80 (post-marketing adverse event reporting requirements acknowledge pre-licensure studies are limited).

[11] *See* Physicians for Informed Consent, *Vaccines and the Diseases they Target* at 55 (PIC Press 2025), https://physiciansforinformedconsent.org/silver-booklet/ (noting that the CDC's framework excludes a history of autoimmune disease, prior adverse reactions in family members, non-anaphylactic adverse events, and other known clinical warning signs such as mitochondrial dysfunction and immunologic anomalies, despite physicians consistently identifying these as risk-enhancing factors for vaccine injury).

37. The framework has not meaningfully changed in two decades, despite thousands of VAERS reports of adverse events annually.[12] Meanwhile, states have adopted these guidelines as binding standards. According to the National Conference of State Legislatures, medical exemptions in "all states" must meet CDC/ACIP criteria.[13] This makes ACIP's narrow contraindications the de facto national mandate.

38. This framework extends beyond school requirements. Medical boards use ACIP guidelines as the exclusive standard of care when evaluating physician conduct. Doctors who write exemptions based on clinical judgment rather than CDC criteria face professional discipline, as both Dr. Thomas and Dr. Stoller discovered.

39. The CDC's contraindication framework is enforced through direct administrative action, including disciplinary proceedings against physicians writing non-ACIP exemptions. In addition, thousands of physician-issued exemptions were overturned based solely on nonconformity with CDC guidelines, regardless of clinical judgment. The result: physicians cannot exercise clinical judgment, and children with family histories of vaccine injury or genetic vulnerabilities must continue the full schedule or lose access to education.[14]

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[12] VAERS Database, https://vaers.hhs.gov/data.html (documenting tens of thousands of reports annually).

[13] National Conference of State Legislatures, "States with Religious and Philosophical Exemptions from School Immunization Requirements" (2023), https://www.ncsl.org/health/state-non-medical-exemptions-from-school-immunization-requirements.

[14] Physicians for Informed Consent, *Vaccines and the Diseases They Target* at 54 (PIC Press 2025), https://picphysicians.org/pic-book/.

B. The IOM's Repeated Warnings: 25 Years of Willful Blindness

40. The Institute of Medicine (now the National Academy of Medicine) is the federal government's most authoritative advisor on health policy. For over two decades, IOM has consistently warned that the safety of the full childhood vaccine schedule remains untested.

41. In 2002, IOM's *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* stated: "The committee was unable to identify any studies that directly evaluated the safety of the entire immunization schedule." IOM 2002 at 152. The report recommended "studies of the health outcomes of fully vaccinated children compared with those following alternative schedules, including no vaccination." *Id.* at 153.

42. IOM reiterated these concerns in multiple reports. Its 2005 *Vaccine Safety Research, Data Access, and Public Trust* criticized CDC's surveillance systems as inadequate to detect rare or delayed adverse events, particularly noting the Vaccine Safety Datalink's limitations. [15]

43. Most comprehensively, IOM's 2013 report, *The Childhood Immunization Schedule and Safety*, found: "No studies have compared the differences in health outcomes... between entirely unimmunized populations of children and fully immunized children... Furthermore, studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted." IOM 2013 at 9-10.

44. The 2013 report specifically recommended CDC prioritize research to: (1) compare health outcomes of vaccinated versus unvaccinated children; (2) examine

[15] IOM, *Vaccine Safety Research* (2005) at 55-57, https://www.nap.edu/catalog/11234/.

cumulative effects of vaccines; and (3) identify potentially susceptible subpopulations. *Id.* at 11-13.

45. CDC has implemented none of these recommendations. No comparative studies. No cumulative safety analysis. No systematic identification of vulnerable subgroups. When Dr. Thomas conducted exactly such a study privately, he lost his license.

46. This is deliberate ignorance. CDC continues expanding the schedule, while refusing to study whether 72+ doses in combination cause more harm than benefit. The agency that claims to "follow the science" has ignored its most important outside scientific advisor for 25 years.

C. Declining Child Health: The Unexplained Epidemic

47. While CDC expands its untested vaccine schedule, American children have become the sickest in the developed world. The MAHA Report documents this crisis: over 50% of U.S. children now suffer from at least one chronic condition. MAHA Report at 8.

48. The numbers are staggering. According to the CDC, autism prevalence exploded from 1 in 150 children (2000) to 1 in 31 (2023).[16] Asthma affects 1 in 12 children, up from 1 in 32 in 1980.[17] Type 1 diabetes incidence increases 3-4% annually.[18] Food allergies increased 50% between 1997-2011.[19] Nearly 20% of children are obese.[20]

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[16] CDC, Autism Data & Statistics, https://www.cdc.gov/autism/data-research/index.html.

[17] CDC, Asthma Facts, https://www.cdc.gov/asthma/nhis/default.htm.

[18] *Lancet Diabetes & Endocrinology* (2019), https://doi.org/10.1016/S2213-8587(19)30412-7.

[19] CDC, NCHS Data Brief No. 121 (2013), https://www.cdc.gov/nchs/data/databriefs/db121.pdf.

[20] CDC, Childhood Obesity Facts, https://www.cdc.gov/obesity/data/childhood.html.

49. This is not normal. No other developed nation approaches these rates. Japanese children receive 12-13 vaccines and have autism rates of 1 in 100. European children receive 20-30% fewer vaccines than Americans yet have better health outcomes across every metric.[21]

50. The temporal correlation is undeniable. The vaccine schedule expanded from 24 doses (1983) to 72+ doses (2025). Chronic illness rates rose in parallel. **Yet, CDC has never investigated whether its aggressive vaccination program contributes to this epidemic**.

51. The Department of Defense now reports 71% of American youth are unfit for military service due to obesity, asthma, ADHD, and other chronic conditions.[22] An entire generation has been damaged while health authorities look the other way.

52. When researchers attempt to investigate, they are destroyed. Dr. Thomas found vaccinated children had approximately 4.5x more asthma, 30x more allergic rhinitis, and 3.3x more ADHD. Rather than replicate his findings, the medical establishment revoked his license and retracted his study.

53. This willful blindness has consequences. While CDC clings to theoretical models about vaccine safety, real children suffer real injuries. The agency tasked with protecting public health refuses to ask whether its signature program has become a cause of the problem.

D. International Success with Voluntary Programs: Proof of a Better Way

54. While American children grow sicker under CDC's coercive mandate, peer nations achieve better outcomes through voluntary consent. Seventeen EU countries, the UK,

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[21] OECD Health Statistics 2023, https://www.oecd.org/health/health-data.htm.

[22] DoD, Qualified Military Available (2023) at 12, https://www.esd.whs.mil/Portals/54/Documents/FOID/Reading%20Room/Personnel_Related/23-F-1060_QMA_Technical_Report_Mar_2022.pdf.

and Japan have no mandatory vaccination—yet maintain 90%+ coverage rates and healthier children.[23]

55. The evidence is unequivocal. Sweden's Public Health Agency states: "All vaccinations within national vaccination programs are voluntary and offered free of charge."[24] Coverage: 97%. Denmark's childhood vaccines are "free of charge and voluntary." Coverage: 95%.[25] Japan abolished mandatory vaccination in 1994. Coverage: 98%.[26]

56. These nations prove CDC's core premise wrong. High vaccination rates don't require coercion. Parents make responsible choices when given honest information and medical freedom. Their children are healthier for it.

57. The UK's approach is instructive. NHS guidance states vaccines "are not mandatory and cannot be given without your consent."[27] British parents discuss risks and benefits with their physicians. Coverage remains at 92.4%.[28] No medical boards hunting doctors. No families expelled from school. Just informed consent—the foundation of medical ethics.

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[23] Farina et al., "Childhood Mandatory Vaccinations," *Vaccines* (2024), https://doi.org/10.3390/vaccines12111296.

[24] Swedish Public Health Agency, https://www.folkhalsomyndigheten.se/the-public-health-agency-of-sweden/.

[25] Danish Health Authority, Vaccination Programme, https://www.sst.dk/en/vaccination.

[26] WHO/UNICEF Coverage Data Japan (2023), https://cdn.who.int/media/docs/default-source/country-profiles/immunization/2023-country-profiles/immunization_jpn_2023.pdf.

[27] NHS, "Booking your child's vaccination appointment, https://www.nhs.uk/vaccinations/booking-your-childs-vaccination-appointment/.

[28] NHS Digital, Childhood Vaccination Coverage Statistics 2023-24, https://digital.nhs.uk/data-and-information/publications/statistical/nhs-immunisation-statistics/england-2023-24.

58. Most damning: these countries do not shield vaccine manufacturers from liability. Market forces and legal accountability ensure safety. Only America combines the world's most aggressive schedule with blanket immunity for drug companies, a toxic combination that removes all incentive for caution.[29]

59. The international data demolishes the CDC's argument that eliminating parental choice is necessary for public health. Countries respecting medical freedom have lower infant mortality, less chronic disease, and comparable vaccination rates. The only thing American exceptionalism has produced is exceptionally sick children.

E. Suppression of Scientific Dissent: Silence Through Destruction

60. Unable to defend their policies scientifically, CDC and its allies enforce orthodoxy through professional annihilation. The message is clear: challenge the vaccine program and face professional destruction.

61. Dr. William Thompson, senior CDC scientist, confessed in 2014 that he and colleagues destroyed data showing MMR vaccine increased autism risk in African American boys. His 10,000 pages of documents remain sealed while CDC pretends the scandal never happened.[30]

62. Dr. Andrew Zimmerman, the government's own expert witness, submitted an affidavit that vaccines can trigger autism in susceptible children. DOJ lawyers buried his opinion

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[29] 42 U.S.C. § 300aa-1 et seq.

[30] Thompson Statement, Aug. 27, 2014, https://cdn.factcheck.org/UploadedFiles/William-Thompson-statement-27-August-2014.pdf.

and misrepresented his views in court. The children he could have helped were denied compensation.[31]

63. Researchers face systematic targeting. When Christopher Exley found aluminum from vaccines in autistic brains, his university terminated his funding after 40 years.[32] When James Lyons-Weiler published Thomas's vaccinated/unvaccinated study, the journal retracted it without allowing response—pure censorship disguised as peer review.

64. Medical boards have become enforcement arms. California alone has revoked licenses of dozens of doctors for writing exemptions based on family history, genetic testing, or prior reactions—medical judgment CDC guidelines don't recognize. The Board told Dr. Stoller explicitly: only ACIP criteria matter, not your clinical assessment.

65. This is the behavior of institutions protecting orthodoxy rather than pursuing truth. Real science invites challenge, replicates findings, debates openly. CDC's vaccine program does the opposite: it destroys challengers, blocks research, and enforces compliance through fear.

F. Twenty-Seven Years of Silence: The Ultimate Proof of Willful Ignorance

66. While the failure to test the vaccine schedule is CDC's most damning scientific breach, HHS's abandonment of its statutory congressional reporting requirements perfectly embodies the federal government's approach to vaccine safety (at least until very recently): don't look, don't tell, don't know. The National Childhood Vaccine Injury Act of 1986 requires HHS to

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[31] Zimmerman Affidavit, Sept. 7, 2018, *Yates v. HHS,* https://icandecide.org/wp-content/uploads/2020/01/zimmerman-affidavit.pdf.

[32] Exley, "My Career and Aluminum," *Hippocratic Post* (2021), https://www.hippocraticpost.com/pharmacy-drugs/infant-vaccines/.

report to Congress every two years on efforts to reduce vaccine adverse reactions. 42 U.S.C. § 300aa-27.

67. In 1990, HHS convened the statutory task force, disbanded it in 1998, but has not reconvened in 27 years, with no extant copy of any HHS report to Congress in the public domain. During this silence, the schedule ballooned from 24 to 72+ doses, autism went from 1 in 150 to 1 in 31, and chronic disease consumed over half of American children—yet Congress received nothing.

68. The *Flores* lawsuit exposed this 27-year abandonment of statutory duty.[33] No reports. No updates. No acknowledgment that the requirement even existed. Just decades of silence about vaccine safety efforts.

69. Agencies confident in their programs showcase their data. Agencies that go dark for decades know exactly what they would find. Twenty-seven years of silence tells this Court everything it needs to know.[34]

FIRST CLAIM FOR RELIEF
Violation of the Administrative Procedure Act - Arbitrary and Capricious Agency Action
(5 U.S.C. § 706(2)(A))

70. Plaintiffs incorporate by reference all preceding paragraphs.

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[33] *Flores v. Kennedy,* (2:25-cv-00916, D. Nev., filed May 27, 2025) https://childrenshealthdefense.org/wp-content/uploads/Flores-II-v.-Kennedy-Jr.-Press_Redacted.pdf.

[34] On August 14, 2025, it was announced that HHS is reinstating the task force which will be headed by the NIH Director and that it will issue its first report within two years. https://www.hhs.gov/press-room/hhs-reinstates-task-force-on-safer-childhood-vaccines.html. This is an encouraging small first step under the bold new leadership. However, it does not detract from the need for the relief requested in this lawsuit, given the lack of safety testing of the entire vaccine schedule.

A. Failure to Consider Important Aspect of the Problem

71. Under the APA, agency action is arbitrary and capricious when the agency has "entirely failed to consider an important aspect of the problem." *Motor Vehicle Mfrs. Ass'n v. State Farm*, 463 U.S. 29, 43 (1983). This is exactly what CDC has done.

72. The "important aspect" CDC ignores is the cumulative safety of administering 72+ vaccine doses to children. While the agency recommends this aggressive schedule as universal Category A policy, it has never studied whether the combination causes more harm than benefit. Individual vaccine trials lasting days cannot answer questions about cumulative effects over years. This represents a fundamental gap in the agency's scientific analysis.

73. This failure is not from lack of notice. The Institute of Medicine explicitly told CDC to study the full schedule's safety in 2002. IOM repeated this recommendation in 2013, finding "no studies have compared the differences in health outcomes between entirely unimmunized populations and fully immunized children." IOM 2013 at 9. CDC offers no explanation for ignoring its most prestigious scientific advisor for over two decades.

74. The real-world consequences prove the arbitrariness. When Dr. Thomas conducted the exact study IOM recommended, namely, comparing vaccinated and unvaccinated children, he lost his license. CDC thus punishes research into the very question it refuses to investigate.

B. Procedural Violation – Binding Rules Without Rulemaking

75. Separately, CDC violated the APA by creating binding rules without notice-and-comment rulemaking. Though ACIP recommendations are statutorily advisory, every state enforces them as mandatory standards. Medical boards revoke licenses for deviation. Schools exclude children. Insurance coverage depends on compliance.

76. When agency "guidance" has binding effect, it must undergo rulemaking. *Texas v. United States*, 809 F.3d 134, 171 (5th Cir. 2015); *Appalachian Power Co. v. EPA*, 208 F.3d 1015, 1021 (D.C. Cir. 2000). CDC evaded this requirement, depriving the public of participation rights while creating a de facto national mandate.

77. Plaintiffs seek a declaration that CDC's recommendation of the childhood vaccine schedule violates the APA on both grounds. The Court should vacate the Category A recommendations and require reclassification of all childhood vaccines as Category B shared clinical decision-making until CDC completes scientifically rigorous studies proving the cumulative schedule is safe.

SECOND CLAIM FOR RELIEF
Violation of Substantive Due Process – Fifth Amendment

78. Plaintiffs incorporate by reference all preceding paragraphs.

79. The Fifth Amendment prohibits the federal government from depriving any person of life, liberty, or property without due process of law.

80. Parents possess a fundamental liberty interest in directing their children's medical care. *See Troxel v. Granville*, 530 U.S. 57, 65 (2000) ("the interest of parents in the care, custody, and control of their children is perhaps the oldest of the fundamental liberty interests recognized by this Court").

81. Children possess a fundamental right to bodily integrity. *See Rochin v. California*, 342 U.S. 165, 172 (1952) ("conduct that shocks the conscience…offends even hardened sensibilities"); *Union Pacific Ry. Co. v. Botsford,* 141 U.S. 250, 251 (1891) ("No right is held more sacred, or is more carefully guarded by the common law, than the right of every individual to the possession and control of his own person.").

82. A right is "fundamental" if it is "deeply rooted in this Nation's history and tradition and implicit in the concept of ordered liberty." *Washington v. Glucksberg*, 521 U.S. 702, 720–21 (1997).

83. This case does not challenge state vaccine mandates or seek personal belief exemptions. Unlike *Jacobson v. Massachusetts*, 197 U.S. 11 (1905), *Zucht v. King,* 260 U.S. 174 (1922), or recent cases upholding school mandates, Plaintiffs challenge the federal government's creation of universal medical standards without scientific basis, which states then enforce as if they were evidence-based. This Court need not revisit *Jacobson*; it need only require that federal medical recommendations be based on actual evidence.

84. The CDC knows that states adopt ACIP recommendations wholesale. Every state medical board uses them as the exclusive standard. Every school mandate incorporates them. By setting these standards without testing the cumulative schedule, CDC effectively eliminates informed consent and physician discretion nationwide—not directly through federal mandate, but through deliberate creation of standards it knows states will enforce.

85. The CDC's own scientific advisors, the Institute of Medicine, have repeatedly warned that "key elements of the immunization schedule, such as the number, frequency, timing, order, and age at administration of vaccines, have not been systematically examined in research studies." Institute of Medicine, *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies* at 2 (2013). The IOM expressly recommended "observational studies using data from the Vaccine Safety Datalink to compare health outcomes in children who receive vaccines according to the recommended schedule with those who receive fewer vaccines." *Id.* at 10.

86. Despite these warnings, CDC has refused for over 25 years to conduct or require any safety study of the cumulative childhood vaccine schedule, even as it continues to expand the schedule and issue "universal" Category A recommendations it knows states will mandate.

87. As a result, more than 72 vaccine doses are required for every American child, even though "no studies have compared the health outcomes of entirely unvaccinated populations with those of fully vaccinated children" as part of a cumulative schedule. *Id.* at 3.

88. This deliberate creation of untested standards, knowing they will be coercively enforced by the states, is not merely arbitrary and capricious; it is so reckless and indifferent to health and safety as to "shock the conscience." *Rochin v. California*, 342 U.S. at 172. The CDC effectively forces millions of children to undergo 72+ medical interventions without ever studying whether the cumulative program causes more harm than benefit.

89. The historic tradition recognized by *Jacobson v. Massachusetts* and its progeny is one of reasonable, rational, and evidence-based public health policy, not blind or deliberate ignorance of risk. Mandates issued without even minimal scientific justification are outside this tradition.

90. Plaintiffs seek only what due process requires: that federal medical recommendations be based on actual evidence of the safety of the series of medical interventions recommended by the CDC. Until that time, Plaintiffs request that childhood vaccines be reclassified to Category B shared decision-making.

THIRD CLAIM FOR RELIEF
Violation of Equal Protection – Fifth Amendment

91. Plaintiffs incorporate by reference all preceding paragraphs.

92. The Fifth Amendment's Due Process Clause includes an equal protection component that prohibits irrational discrimination. *Bolling v. Sharpe*, 347 U.S. 497 (1954).

93. CDC's framework irrationally denies the existence of medically vulnerable children. According to CDC, a child who suffered seizures, regression, or autoimmune disease after vaccination is medically identical to a child with no adverse reactions. The agency refuses to recognize any category of "vaccine-vulnerable" children despite mounting evidence they exist.

94. This denial of medical reality is irrational. Children who react badly to one vaccine often react to others containing similar adjuvants (such as aluminum in 7+ vaccines), preservatives, or antigens. Yet CDC's framework treats each vaccine as if administered in a biological vacuum, ignoring cross-reactivity and cumulative burden on vulnerable immune systems.

95. The irrationality deepens: CDC admits it has never studied which children face higher risks. It refuses to investigate whether genetic markers, family history, or prior reactions predict future injury. Having chosen ignorance about differential risks, it then declares all children medically identical, a conclusion that can only be maintained by refusing to examine contradictory evidence.

96. Even under rational basis review, government cannot deny reality to achieve its goals. CDC's pretense that vaccine-vulnerable children don't exist—maintained by refusing to study them—fails any conception of rationality. It is equivalent to denying peanut allergies exist because acknowledging them would complicate school lunch programs.

97. The harm is concrete: vaccine-injured children are forced to continue receiving vaccines that may cause further damage, or forfeit their education. This Sophie's choice flows directly from CDC's irrational insistence that medically fragile children are a myth.

98. Plaintiffs seek recognition that CDC's denial of medical vulnerability violates equal protection's minimal rationality requirement.

FOURTH CLAIM FOR RELIEF
Violation of the First Amendment – Suppression of Medical and Scientific Dissent

99. Plaintiffs incorporate by reference all preceding paragraphs as if fully set forth herein.

100. The First Amendment prohibits the government from silencing disfavored viewpoints or orchestrating the suppression of scientific debate through regulatory capture and professional retaliation. Yet that is precisely what has occurred here.

101. The CDC's contraindications framework has become a tool of censorship, operating through state medical boards to silence physicians who dare to question the agency's untested assumptions about vaccine safety. This is viewpoint discrimination masquerading as public health policy.

102. Plaintiffs Thomas and Stoller exemplify this unconstitutional regime. Dr. Thomas published peer-reviewed research questioning vaccine safety based on data from his own patients—the very type of study the Institute of Medicine had urged for decades. His reward? Professional destruction within days of publication. Dr. Stoller used emerging genetic science to identify children at risk. He tried to apply personalized medicine to protect vulnerable patients. His reward? License revocation for deviating from CDC orthodoxy.

103. This suppression extends beyond individual physicians. When researchers publish findings that challenge the CDC's narrative, their studies are retracted without findings of fraud. When physicians testify about vaccine injuries they've witnessed, medical boards threaten their licenses. When scientists within the CDC itself, like William Thompson, attempt to expose data manipulation, they are silenced by agency leadership.

104. The pattern is unmistakable: the government has created a system where only one viewpoint on vaccine safety may be expressed without professional consequences. Physicians

must either parrot the CDC's position that the untested schedule is universally safe, or face career annihilation. This forced orthodoxy violates the core of the First Amendment, which exists precisely to prevent the government from decreeing official truths in matters of scientific debate.

105. Parents too are victims of this censorship regime. The First Amendment protects not only the right to speak but the right to receive information. *Virginia State Bd. of Pharmacy v. Va. Citizens Consumer Council*, 425 U.S. 748, 756–57 (1976). When the government systematically silences physicians who might offer different risk assessments or individualized medical advice, it deprives parents of the informed consent that is the cornerstone of medical ethics and constitutional liberty.

106. The government cannot accomplish through coordinated suppression what the First Amendment forbids it to do directly. *NRA v. Vullo*, 602 U.S. 175 (2024). By establishing contraindication criteria that operate as professional speech codes, enforced through state medical boards with career-ending consequences, the CDC has created an unconstitutional system of viewpoint discrimination.

107. This is not about regulating medical fraud or malpractice. This is about enforcing ideological conformity. The bitter irony: the medical establishment ruthlessly enforces professional adherence to a 'scientific consensus' about vaccine safety that rests on no science at all, having never studied the cumulative effects of the recommended schedule. This is the antithesis of both scientific integrity and First Amendment freedom.

108. Accordingly, Plaintiffs seek declaratory and injunctive relief against this unconstitutional suppression of medical and scientific speech, and the restoration of physicians' ability to exercise professional judgment without fear of retaliation.

CONCLUSION

109. The facts establish a continuing public health outrage hiding in plain sight: America administers more vaccines than any nation on earth while producing the sickest children in the developed world. Yet CDC demands proof of harm while refusing to conduct the studies that could provide it. This Court should reallocate the burden of proof in public health: they who recommend dozens of medical interventions for millions of children must first prove that these interventions taken together result in more good than harm. Other free nations trust parents with this choice, and achieve better outcomes. American children deserve the same trust and protection, and they deserve better from their government.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that this Court:

1. Declare that CDC's contraindications and precautions framework violates the Administrative Procedure Act by failing to consider the important aspect of cumulative vaccine safety and by imposing binding rules without required rulemaking;
2. Declare that CDC's framework is arbitrary and capricious
3. Declare that CDC's enforcement of an untested 72+-dose vaccine schedule violates the Fifth Amendment's Due Process Clause by compelling medical interventions without scientific basis while punishing those who seek evidence of safety;
4. Declare that CDC's denial of medically vulnerable children violates the Fifth Amendment's Equal Protection guarantee by irrationally treating all children identically despite refusing to study differential risk;
5. Declare that CDC's contraindication framework violates the First Amendment by suppressing medical and scientific dissent through coordinated professional retaliation.

6. Enjoin CDC from maintaining any Category A recommendations for childhood vaccines and order immediate reclassification of all childhood vaccines to Category B shared clinical decision-making, until such time as CDC demonstrates through scientifically rigorous studies that the cumulative schedule is safe.
7. Order CDC to conduct scientifically rigorous studies of the cumulative safety of the full childhood vaccination schedule as recommended by the Institute of Medicine, including comparison of health outcomes between fully vaccinated and unvaccinated populations;
8. Maintain jurisdiction until CDC demonstrates through proper studies that any vaccine proposed for Category A recommendation is safe when administered as part of the cumulative schedule;
9. Award Plaintiffs their costs and reasonable attorneys' fees; and
10. Grant such other relief as the Court deems just and proper.

Dated: August 15, 2025

Respectfully submitted,

/s/ Richard Jaffe

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EXHIBIT B

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

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SHANTICIA NELSON

JANE DOE

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CHILDREN'S HEALTH DEFENSE,
a non-profit organization,
852 Franklin Ave., Suite 511
Franklin Lakes, NJ 07417,

Plaintiffs,

v.

AMERICAN ACADEMY OF PEDIATRICS
345 Park Boulevard
Itasca, IL 60143,

Defendant.

Civil Action No.

Jury Trial Requested

COMPLAINT FOR DECLARATORY AND INJUNCTIVE RELIEF AND DAMAGES

I. INTRODUCTION AND SUMMARY OF ACTION

1. This complaint is brought under the Racketeer Influenced and Corrupt Organizations Act ("RICO"), 18 U.S.C. §§ 1962(c) and (d), against the American Academy of Pediatrics ("AAP") for its central role in an enterprise that has defrauded American families about the safety of the childhood vaccine schedule for several decades.

2. The fraud set out hereinafter affects the U.S. childhood vaccine market, which one estimate puts at $15.08 billion in 2024.[1] The vaccine schedule has expanded from 11 doses targeting four diseases in 1983, to over 72 doses targeting 18 diseases (until recent action by the government discussed below). This expansion dramatically accelerated after the National Childhood Vaccine Injury Act of 1986 granted manufacturers immunity from liability, allowing unfettered growth of the childhood immunization schedule, and transforming AAP into a co-beneficiary of the vaccine enterprise. (Section IV, Factual Background, E.)[2]

3. To help fuel this explosive growth in childhood vaccine products, AAP has repeatedly represented through its official journal *Pediatrics*, the Red Book, policy statements, and public communications that the childhood vaccine schedule has been fully tested and proven safe.

4. These representations are false and fraudulent. In 2002, the Institute of Medicine ("IOM")[3] found that no study had ever compared health outcomes between vaccinated and unvaccinated children, and recommended such studies be conducted. In 2013, the IOM found

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[1] Nova One Advisor, "Pediatric Vaccines Market Size, Share & Trends Analysis Report By Type (Monovalent, Multivalent), By Technology (Live Attenuated Vaccines), By Application (Cancer), By Region,- Industry Analysis, Share, Growth, Regional Outlook and Forecasts, 2025-2034," https://www.novaoneadvisor.com/report/pediatric-vaccines-market, perma.cc/C5FB-968H. CDC's Vaccine for Children program obligated $4.7 billion in 2023 on childhood vaccines for Medicaid and other programs covering children. KFF, "CDC's Funding for State and Local Public Health: How Much and Where Does it Go?" Published April 7, 2025, https://www.kff.org/other-health/cdcs-funding-for-state-and-local-public-health-how-much-and-where-does-it-go/ (last visited Jan. 12, 2026).

[2] Unless otherwise indicated, all section references are to the Factual Background.

[3] The Institute of Medicine, renamed the National Academy of Medicine in 2015, was established by Congress in 1970 to provide unbiased, evidence-based advice to policymakers and the public. Its recommendations on vaccine safety carry weight as it is supposed to operate independently of both government and industry.

that the recommended studies have not been undertaken, and again recommended them. (*See* ¶¶ 58-59 for the citations and discussion of these reports.)

5. Despite IOM's recommendations, the Defendant directly and through enterprise participants forcefully argued against conducting the IOM recommended studies by fraudulent misdirection. Section A.

6. AAP participates in an association-in-fact enterprise with vaccine manufacturers (including Pfizer, Merck, GlaxoSmithKline, and Sanofi Pasteur), aligned entities such as the American Board of Pediatrics, and key spokespersons including members of AAP's Committee on Infectious Diseases. The enterprise's common purpose is to maintain and expand vaccine uptake by assuring pediatricians, hospitals, parents, and policymakers that the schedule is categorically safe, while concealing material facts about the lack of testing, inadequacies in the vaccine safety monitoring programs, and financial incentives tied to vaccine schedule compliance.

7. This scheme is anchored by a foundational fraud AAP published: a January 2002 article in *Pediatrics* claiming infants could "theoretically" respond to 10,000 vaccines at once, a calculation about B-cell capacity that deflected from the safety questions parents were asking. For twenty-four years, AAP has deployed this theoretical reassurance to block the studies the IOM recommended. *See* Section A.

8. The AAP is the enterprise's primary information distribution network. Its 67,000 members (virtually every pediatrician in America) deliver the enterprise's safety claims directly to families as their own medical advice. Physicians who deviate face professional destruction, as Plaintiffs Paul Thomas, M.D. and Kenneth P. Stoller, M.D. experienced. ¶¶ 34-44.

9. When the Department of Health and Human Services has attempted reform, AAP leads the opposition: it sued to restore the childhood COVID-19 vaccine recommendation after the CDC removed it and issued inflated statistics about the effects of the December 2025 ACIP hepatitis B decision. ¶¶ 111-114. AAP and its enterprise associates' lawsuit to derail the CDC's January 5, 2026 announcement bringing its vaccine schedule more in line with other industrialized countries (and U.S. states) is the latest evidence of its racketeering activities. ¶¶ 115-123.

10. The same pharmaceutical conglomerates that serve as enterprise participants in manufacturing childhood vaccines have systematically acquired companies treating the chronic conditions those vaccines cause, creating a closed-loop system that financializes childhood illness. Section D.

11. Military medicine has recognized what AAP denies. Following the Gulf War, research linked multiple simultaneous vaccinations to chronic illness in soldiers. At various times, military regulations have limited healthy adults, selected for physical resilience, to five vaccines at a time. Infants face no limit whatsoever. ¶¶ 78-79.

12. Plaintiffs Andrea Shaw and Shanticia Nelson are mothers whose children died following routine vaccinations administered according to AAP guidelines. Plaintiff Jane Doe is a mother whose daughter held a valid medical exemption based on documented anaphylaxis for nearly a decade. A school medical consultant applying the narrow ACIP contraindications framework that AAP's paradigm justifies, overrode two treating physicians and forced the catch-up vaccination, resulting in documented injuries.

13. Plaintiffs Shaw and Nelson's stories show what happens when AAP's paradigm corrupts medical judgment at the point of care. AAP assured parents (through its Fellows) that

multiple vaccines were safe because infants can theoretically handle 10,000 vaccines at once. See ¶¶ 51-53. Three children died. Jane Doe's story shows what happens when treating physicians get it right and the AAP paradigm overrides them. Doe's daughter's pediatrician and a board-certified allergist each concluded vaccination was contraindicated. A school medical consultant with no treating relationship rejected both opinions because AAP's framework does not recognize their reasons.

14. Plaintiffs Thomas and Stoller are pediatricians whose licenses were revoked or suspended for conducting research contradicting AAP's safety claims or issuing individualized medical exemptions based on clinical judgment rather than AAP-endorsed criteria. Plaintiff Children's Health Defense sues in its associational capacity for declaratory and injunctive relief on behalf of families harmed by AAP's fraud.

15. This action is based on successful RICO civil cases, most notably this circuit's *United States v. Philip Morris USA, Inc.*, 449 F. Supp. 2d 1 (D.D.C. 2006), *aff'd,* 566 F.3d 1095 (D.C. Cir. 2009), wherein the district court found non-profit tobacco trade associations liable for decades of fraudulent health-risk denials. The parallels include suppression of adverse research, use of "independent" scientific voices to block studies, and coordinated enterprise activity to mislead the public.[4] Section J.

II. JURISDICTION AND VENUE

16. This Court has jurisdiction under 28 U.S.C. § 1331, 18 U.S.C. § 1964(c), 28 U.S.C. § 2201, and possesses inherent equitable authority to grant necessary injunctive relief.

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[4] The *Philip Morris* district court's judgment against the two non-profits, the Tobacco Institute and the Center for Tobacco Research, was vacated as moot because both organizations had dissolved and were winding down before the case reached the circuit court.

Venue is proper under 28 U.S.C. § 1391(b) and 18 U.S.C. § 1965 because Defendant maintains offices and conducts business in this District.

III. THE PARTIES

A. The Plaintiffs

17. Andrea Shaw is the mother of fraternal twins Dallas and Tyson Shaw, who both died May 1, 2025, eight days after receiving their 18-month vaccines. On April 23, 2025, both twins were administered hepatitis A, influenza, and DTaP vaccines at their pediatrician's office in Payette, Idaho.[5] Prior to vaccination, Mrs. Shaw and her mother-in-law warned the pediatrician about a family history of adverse reactions to the flu vaccine on the father's side. The pediatrician dismissed these concerns, consistent with AAP's contraindications framework, which does not generally recognize family history of vaccine reactions as a basis for delaying or declining vaccination.[6]

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[5] The Shaw family previously resided in Payette, Idaho, where their children's deaths occurred. Local police appeared on television implying wrongdoing. The family received death threats and was forced to relocate.

[6] AAP's Red Book lists contraindications and precautions for vaccination, but family history of adverse vaccine reactions is not among them. AAP Committee on Infectious Diseases, *Red Book: 2024–2027 Report of the Committee on Infectious Diseases* at 85-91 (33d ed. 2024); CDC, "Guide to Contraindications and Precautions to Commonly Used Vaccines," https://www.cdc.gov/vaccines/hcp/imz-best-practices/contraindications-precautions.html. The only recognized contraindications in the Red Book are severe allergic reaction (anaphylaxis) to a prior dose or vaccine component, and certain specific conditions for vaccines (e.g., immunocompromise for live vaccines). A parent's report that family members have experienced adverse reactions—even serious ones (with two exceptions that do not apply here)—is classified as a "condition commonly misperceived as a contraindication" that should *not* delay vaccination. CDC, *General Best Practice Guidelines for Immunization*, Table 4-2 ("Conditions Incorrectly Perceived as Contraindications") https://www.cdc.gov/vaccines/hcp/imz-best-practices/contraindications-precautions.html. Thus, when Mrs. Shaw warned her pediatrician about the father's family history of flu vaccine adverse reactions, the pediatrician followed AAP guidance in dismissing her concern. The framework is designed to override justifiable parental caution.

18. The following day, April 24, 2025, both twins were brought to the St. Luke's Emergency Room with severe symptoms including blue lips, lethargy, and sunken eyes. The treating emergency room physician documented the diagnosis as "post-immunization reaction, initial encounter."

19. On May 1, 2025, both Dallas and Tyson Shaw died. Their autopsies are pending. No alternative cause of death has been identified for either child.

20. Rather than investigating the documented post-immunization reaction as a potential cause of death, local authorities opened a homicide investigation targeting Mrs. Shaw. Prosecutors have theorized that she caused her children's deaths through a "postpartum blackout" or that "the house was too hot." This criminal investigation is a foreseeable consequence of AAP's fraudulent safety claims: when the medical system has been told that vaccines cannot cause serious injury or death, grieving parents become suspects rather than victims.

21. Plaintiff Shaw's injuries are the foreseeable and proximate result of AAP's racketeering scheme. AAP's categorical safety claims, disseminated through pediatricians and public-facing materials, induced Mrs. Shaw to consent to vaccination despite her expressed concerns about family history. Those same categorical claims now form the basis for criminal suspicion against her, as investigators assume vaccines could not have caused her children's deaths. Mrs. Shaw's injuries are continuing because AAP continues to disseminate the same false safety claims that induced her consent and that now imperil her liberty.

22. Shanticia Nelson is the mother of Sa'Niya Carter, who died on March 27, 2025, less than twelve hours after receiving six injections containing twelve antigens at the Golisano Children's Hospital Pediatric Practice. The vaccines included Pediarix (DTaP-HepB-IPV),

ActHIB (Hib), Prevnar 20 (PCV20), MMR, varicella, and hepatitis A. At this appointment Sa'Niya also received a topical fluoride application. The vaccines were administered at approximately 4:00 p.m. on March 26, 2025, as part of a "catch-up" protocol following Sa'Niya's first birthday.[7] Sa'Niya was ill at the time of the appointment, and Ms. Nelson expressed concern about proceeding. Clinic staff assured her that vaccinating a mildly ill child was safe and standard per AAP guidelines. Ms. Nelson was told by clinic staff relying on AAP guidelines and Red Book recommendations that this aggressive schedule was "completely safe."

23. Later that evening, while Ms. Nelson was driving, Sa'Niya began having seizures. Emergency responders transported her by ambulance to the hospital, where she went into cardiac arrest and died, less than twelve hours after vaccination.

24. The death certificate listed SUDC (sudden unexpected death in childhood) as the cause of death. However, the coroner verbally informed witnesses that he found a swollen brain consistent with encephalitis which is a known adverse event listed on the DTaP package insert and is a recognized Table Injury for DTaP vaccines when occurring within 72 hours of vaccine administration under the National Childhood Vaccine Injury Act. The discrepancy shows the

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[7] The catch-up immunization schedule is developed by ACIP and published jointly by CDC and AAP as Table 2 of the annual immunization schedule. AAP, "Recommended Childhood and Adolescent Immunization Schedule: United States, 2025," *Pediatrics* 2025;155(2):e2024069987. Neither the catch-up schedule nor the Red Book imposes any upper limit on the number of vaccines that may be administered at a single visit. AAP Committee on Infectious Diseases, *Red Book: 2024–2027 Report of the Committee on Infectious Diseases* at 63 (33d ed. 2024) ("Simultaneous administration of most vaccines according to the recommended immunization schedule is safe and effective. Infants and children have sufficient immunologic capacity to respond to multiple vaccine antigens administered at the same time."); CDC, *General Best Practice Guidelines for Immunization* ("As a general rule, almost all vaccines can be administered at the same visit."). Despite authorizing unlimited simultaneous vaccine loading, as stated (¶¶ 58-59 below), the Institute of Medicine found that the vaccine schedule had not been safety tested. The aggressive catch-up protocol administered to Sa'Niya Carter, six multi-antigen injections targeting twelve separate diseases in a single visit, has never been studied for safety.

concealment AAP's categorical safety claims produce: when the medical system is told vaccines cannot cause harm, documented injuries are reclassified or erased.

25. Ms. Nelson did not know that the IOM (now the National Academy of Medicine) twice concluded, in 2002 and 2013, that the cumulative safety of the full childhood vaccine schedule had never been studied. She also did not know that the AAP and its leading spokesperson, Paul Offit, M.D., publicly opposed such studies while continuing to claim the schedule was fully tested. These revelations directly contradicted the assurances she relied upon when consenting to Sa'Niya's fatal vaccinations.

26. As a result of AAP's fraudulent representations, Ms. Nelson suffered recoverable economic injuries, including funeral expenses, unreimbursed medical costs, lost income, and diversion of family resources to public advocacy and legal efforts seeking accountability. She has since participated in public awareness efforts on CHD.TV and in CHD-supported campaigns to obtain recognition of vaccine-related infant deaths.

27. Her injuries are the proximate result of AAP's racketeering scheme: false and misleading statements transmitted through pediatric offices to parents to maintain vaccine uptake despite the absence of required safety evidence. Ms. Nelson's injuries are continuing and fall within the limitations period because AAP continues to disseminate the same false safety claims that induced her to consent to Sa'Niya's vaccinations, including through its HealthyChildren.org website and ongoing public statements asserting that the childhood vaccine schedule is "thoroughly tested for safety" despite the absence of cumulative safety studies.

28. Jane Doe is the mother of E, a minor child currently in high school. E experienced anaphylaxis following a HepA-Adult vaccine in 2012. In 2014, E experienced another allergic reaction, this time to the Polio vaccine. Because of her severe reaction to these two egg-based

vaccines, she received an exemption from all egg-based vaccines. In 2022, E experienced an anaphylactic reaction, causing vaccine injuries from the DTaP shot, which is not egg-based. As a result, she received a medical exemption from all further vaccines.

29. In late 2024, the medical consultant of E's school revoked E's medical exemption. He is a family practice physician who serves as school consultant/medical director for multiple school districts. He never examined her and had no statutory authority to reject a medical exemption issued by a licensed physician.

30. Operating under AAP's paradigm, the consultant arrogated that authority to himself. He demanded another medical exemption from the treating pediatrician. Plaintiff Doe complied, but the consultant rejected it and demanded documentation from an allergist. Doe complied and supplied the additional (and legally unnecessary) confirmation. But the consultant rejected that exemption letter also, justified by a paradigm that says treating physicians who identify contraindications outside the approved ACIP/AAP guidelines must be wrong.

31. Barred from school and threatened with exclusion, E expressed feelings of self-harm. Jane Doe's family faced an impossible choice: keep her daughter out of school indefinitely, or consent to vaccination against the medical judgment of two treating physicians. The family chose to vaccinate. Between January and March 2025, E received the MMR, Varicella, and Meningococcal vaccines on an AAP approved catch-up schedule. The allergist performed allergy testing before each dose. However, even with these precautions, the treating physicians' original judgment proved correct.

32. Following vaccination, E developed hives covering her back and chest, then progressive joint stiffness and difficulty walking, exacerbating a prior vaccine injury. She was eventually diagnosed with a torn meniscus in four places and a stress fracture in her foot.

Arthropathy (a disease or abnormal condition affecting a joint) is a documented adverse event following MMR vaccination in patients over age 12 receiving the vaccine for the first time. E had surgery in April 2025 for this MMR package insert-listed side effect. E will need ongoing care for this and other side effects related to the administration of the vaccines she received in 2025.

33. Jane Doe's loss to property flows directly from AAP's fraudulent scheme. The medical consultant had no legal authority to override E's treating physicians. He claimed it anyway, based on AAP's paradigm and the narrow contraindication and precaution it promoted. Jane Doe has suffered and continues to suffer economic injury including medical expenses, and other costs resulting from E's vaccine injuries.

34. Plaintiff Paul Thomas is a resident of Beaverton, Oregon. He was a licensed, board-certified pediatrician, and a Fellow of the American Academy of Pediatrics (FAAP). He founded and operated a large pediatric practice serving thousands of families.

35. In late 2020, Dr. Thomas published a study comparing chronic health outcomes in vaccinated and unvaccinated pediatric patients. The study addressed the vaccinated-versus-unvaccinated comparative research that the IOM had twice recommended federal health authorities undertake, and that Defendant and its affiliates had publicly opposed.

36. Eleven days after publication, in December 2020, the Oregon Medical Board emergency-suspended Dr. Thomas's medical license based on his being a "threat to public health." The suspension targeted his individualized vaccination practices contrary to the Red Book, and the scientific conclusions of his research, which contradicted Defendant's categorical public claims that the childhood vaccine schedule is fully tested and safe.

37. Following the emergency suspension, the Oregon Medical Board conducted an extended investigation and enforcement proceeding that continued for more than two years. His license was temporarily reinstated with restrictions.

38. After it became clear the Board would not let him continue to practice outside of the CDC/AAP vaccine guidelines, Dr. Thomas agreed to "voluntarily" surrender his license.

39. Following the surrender, AAP revoked his membership. The surrender permanently ended his ability to practice pediatrics, destroyed the goodwill of his medical practice, eliminated his primary source of income, and caused concrete injury to his business and property.

40. Dr. Thomas was injured by the racketeering conduct: the suppression of opposing scientific views, branding legitimate research as "misinformation," and professional discipline to enforce conformity. As a proximate result of Defendant's conduct, Dr. Thomas suffered loss of licensure, destruction of his medical practice, loss of income, loss of business expectancy, and enduring reputational injury.

41. Plaintiff Kenneth P. Stoller is a resident of Bozeman, Montana. He is formerly a licensed, board certified, and AAP fellow physician. He practiced pediatric integrative and hyperbaric medicine for over four decades, specializing in treating children with neurological and immunological injuries, including vaccine-related conditions. Until 2021, Dr. Stoller held an active California medical license, which was revoked following disciplinary proceedings arising from his issuance of individualized medical exemptions that deviated from CDC and AAP guidelines. In 2023, New Mexico revoked his New Mexico license because of the California action, at which point he became unable to practice medicine.

42. Dr. Stoller's approach relied on peer-reviewed research and genetic testing to identify children at risk for vaccine injury, including mitochondrial dysfunction and immune system irregularities. He issued medical exemptions only after clinical evaluation, family history review, and genetic confirmation of risk factors. His "professional misconduct" was using individualized medical judgment in violation of the standard of care.

43. The disciplinary actions caused Dr. Stoller severe economic injury. He lost his patient base, clinical income, and professional reputation. Following the revocations, he incurred substantial costs relocating and attempting to regain licensure in other states. Dr. Stoller remains unable to resume full medical practice and continues to lose income and business expectancy.

44. Dr. Stoller's ongoing inability to practice, his loss of income, and reputational harm constitute concrete injuries to business and property under 18 U.S.C. § 1964(c). His injuries are continuing.

45. Children's Health Defense ("CHD"), a nonprofit organization headquartered in Franklin Lakes, New Jersey, has employees, volunteers, participants, donors, and followers nationwide and throughout the world. Its mission is to end the epidemic of childhood chronic disease caused by toxic environmental exposures. It seeks to hold responsible parties accountable and to establish safeguards to prevent future harm to children's health. It has over 20 state chapters, most of which are incorporated within CHD, as well as a chapter dedicated to military members, and several international chapters. The chapters, *inter alia*, act as a communication channel by which members of the CHD community impact the policies, advocacy, actions, and lawsuits the organization files.

46. CHD has a vibrant community of over 500,000 people in the United States who interact with CHD through a variety of channels. These community members bring potential

education, advocacy, litigation, and science projects to the organization for funding, collaboration, and publicity on a constant basis, as well as topics of interest for publications by CHD's online news sources, The Defender and CHD TV.

47. Attorneys within the CHD community bring potential lawsuits to the CHD litigation committee for potential funding; scientists within the community bring potential scientific studies to the CHD science committee for funding. Advocates and educators who are part of the CHD community bring advocacy efforts and articles to CHD for support and publication. In this way, the CHD community directly shapes the organization's priorities, determines which cases CHD pursues, and guides its advocacy, educational, and publication initiatives.

48. CHD exists solely because of donations of its supporters. If CHD did not serve the interests of its community, it would cease to exist. A strong financial nexus binds CHD and its supporters to end the epidemic of childhood chronic disease. AAP's actions, as described herein, harm the financial well-being of CHD community members, limiting the resources they would otherwise choose to devote to CHD. CHD sues in its associational capacity on behalf of its community members for declaratory and injunctive relief only.

B. The Defendant

49. Upon information and belief, the AAP is a non-profit corporation headquartered in Itasca, Illinois, with an office in the District of Columbia. AAP generates $115-125 million in annual revenue, employs 475 staff, and represents approximately 67,000 pediatricians, which is virtually the entire specialty.

IV. FACTUAL BACKGROUND

A. AAP's Foundational Fraud: Substitute Theory for Testing, Immunogenicity for Safety

50. The childhood vaccine schedule expanded from 11 doses targeting four diseases in 1983 to 20 doses by 2000, with more additions imminent. By the late 1990s and early 2000s, there was widespread concern among parents that cumulative exposure to multiple vaccines and their adjuvants might pose risks to infants and young children. Surveys found that 23% of parents questioned the number of shots their children received, and 25% were concerned that vaccines might weaken the immune system. AAP needed a response.

51. In January 2002, AAP published its response in its journal *Pediatrics*: an article with lead author Paul A. Offit, M.D., FAAP, a member of AAP's Committee on Infectious Diseases, titled "Addressing Parents' Concerns: Do Multiple Vaccines Overwhelm or Weaken the Infant's Immune System?" Offit PA, et al. (hereinafter "Offit"), *Pediatrics* 2002;109(1):124-129, https://publications.aap.org/pediatrics/article/109/1/124/79755/Addressing-Parents-Concerns-Do-Multiple-Vaccines, https://pubmed.ncbi.nlm.nih.gov/11773551/ (last visited Jan. 13, 2026).

52. The title reveals the article's purpose: public relations to reassure worried parents. The article contained theoretical and modeling extrapolations for the 67,000 AAP member pediatricians to use to reassure parents with concerns.

53. Parents were asking a toxicological and clinical question: *Is it safe to inject my infant with multiple vaccines containing aluminum adjuvants, thimerosal, formaldehyde, polysorbate 80, residual DNA fragments, and other components?* Offit answered a different question, an immunological one about whether the immune system could theoretically generate antibody responses. Offit produced a purely theoretical calculation about B-cell epitope capacity,

concluding that "each infant would have the theoretical capacity to respond to about 10,000 vaccines at any one time." This is like answering "Is it safe to drink ten beers?" with "The liver can theoretically process unlimited water," a response about organ capacity, but non-responsive to the actual safety question. Offit's calculation said nothing about cumulative aluminum dose and tissue retention in developing brains, mercury toxicokinetics in infants, synergistic effects of multiple adjuvants, neuroinflammation, autoimmune activation, or any clinical safety endpoint.

54. This is fraud: using the trappings of science to deceive parents (or providing AAP's Fellows a document to help them effectuate the fraud). Offit's paper created the illusion that parents' safety concerns about the cumulative effect of the vaccine schedule had been resolved when they had been misdirected. Offit's theoretical PR article did not study, and could not prove, the safety of the cumulative schedule. It just changed the subject.

55. But the misdirection accomplished something more insidious. It created a framework that made the question appear illegitimate. Under Offit's paradigm, concerns about cumulative vaccine load became anti-science; the paradigm declared that immunological capacity was theoretically infinite. Questioning the schedule was no longer a scientific inquiry to be resolved by evidence; it was a failure to understand basic immunology. The paradigm foreclosed the safety question.

56. This foreclosure had immediate practical consequences. The contraindication framework, which determines when vaccination should be delayed or avoided, was already narrow before 2002, limited essentially to anaphylaxis following a prior dose and unexplained encephalopathy. But as the schedule expanded from 20 doses to 30 to 40 to 70, the question arose: Should contraindications expand to account for cumulative load? Family history of adverse reactions? Prior non-anaphylactic events? Concurrent illness? Offit's paradigm

answered: No. If infants can theoretically handle 10,000 vaccines, then there is no biological basis for expanded contraindications regardless of how many vaccines are added to the schedule. The narrow framework designed for 11 doses became locked in for 72+ doses.

57. AAP then distributed this paradigm through its 67,000-member network. Pediatricians learned to cite the 10,000 vaccines figure when parents expressed concern. The Red Book incorporated it. HealthyChildren.org repeated it. Board certification and continuing medical education reinforced it. The American Academy of Family Physicians co-signed these recommendations without independent analysis. Within months, a speculative calculation in a journal article had become the standard response to any question about cumulative vaccine safety, delivered by trusted physicians in examination rooms across America.

58. One month after Offit's paper, the IOM issued its first report on vaccine schedule safety. The IOM acknowledged that no study had ever compared health outcomes between vaccinated and unvaccinated children, which is the question Offit's article and paradigm foreclosed. The IOM recommended studying the safety of the entire schedule. *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction*. https://www.ncbi.nlm.nih.gov/books/NBK220490/ ("IOM 2002"), at 14-15 (Executive Summary), and 107-108 (Recommendations for Public Health Response, Research). Anticipating the objection, the IOM explicitly stated it was *not* calling for new prospective trials that would withhold vaccines from children. The IOM specifically told CDC to "explor[e] the feasibility of using existing vaccine surveillance systems," naming the Vaccine Safety Datalink ("VSD"), to study "safety questions about the immunization schedule." The VSD already contained health records for millions of children, some fully vaccinated, some partially vaccinated, some

unvaccinated. The data existed in this giant digital filing cabinet. The IOM was just asking the CDC to analyze the data.

59. In 2013, the IOM returned to this issue and concluded that the studies had not been done; the filing cabinet remained unexamined. *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and* ***Future Studies***, https://doi.org/10.17226/13563 ("IOM 2013") IOM 2013 at 6, 12 (emphasis added). Presumably for emphasis, "Future Studies" was added to the title. And again, IOM explicitly said it was not recommending randomized controlled trials. IOM 2013 at 13.

60. When pressed to explain why the recommended studies had never been conducted, Offit argued publicly that it would be "unethical" to conduct placebo-controlled trials withholding vaccines from children. As demonstrated above, this answered a recommendation that the IOM had never made. The children in the VSD had already been vaccinated or not. The health outcomes had already occurred. No one needed to withhold anything from anyone. But by conflating database analysis with randomized trials, Offit made an easy study sound impossible and an ethical study sound unethical. The misdirection worked. Twenty-four years later, the filing cabinet remains unexamined.

61. And twenty-four years later, Offit's theoretical calculation remains the cornerstone citation for the proposition that vaccines cannot overwhelm the immune system. The Children's Hospital of Philadelphia Vaccine Education Center, which Offit directs—continues to cite it today, stating that "infants have the theoretical capacity to respond to at least 10,000 vaccines at one time." https://www.chop.edu/vaccine-education-center/human-immune-system/immune-system-and-vaccines, https://perma.cc/VCT8-2XRW. GAVI, the Vaccine Alliance (a partnership of WHO, UNICEF, the World Bank, and the Bill & Melinda Gates Foundation),

describes Offit 2002 article as a landmark study confirming that children's immune systems are not "overloaded" by multiple vaccines. https://www.gavi.org/vaccineswork/do-multiple-vaccines-overload-childs-immune-system-heres-what-science-says, https://perma.cc/T73E-JEBZ. The History of Vaccines project cites it to rebut the "misconception" that vaccines can overwhelm immune systems. https://historyofvaccines.org/vaccines-101/misconceptions-about-vaccines/, https://perma.cc/PM97-5XMP. AAP and the RICO enterprise created this fraudulent misdirection, published it in AAP's own journal, and has deployed it for twenty-four years to allow its trade organization's member "Fellows" to allay parents' concerns, to sell the ever-expanding vaccine schedule.

62. The fraud was creating an intellectual framework that made the truth unreachable within the system it established. Questioning cumulative effects marks one as unethical and scientifically illiterate; demanding safety studies is unnecessary because the paradigm proves safety theoretically; pointing to injured children is mere anecdote.

63. The *Philip Morris* defendants employed similar tactics. While Offit's framework created false certainty by deflection, the tobacco research institutes created false uncertainty to generate doubt.

B. Protecting the Fraud: Block the Studies, Exaggerate the Risks

64. Having published a theoretical calculation as proof of safety, AAP's task became ensuring that actual safety studies would never challenge the deflection to the theoretical. Offit became the enterprise's primary voice for blocking research, declaring that randomized vaccinated-versus-unvaccinated studies would be "highly unethical" and that "no Institutional Review Board, and frankly no ethical researcher, could ever do that study…." PBS Frontline interview, Offit P., interview with PBS Frontline, "The Vaccine War," April 27, 2010,

https://www.pbs.org/wgbh/frontline/article/paul-offit-a-choice-not-to-get-a-vaccine-is-not-a-risk-free-choice/ (last visited Jan. 12, 2026).

65. But Offit failed to mention that observational studies comparing health outcomes in existing vaccinated and unvaccinated populations require no withholding of vaccines.

66. Paul Offit's financial conflicts may explain his obstruction. As co-inventor of the RotaTeq rotavirus vaccine, he received substantial royalties, according to one detailed analysis, approximately $10 million through 2009, with potential lifetime earnings estimated between $13-35 million. He holds the Maurice R. Hilleman Chair of Vaccinology at Children's Hospital of Philadelphia, a position funded by a $1.5 million endowment from Merck, RotaTeq's manufacturer. Olmsted D. & Blaxill M., "Counting Offit's Millions: More on How Merck's Rotateq Vaccine Made Paul Offit Wealthy," Age of Autism, Dec. 2009, https://web.archive.org/web/20191230160433/https://www.ageofautism.com/2009/12/counting-offits-millions-more-on-how-mercks-rotateq-vaccine-made-paul-offit-wealthy.html; Attkisson S., "How Independent Are Vaccine Defenders?" CBS News, July 25, 2008, https://www.cbsnews.com/news/how-independent-are-vaccine-defenders/, https://perma.cc/CZQ8-S4TJ.

67. The fraud continues today. On December 5, 2025, while ACIP was meeting to consider the hepatitis B birth dose recommendation, Paul Offit appeared on CNN and PBS and stated that before universal infant vaccination, "30,000 children under the age of 10" contracted hepatitis B annually. The CDC surveillance data show actual cases in that age group were approximately 400 per year, a 75-fold exaggeration. Demasi M., "EXCLUSIVE: Internal documents show Paul Offit made false claims on CNN," MD Reports, Dec. 10, 2025,

https://blog.maryannedemasi.com/p/exclusive-internal-documents-show, perma.cc/NW48-ZZFW.

68. The causation chain is direct: Offit publishes theoretical reassurance to preempt safety concerns. AAP amplifies it as a scientific consensus answering the parents' concerns. When the IOM calls for observational studies using existing records, Paul Offit declares vaxed vs. unvaxed studies unethical and insists "you can't do that study"; when reform is proposed, Paul Offit exaggerates risks to block it.

C. The Suppressed Studies Show the Harm

69. While AAP blocked the IOM-recommended safety studies of the cumulative schedule, independent researchers worldwide have conducted exactly such comparative analyses, consistently finding superior health outcomes in unvaccinated children.

70. A 2025 systematic review by McCullough et al., "Determinants of Autism Spectrum Disorder," McCullough Foundation Report, Oct. 27, 2025, https://doi.org/10.5281/zenodo.17451259, analyzed 136 studies examining vaccines or their excipients, finding 107 (79%) inferred possible links between immunization or vaccine components and ASD or other neurodevelopmental disorders through mechanistic, clinical, or epidemiologic evidence. Similar findings emerged from Mawson et al., "Pilot comparative study on the health of vaccinated and unvaccinated 6- to 12-year-old U.S. children," J. Transl. Sci. 2017;3(3), DOI: 10.15761/JTS.1000186; Hooker & Miller, SAGE Open Medicine 2020;8:2050312120925344, PMID: 32537156; and Plaintiff Dr. Thomas's study (Lyons-Weiler

& Thomas, Int J Environ Res Public Health 2020;17(22):8674, subsequently retracted), all showing better health outcomes in unvaccinated populations.[8]

71. The most recent evidence that the childhood vaccine schedule may be harming infants comes from Louisiana state vaccination records. In December 2025, researchers employed by Plaintiff Children's Health Defense analyzed Louisiana Department of Health records linking infant deaths to vaccination histories for over 1,200 children who died between 2013 and 2024. They found that infants vaccinated at two months of age were significantly more likely to die in their third month of life than infants who were not vaccinated during that window. Infants who received all six vaccines recommended for two-month-olds were 68% more likely to die in the following month, which is a statistically significant finding. The disparity was even starker in certain groups: Black infants showed 68% higher mortality, and female infants showed 112% higher mortality. Jablonowski K, Hooker B, "Increased Mortality Associated with 2-Month-Old Infant Vaccinations," https://zenodo.org/records/18262931. (Last visited Jan. 20, 2026). (Originally preprinted with another service, but withdrawn by the advisory board for unspecified reasons. Another example of the point of this section.)

72. This study analyzed the very type of linked immunization-mortality data that federal health authorities possess. The pattern is consistent: when researchers conduct the studies AAP insists are impossible, the results contradict AAP's safety assurances.

73. The consistency of these findings across different methodologies and populations explains the enterprise's suppression efforts. Widespread knowledge that AAP's "impossible"

[8] Mawson's article was initially withdrawn under pressure from Frontiers in Public Health before republication in Journal of Translational Science. Lyons-Weiler & Thomas was retracted 11 days after publication. The publication history of these studies is itself evidence of the suppression alleged herein.

studies have been done *with damaging results*, would undermine the vaccine schedule's credibility.

74. Dr. Peter Aaby has conducted decades of vaccine research in Guinea-Bissau, publishing hundreds of peer-reviewed studies on vaccine effects. His research found that vaccines have "non-specific effects" beyond protection against the target disease, and that these effects are not always beneficial.

75. His research found that while the DTP vaccine protected against its target diseases, children who received it had five-fold higher all-cause mortality than unvaccinated children. In short, the vaccine worked as intended, but caused overall net harm (i.e., more death). Mogensen SW, et al., "The Introduction of Diphtheria-Tetanus-Pertussis and Oral Polio Vaccine Among Young Infants in an Urban African Community: A Natural Experiment," EBioMedicine 2017;17:192-198. https://pmc.ncbi.nlm.nih.gov/articles/PMC5360569/.

76. The World Health Organization's Strategic Advisory Group of Experts (SAGE) reviewed these non-specific effects and acknowledged that "the majority of studies found a detrimental effect of DTP," but dismissed the findings as "inconsistent" and took no action.

77. But the pattern is consistent: when researchers study what vaccine authorities claim cannot be studied, and the results contradict categorical safety claims, the research is marginalized rather than replicated. AAP is the American franchise of an international enterprise that protects the vaccine schedule by discrediting any science that threatens it.

78. Finally, unlike U.S. pediatric medicine, military medicine has grappled with the safety of administering multiple vaccines simultaneously. Following the 1991 Gulf War, a British Medical Journal study of UK veterans found "a specific relation between multiple vaccinations given during deployment and later ill health," with the strongest association for

multisymptomatic illness (odds ratio 5.0). Hotopf M, et al., BMJ 2000;320:1363-67, https://pmc.ncbi.nlm.nih.gov/articles/PMC27378/.

79. The U.S. Marine Corps operationally limits simultaneous vaccinations: a November 2025 Officer Candidates School preparation letter states that "[m]edical restrictions prevent officer candidates from receiving more than five immunizations over a short period of time." U.S. Marine Corps, Officer Candidates School, "Officer Candidates Class 251 Pre-Ship Preparation Letter" § 13(a)(2) (Nov. 12, 2025), *available at* https://www.ocs.marines.mil/Information/Candidates/.

80. The disparity is indefensible. Marine candidates selected for physical resilience have been limited to five vaccines in one sitting. Infants with immature immune systems face no limit whatsoever, because consensus science created and promoted by the enterprise has established that the immune system can handle 10,000 vaccines at once, (theoretically).

D. The Vaccine Racket: Create the Condition, Sell the Treatment, Keep the Sick Customer for Life

81. A racket is a service that creates its own demand. The same pharmaceutical conglomerates that serve as enterprise participants in manufacturing childhood vaccines have systematically acquired companies developing treatments for autoimmune disorders, allergies, and neurodevelopmental conditions, many of which are listed as adverse events in vaccine package inserts produced by them.

82. In 2016, Pfizer acquired Anacor Pharmaceuticals for $5.2 billion, gaining Eucrisa for pediatric eczema in children two years old (subsequently expanded to as young as three months). Eczema is listed as a postmarketing adverse event in vaccines manufactured by other enterprise participants, such as GlaxoSmithKline's ENGERIX-B. Pfizer manufactures Prevnar. In 2020, Sanofi acquired Principia Biopharma for $3.7 billion, securing rilzabrutinib for immune

thrombocytopenia, an autoimmune blood disorder is which listed as an adverse event in vaccines manufactured by enterprise participants, including Merck's M-M-R II and GlaxoSmithKline's PEDIARIX.

83. In 2012, GSK acquired Human Genome Sciences for $3.6 billion, obtaining Benlysta for systemic lupus, later expanded to treat children as young as five (vasculitis and arthritis are listed as adverse events in vaccines manufactured by enterprise participants, such as Merck's M-M-R II and GlaxoSmithKline's ENGERIX-B). GSK manufactures Pediarix and Kinrix. In 2021, Merck bought Pandion Therapeutics for $1.85 billion, adding treatments for inflammatory bowel disease (IBD, including ulcerative colitis and Crohn's disease, is listed in clinical trial safety data for Merck's GARDASIL 9).

84. These acquisitions create a closed-loop revenue system across the enterprise. The vaccine serves as the customer acquisition mechanism. A child who develops eczema after vaccination with an enterprise participant's vaccine becomes a customer for another participant's eczema treatment. A child who develops an autoimmune disease becomes a customer for the enterprise's immunosuppressants. These are just a few of many examples. The enterprise profits from the vaccines, and profits again from the treatment of the vaccine package insert documented side effects.

85. The *Philip Morris* defendants sold cigarettes knowing they caused lung cancer, but they did not own oncology clinics. AAP helps the enterprise financialize childhood illness.

86. AAP ensures this revenue stream continues. It blocks studies that might reveal connections between schedule expansion and chronic disease. It promotes ever-expanding schedules. The $115-125 million AAP generates annually is a fraction of the tens of billions at stake.

E. AAP: The Racketeering Enterprise's Distribution Network

87. AAP controls pediatric medicine and dominates childhood vaccine policy. Its Red Book defines the standard of care. Section G below. Its Bright Futures guidelines dictate the content and timing of well-child visits. Physicians who deviate from AAP guidelines face medical board discipline, loss of hospital privileges, exclusion from insurance networks, and professional destruction, as Plaintiffs Thomas and Stoller experienced. ¶¶ 34-44, 100.

88. And when HHS attempts reform, AAP leads the opposition, suing to restore the childhood COVID-19 vaccine recommendation after the CDC removed it, issuing false and alarmist statements about the ACIP hepatitis B decision, and publicly attacking every effort to introduce flexibility into the schedule. ¶¶ 111-123.

89. AAP's 67,000 members control the information families receive about vaccines. This is the enterprise's distribution network: trusted physicians delivering the enterprise's safety claims as medical advice. The enterprise's purpose is to control the information the families receive, and AAP's Fellows do the job.

90. On information and belief, AAP was not always this powerful. It was founded in 1930 by 35 pediatricians in Detroit, a small professional society that grew modestly for its first fifty years: 834 members by 1935, approximately 1,300 by 1940, and 20,000 by 1980. Its first publication, an eight-page pamphlet in 1938 titled "Immunization Procedures" (later the Red Book), recommended vaccines against just four diseases. For many decades, vaccines were a minor part of pediatric practice.

91. The National Childhood Vaccine Injury Act of 1986 transformed both the vaccine market and AAP's role in it. The Act shielded manufacturers from liability claims, which both fueled the vaccine schedule expansion, and eliminated accountability for safety. In 1993,

Congress created the Vaccines for Children program, now a $4.7 billion annual federal program providing free vaccines to practices while allowing administration fees. And in 1995, AAP, ACIP, and the American Academy of Family Physicians jointly launched the first "harmonized" schedule, creating the unified standard that state mandates, insurance metrics, and medical board enforcement would treat as obligatory. The post-1986 framework made AAP a co-beneficiary of the vaccine enterprise.

92. AAP's growth after 1986 tracks the schedule expansion. In 1983, the schedule required 11 doses of 4 vaccines. By 1995, it had grown to 19 doses. Today, children can receive over 72 or more doses before age 18. AAP membership more than tripled during this period, from 20,000 in 1980 to 67,000 today, while its institutional infrastructure expanded correspondingly. So did its revenues, now between $115 and $125 million annually. https://www.aap.org/en/membership-application/faq/; perma.cc/KBY4-JTPW.

93. The 1986 Act also locked pediatric practices into this increasing vaccination model. Pediatricians are among the lowest-paid physician specialties in America, earning on average around $265,000 annually, less than half what top specialists earn.[9] This economic vulnerability made the specialty susceptible to capture. Well-child visits became vaccine delivery appointments. Administration fees, multiplied across dozens of vaccines, became essential revenue. Insurance payments tied to vaccination rates created further dependency. Pediatricians who question the schedule risk professional discipline and financial ruin. AAP offers practice management resources designed to help pediatricians stay current on healthcare trends;

[9] Doximity, "2025 Physician Compensation Report" https://www.doximity.com/reports/physician-compensation-report/2025, perma.cc/FKM9-TPE7.

effectively manage their careers, and practices and patient panels. These resources specifically address vaccine hesitancy and refusal.

F. The Racket's Financial Trap: Why Pediatricians Cannot Say No

94. Vaccine administration is essential revenue for pediatric practices. Pediatricians collect administration fees for each injection, performance bonuses tied to vaccination rates, and bill for the well-child visits into which vaccinations are bundled. Major insurers enforce the schedule through incentive programs; Blue Cross and Blue Shield of Michigan, for example, pays $175 for each child achieving full immunization status. Blue Cross Blue Shield of Michigan, *2024 Quality Rewards: Performance Recognition Program and Physician Group Incentive Program* (Winter 2024), https://uopdocs.com/wp-content/uploads/2024/07/BCN_2024-Quality-Rewards-Booklet.pdf, perma.cc/Y5J7-KCQY.

95. AAP acknowledges these pressures. In its 2024 clinical report, AAP stated: "under value-based care models, pediatricians may receive a significant part of their payments based on performance metrics, one of which is completion of childhood and adolescent immunizations" and that "[c]urrent pay-for-performance models do not recognize the impact of vaccine refusal on pediatricians' metrics, which can lead to reduced payments despite pediatricians' best efforts." O'Leary ST, et al., "Strategies for Improving Vaccine Communication and Uptake," *Pediatrics* 2024;153(3):e2023065483, https://publications.aap.org/pediatrics/article/153/3/e2023065483/196695/Strategies-for-Improving-Vaccine-Communication-and (last visited Jan. 10, 2026). In other words, doctors who cannot talk parents into full vaccine schedule compliance lose money.

96. Yet AAP publicly denies that pediatricians profit from vaccines. In July 2025, AAP posted on social media: "Pediatricians do not profit off vaccines," adding that "most

pediatricians either break even or even lose money when they offer vaccines." American Academy of Pediatrics (@AmerAcadPeds), X post (July 16, 2025), https://x.com/AmerAcadPeds/status/1945522940839178504, perma.cc/FQ3Y-LQHK. This is like a car salesman who swears he sells "below cost" while collecting manufacturer rebates and volume bonuses. AAP's denial focuses on vaccine product margins while omitting administration fees, quality bonuses, and the well-child visits into which vaccinations are bundled. The dealership would not exist if the math worked as claimed. Neither would pediatric practices.

G. The Racket's Rulebook: How the Red Book Became the Law

97. AAP's Committee on Infectious Diseases publishes the Red Book, which AAP markets as "the authoritative guide" to pediatric infectious disease prevention, management, and control. The 2024-2027 edition provides guidance on more than 200 childhood conditions and is "updated to be consistent with 2024 AAP and the CDC vaccine recommendations." AAP, Red Book: 2024-2027 Report of the Committee on Infectious Diseases (33rd ed.), https://publications.aap.org/aapbooks/monograph/756/. It is sold for $175 to pediatricians, hospitals, and public health departments nationwide. For pediatricians, the Red Book is their Bible, the definitive reference that establishes what the profession considers the standard of care.

98. But the Red Book incorporates the CDC schedule without acknowledging what IOM found in 2013: that "studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted." IOM 2013 at 6. The schedule the Red Book endorses as standard of care has never been tested. Pediatricians following it are not following science. They are following an untested, long-term, multi-agent biologic protocol blessed by their trade organization.

99. The American Board of Pediatrics requires physicians to pass certification examinations and complete Maintenance of Certification to remain board-certified. ABP, Maintenance of Certification (MOC), https://www.abp.org/content/maintenance-certification-moc (last visited Jan. 12, 2026); ABP, General Pediatrics Content Outline, https://www.abp.org/content/general-pediatrics-content-outline, https://perma.cc/7MFB-DN6S. Hospitals typically require board certification for privileges. Insurers reference vaccination rates for quality metrics and pay-for-performance bonuses. Deviation from the schedule is not treated as a difference of medical opinion; it is a disciplinary offense.

100. Medical boards enforce AAP's guidelines as the benchmark for acceptable practice. Physicians who publicly question vaccine safety, offer alternative schedules, or write medical exemptions inconsistent with ACIP contraindications face investigation, suspension, or license revocation, as Plaintiffs Thomas and Stoller can attest. The message to every pediatrician is clear: publish research contradicting the schedule, lose your license. Write exemptions based on individual patient assessment rather than ACIP criteria, lose your license. Question the safety of the untested schedule, lose your livelihood. AAP's Red Book is the racket's rulebook. The penalty for breaking the rules is professional annihilation.

H. Protecting the Racket: How Scientific Debate Became "Misinformation"

101. AAP conducts a coordinated campaign to brand scientific dissent as "misinformation." Through its parent-targeted website (HealthyChildren.org), policy statements, press releases, and media appearances, AAP promotes the vaccine schedule as categorically safe while labeling critics, dissenting research, and documented adverse events as dangerous falsehoods requiring suppression.

102. In 2016, AAP published "Countering Vaccine Hesitancy," a policy statement that framed vaccine safety questions as "misinformation" to be countered rather than answered. *Pediatrics* 2016;138(3):e20162146, https://doi.org/10.1542/peds.2016-2146. In February 2019, AAP President Kyle Yasuda sent a public letter urging Facebook, Google, and Pinterest to "combat vaccine misinformation" by suppressing content that questions vaccine safety. AAP News Release, "AAP Urges Social Media Platforms to Combat Vaccine Misinformation," February 14, 2019, https://healthychildren.org/English/news/Pages/AAP-Urges-Major-Technology-Companies-to-Combat-Vaccine-Misinformation.aspx, perma.cc/AR22-ZVHE. The letter did not define "misinformation." It did not distinguish between fabricated claims and peer-reviewed research. It asked tech platforms to silence debate AAP could not win on the merits.

103. The strategy has worked. AAP blocks the IOM-recommended safety studies. When independent researchers conduct those studies and find concerning results, AAP and its enterprise associates label them "misinformation." When physicians cite that research to support individualized patient care, the enterprise brands them dangerous. When those physicians lose their licenses, AAP points to the revocations as proof the physicians were wrong. The racket ensures that the only permissible science is the science that supports the racket.

104. AAP's categorical claims are themselves misinformation. AAP states on HealthyChildren.org: "Vaccines are not associated with autism or developmental delay. Multiple studies have proven this." https://www.healthychildren.org/English/safety-prevention/immunizations/Pages/vaccine-studies-examine-the-evidence.aspx, perma.cc/W3LJ-W8ZY. ("URL") This is false. The IOM's 2012 report concluded that for most vaccine-autism hypotheses, evidence was "inadequate to accept or reject a causal relationship." https://nap.nationalacademies.org/catalog/13164. The federal Vaccine Injury Compensation

Program conceded compensation in the Hannah Poling case (2008) for vaccine-induced encephalopathy with autism features. On November 19, 2025, the CDC itself revised its position, stating: "The statement 'Vaccines do not cause autism' is not an evidence-based claim because studies have not ruled out the possibility that infant vaccines cause autism." https://doi.org/10.17226/13164. Yet AAP continues to assert the issue is "proven" and "settled."

I. The Lies Exposed: AAP's Material Misrepresentations/Omissions of Fact

1. The Foundational Misdirection: Paul Offit's Claim that Infants Can Safely Receive 10,000 Vaccines at Once

105. As detailed in Section A above, AAP published in *Pediatrics* a speculative calculation by Offit et al. claiming infants could "theoretically" respond to 10,000 vaccines at once. This substituted immunogenicity for safety, addressing B-cell capacity rather than parents' actual concerns about cumulative toxicological effects. AAP deployed this theory to preempt and block the IOM-recommended studies, creating a false consensus that made actual research seem unnecessary, mirroring tobacco industry tactics. For twenty-four years, AAP has disseminated this fraud through mail and wire, so their Fellows could assure parents that their children can receive all the vaccines in the vaccine schedule since they could "respond" to 10,000 vaccines at once.

2. "The Schedule Is Fully Tested and Safe"

106. On multiple occasions, AAP has falsely represented that the childhood vaccine schedule has been fully tested and proven safe. In its official policy position, AAP states: "The AAP believes immunizations are safe and effective for children." (URL at ¶ 104).

107. In its clinical report "Countering Vaccine Hesitancy," published in *Pediatrics* and distributed to members nationwide, AAP instructs pediatricians that "[t]he clear message parents should hear is that vaccines are safe and effective," and describes the CDC schedule as "the only

evidence-based schedule that has been tested and approved by multiple authoritative experts for safety and efficacy." AAP, "Countering Vaccine Hesitancy," *Pediatrics* 2016;138(3):e20162146, https://doi.org/10.1542/peds.2016-2146.

108. Remarkably, the same clinical report claims "[t]he safety of the currently recommended vaccines administered according to their established schedules was strongly affirmed by the [IOM] in 2013." *Id.* This is a material omission of fact. AAP omits the report's central finding: "studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted." IOM 2013 at 6, which the IOM had recommended be undertaken back in 2002 (as detailed *supra* ¶ 58.) AAP omitted this so that its pediatrician Fellows would misinform the parents of their patients that IOM had "strongly affirmed" the schedule's safety.

109. On HealthyChildren.org (AAP's parent-targeted website), in an article titled "Vaccine Safety: Examine the Evidence," AAP represents that "[f]or a vaccine to be recommended—as part of the childhood and adolescent immunization schedule, it must be tested, found safe and closely monitored." (URL at ¶ 104). The article claims "[r]esearch continues to confirm that vaccines are safe and effective." These representations omit that no study has ever compared health outcomes between children receiving the complete schedule and unvaccinated children, the very gap IOM identified in 2002 and confirmed as unresolved in 2013.

110. These statements are materially false: no study has ever tested the cumulative safety of the 72+ dose schedule. AAP knew this since it cites the report.

3. AAP's Fraudulent Alarmism

a. December 2025: The Hepatitis B Dress Rehearsal

111. On December 5, 2025, ACIP voted eight-three to recommend individual decision-making for hepatitis B birth doses in low-risk infants (99.6% of U.S. births), vaccinating no earlier than two months. https://www.cdc.gov/media/releases/2025/2025-acip-recommends-individual-based-decision-making-for-hepatitis-b-vaccine-for-infants-born-to-women.html. This aligns with practices in the UK and Canada, where similar delays have caused no infection increases.

112. AAP immediately issued false warnings. AAP President Susan Kressly declared the decision "irresponsible and purposely misleading," claiming it would cause "99,000 preventable hepatitis B infections" and "devastating results" including chronic disease, liver cancer, and death.[10] Committee member José Romero claimed that delaying the birth dose would cause "children [to] die preventable deaths" and result in "liver cancers."[11]

113. These projections derive from unpublished models, not observed outcomes. The United Kingdom, Canada, and seventeen EU member states delay birth doses without infection surges or increased liver cancers. AAP knew that 99.5% of U.S. infants face no hepatitis B transmission risk at birth (CDC data shows 0.5% of pregnancies are HBsAg-positive).

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[10] AAP: "Changes to hepatitis B recommendations 'irresponsible and purposely misleading,'" *AAP News* (Dec. 5, 2025), https://publications.aap.org/aapnews/news/33915 (last visited Jan. 10, 2026); "Report: Hepatitis B vaccine safe; delaying would lead to increased infections," *AAP News* (Dec. 2, 2025), https://publications.aap.org/aapnews/news/33888 (last visited Jan. 10, 2026).

[11] J. Fitch, "ACIP delays vote on hepatitis B virus vaccine to December 5," *Contemporary Pediatrics* (Dec. 4, 2025), https://www.contemporarypediatrics.com/view/acip-delays-vote-on-hepatitis-b-virus-vaccine-to-december-5, perma.cc/D9L7-AC6Q.

114. These December 2025 transmissions constitute fresh predicate acts of mail and wire fraud, knowingly false statements designed to maintain revenue streams by preventing even minimal schedule modifications.

b. January 2026: A Very Dark Day for Vaccine Revenue

115. One month later, AAP's conduct became even more revealing. On January 5, 2026, Acting CDC Director Jim O'Neill signed a decision memorandum revising the childhood immunization schedule, moving six vaccines — rotavirus, influenza, hepatitis A, hepatitis B, meningococcal disease, and COVID-19 — from universal recommendations to "shared clinical decision-making." The revision does not remove any vaccine from availability; all remain fully covered by insurance without cost-sharing. HHS's scientific assessment found that the United States was "a global outlier" in recommended doses, yet "does not have higher vaccination rates" than peer nations relying on recommendation-only models. Seventeen EU member states, the United Kingdom, and Japan use such models while maintaining rates exceeding 90%.

116. AAP's response was immediate. Sean O'Leary, chair of AAP's Committee on Infectious Diseases, instructed parents to "trust the professional societies like the American Academy of Pediatrics," but "for now, unfortunately, we have to ignore everything about vaccines that is coming from our federal government." He described the announcement as "a very dark day for children and for their parents and for our country generally" and predicted "[t]here will be more diseases, more infection, more hospitalization." CIDRAP, "HHS announces unprecedented overhaul of US childhood vaccine schedule" (Jan. 5, 2026), https://www.cidrap.umn.edu/childhood-vaccines/hhs-announces-unprecedented-overhaul-us-childhood-vaccine-schedule (last visited Jan. 16, 2026).

117. AAP announced it would publish its own schedule contradicting CDC guidance, positioning itself not as a scientific organization deferring to federal health authorities but as a competing authority that supersedes the government when government policy threatens AAP's member interests. The policies AAP opposes threaten the enterprise's revenue model: under shared decision-making, physicians must discuss rather than simply administer, the bundled well-child visit becomes less efficient, and pay-for-performance metrics become harder to achieve.

118. AAP has added to its existing lawsuit seeking to overturn this reduction of recommended vaccines with a hearing scheduled for February 13, 2026. CNN, "Medical Group will ask court to block new CDC recommendation." (Jan. 14, 2026), https://www.cnn.com/2026/01/15/health/vaccine-recommendation-aap-block (last visited Jan. 16, 2026).

c. If CDC's Recommendations for 11 Diseases is "Dangerous," What Is California's 10?

119. AAP's representations are false and fraudulent. California law requires vaccines for only 10 diseases for school entry (diphtheria, Haemophilus influenzae type b, measles, mumps, pertussis, poliomyelitis, rubella, tetanus, hepatitis B, and varicella). Cal. Health & Safety Code § 120335(b)(1)–(10). California eliminated all personal belief exemptions in 2015, creating the strictest vaccine mandate in the nation. The new schedule that the AAP calls "dangerous" recommends 11 vaccines for all children, one more than California mandates.

120. If recommending 11 vaccines is "dangerous," "a very dark day for children," " and will cause "more disease, more infection, more hospitalizations," then California's 10 vaccines mandate is even more dangerous. Except that California children have not suffered the catastrophic outcomes AAP predicts. AAP has never called California's schedule dangerous,

never sought to enjoin California officials, and has never told parents to "ignore everything" from the California Department of Public Health.

121. AAP filed its lawsuit in the District of Massachusetts seeking to enjoin a federal schedule recommending vaccines for 11 diseases. Ironically, Massachusetts requires only vaccines for 9 diseases for grades K-6, and 10 for grades 7-12. Massachusetts Department of Public Health, Immunization Requirements for School Entry (updated Apr. 16, 2025), available at https://www.mass.gov/doc/immunization-requirements-for-school-entry-1/download. AAP has never sued Massachusetts. AAP has never called Massachusetts' schedule dangerous. It is currently in federal court, but it is not seeking to overturn Massachusetts' 10 disease mandate and is not telling Massachusetts parents to ignore the Massachusetts Department of Public Health.

122. This inconsistency is fatal to AAP's credibility, and explains its true motive: Money, selling more vaccines, and protecting the ever-growing vaccine schedule that has taken it from a small organization to the chief architect of the dramatic and worrisome decline of the health of American children.

123. AAP's stated concerns are pretextual. This action presents them as predicate acts of racketeering.

4. AAP's False Attribution of Mortality Declines to Vaccines

124. AAP claims that its vaccine recommendations "have saved millions of lives." Sean O'Leary, MD, Chair of AAP's Committee on Infectious Diseases, stated on AAP's HealthyChildren.org website: "The AAP recommendations, based on decades of ongoing research, have saved millions of lives." https://www.healthychildren.org/English/tips-tools/ask-

the-pediatrician/Pages/what-is-the-difference-between-the-AAP-recommended-immunization-schedule-and-other-vaccine-schedules.aspx (last updated Jan. 18, 2026).

125. This representation is false or highly misleading. A study from Johns Hopkins and CDC researchers, Guyer et al., "Annual Summary of Vital Statistics: Trends in the Health of Americans During the 20th Century," *Pediatrics* 2000;106(6):1307-1317, https://doi.org/10.1542/peds.106.6.1307, analyzed 100 years of U.S. mortality data. The conclusion: nearly 90% of all mortality reductions from infectious diseases occurred before 1940, which is before almost all of the vaccines on the current vaccine schedule were invented or in widespread use.[12]

126. Measles mortality dropped 97% before the vaccine was licensed. Pertussis and polio mortality fell dramatically before their vaccines. Scarlet fever mortality plummeted along the same timeline, and no vaccine has ever been developed for that disease. The CDC's own report attributes these declines to sanitation, nutrition, housing, and antibiotics—not vaccination. "Achievements in Public Health, 1900–1999," MMWR 1999;48(29):621-629, https://www.cdc.gov/mmwr/preview/mmwrhtml/mm4829a1.htm.

127. McKinlay and McKinlay's landmark 1977 study estimated that all medical interventions, including vaccines and antibiotics combined, accounted for less than 3.5% of mortality decline from infectious disease. Clean water, sanitation, refrigeration, nutrition, and flush toilets caused the other 96.5%. McKinlay JB & McKinlay SM, "The Questionable Contribution of Medical Measures to the Decline of Mortality in the United States in the

[12] Diphtheria was available from the mid-1930s, Tetanus since the late 1930s, and Pertussis was available but still experimental in the early 1940s.

Twentieth Century," *Milbank Memorial Fund Quarterly* 1977;55(3):405-428, https://pubmed.ncbi.nlm.nih.gov/413067/.

128. By claiming credit for mortality reductions caused by sanitation and public health infrastructure, AAP knowingly misattributes historical fact to support the enterprise's commercial objectives.

5. Pointing to VAERS/VSD as "Proof of Safety"

129. AAP represents to parents and pediatricians that post-licensure monitoring systems, specifically the Vaccine Adverse Event Reporting System (VAERS) and VSD, demonstrate that vaccines are safe. On August 29, 2016, AAP published in AAP News that "[p]ost-licensure monitoring includes the Vaccine Adverse Events Reporting System (VAERS), the [VSD]," and other systems—implying these mechanisms validate vaccine safety. AAP News, "How to address vaccine hesitancy," https://publications.aap.org/aapnews/news/11050. (Last visited Jan. 10, 2026).

130. These representations are fraudulent because AAP exploits the limitations of these systems asymmetrically, citing them as proof of safety while invoking those same limitations to dismiss evidence of harm.

a. The VAERS Double Standard

131. AAP's own 2024 Clinical Report "Strategies for Improving Vaccine Communication and Uptake" acknowledges that VAERS "cannot generally assess causality" and "serves as a hypothesis-generating system." *Pediatrics* 2024;153(3):e2023065483, https://doi.org/10.1542/peds.2023-065483. CDC's website similarly states: "VAERS data alone cannot determine if the vaccine caused the reported adverse event." https://www.cdc.gov/vaccine-safety-systems/vaers/index.html.

132. Yet AAP directs parents to rely on VAERS as evidence of vaccine safety, assuring them that "based on VAERS reports, vaccine safety professionals continuously look for any problem with a vaccine" and that VAERS monitoring ensures vaccines "remain safe." American Academy of Pediatrics, *Vaccine Safety: Parent Handout* (2008), http://www.rainbowvt.com/forms/AAP_Vaccine_Safety_Parent_Handout.pdf; AAP, *Fact Checked: Childhood Vaccines Are Carefully Studied* (2024), https://www.aap.org/en/news-room/fact-checked/fact-checked-childhood-vaccines-are-carefully-studiedincluding-with-placebosto-ensure-theyre-safe-and-effective/. But when parents cite VAERS reports of deaths and serious adverse events, AAP dismisses the same data as incapable of determining causation. *A system that cannot assess causality cannot prove safety any more than it can prove harm.* AAP's selective use of VAERS, asserting safety while dismissing harm, constitutes knowing misrepresentation.

133. The inadequacy of VAERS is compounded by severe underreporting. A 2010 Harvard Pilgrim Health Care study funded by HHS estimated that "fewer than 1% of vaccine adverse events are reported" to VAERS. The study developed an automated system to improve capture rates, but the project was abandoned when CDC stopped responding. Ross Lazarus, *Electronic Support for Public Health--Vaccine Adverse Event Reporting System (ESP:VAERS): Final Report*, Grant No. R18 HS 017045 (2010), https://digital.ahrq.gov/sites/default/files/docs/publication/r18hs017045-lazarus-final-report-2011.pdf. CDC refused to improve a system it knew captured less than 1% of adverse events. AAP continued to cite that system as proof of safety.

b. The VSD Fraud

134. The VSD is not a safety system. It is a database, a collection of electronic health records from eleven healthcare organizations covering approximately 12 million Americans. The VSD contains vaccination records alongside subsequent health outcomes: doctor visits, diagnoses, hospitalizations, deaths. It is like a giant filing cabinet containing the medical history of millions of children. The files are there. But a filing cabinet does not "monitor" anything. It sits there. Whether those files reveal safety or danger depends entirely on whether anyone opens the filing cabinet and examines what is inside.

135. As detailed above (¶ 58), in 2002, the IOM told CDC to "explor[e] the feasibility of using existing vaccine surveillance systems"—specifically naming VSD—to study "safety questions related to … the immunization schedule" to address the gap in vaccine safety. *Id.* The IOM was asking the CDC to open its filing cabinet and analyze the records.

136. As indicated, the IOM checked back in 2013 and found that the CDC never opened the filing cabinet: "studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted." *Supra,* ¶ 59. As of 2026, twenty-four years after the IOM's recommendation, the CDC has still not used VSD to answer the fundamental question: Is the cumulative vaccine schedule safe and creates an overall benefit? The filing cabinet has grown larger; more files accumulate every year. And no one is permitted to examine them; but the AAP keeps saying that this filing cabinet proves the safety of the vaccine schedule.

c. Deflecting and Conflating the Studies

137. The AAP used an asserted ethical problem of using an unvaccinated cohort in a randomized prospective clinical trial (vaxed vs. unvaxed) with the IOM twice recommending

retrospective studies using VSD data to determine safety and net benefit (if any) of the vaccine schedule. S*upra,* ¶¶ 58-60. These statements are fraudulent.

6. "Vaccines do not cause autism — this has been proven."

138. On its HealthyChildren.org website, the AAP states: "Vaccines are not associated with autism or developmental delay," and "[r]esearch continues to confirm that vaccines are safe and effective." (URL at ¶ 104).

139. On November 20, 2025, one day after the CDC admitted that "vaccines do not cause autism" was "not an evidence-based claim,"[13] the AAP updated this page with a statement from its President, Dr. Susan Kressly: "Parents deserve peace of mind. Decades of rigorous research have shown vaccines do not cause autism." (URL at ¶ 104). The AAP thus doubled down on its categorical denial with actual knowledge that the CDC had just retracted the same claim.

140. These categorical claims are false. The IOM's 2012 report *Adverse Effects of Vaccines* concluded that for DTaP and autism, evidence was "inadequate to accept or reject a causal relationship"; for other infant vaccines (HepB, Hib, IPV, PCV), no studies examining autism were even reviewed because none existed. https://nap.nationalacademies.org/catalog/13164.

141. In 2008, the federal Vaccine Injury Compensation Program conceded compensation in the Hannah Poling case for vaccine-induced encephalopathy resulting in autism features. These findings long predate the current administration. In November 2025, the CDC acknowledged what the IOM found thirteen years earlier: "The claim 'vaccines do not cause autism' is not an evidence-based claim." https://www.cdc.gov/vaccine-safety/about/autism.html.

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13 https://www.cdc.gov/vaccine-safety/about/autism.html.

142. The AAP knew or should have known these limitations. Its committee members participate in National Academy reviews and are aware of the "inadequate to accept or reject" findings. The AAP was notified of the Poling concession. The AAP knows the CDC has retracted its categorical denial. Yet the AAP continues to claim the issue is "proven" and "settled." That the AAP transmitted this categorical denial via its website to millions of parents, one day after the CDC finally admitted the claim was "not evidence-based," constitutes wire fraud in furtherance of the enterprise.

7. AAP's Fraudulent Marketing of the Red Book as "Authoritative"

143. The AAP markets its Red Book as "the most authoritative and comprehensive" resource for pediatric infectious diseases, with "evidence-based policy recommendations" updated throughout. The 2024 Red Book (33rd Edition) provides recommendations from "the combined expertise of the CDC, the FDA, the NIH, and hundreds of physician contributors." https://shop.aap.org, perma.cc/L3SA-UGLX. The Red Book is sold for $175.00 to pediatricians, hospitals, and public health departments across all states.

144. These representations of authority and evidence are false. As detailed in Section G, the Red Book presents the CDC schedule as fully tested without disclosing the National Academy of Medicine's finding that "studies designed to examine the long-term effects of the cumulative number of vaccines have not been conducted." IOM 2013 at 5. The Red Book recommends vaccines as "safe and effective" without disclosing that most were licensed without true saline placebo controls. AAP Committee members participated in the IOM review and knew these limitations when publishing the 2024 Red Book. Yet it continues to present untested recommendations as "authoritative" and "evidence-based."

J. Tobacco Litigation Precedent with Comparable Fraudulent Statements

145. The misrepresentations alleged herein are not novel. Federal courts have already found that materially identical statements (categorical safety assurances, false claims of adequate testing, denials of known risk, and assertions of independent scientific validation) constitute actionable fraud under 18 U.S.C. §§ 1341 and 1343 when used to mislead the public through coordinated enterprise activity. *See United States v. Philip Morris USA, Inc.*, 449 F. Supp. 2d 1 (D.D.C. 2006), *aff'd*, 566 F.3d 1095 (D.C. Cir. 2009); *Blue Cross & Blue Shield of N.J., Inc. v. Philip Morris, Inc.*, 113 F. Supp. 2d 345 (E.D.N.Y. 2000).

146. In *Philip Morris*, the courts found that cigarette manufacturers and allied "research" organizations operated a RICO enterprise by: (a) falsely denying known health risks while internally acknowledging them; (b) representing that "independent" scientific investigation had failed to establish any causal link between smoking and disease, while suppressing adverse research; and (c) using purportedly independent entities like the Council for Tobacco Research to conduct "objective" research while concealing adverse findings. 566 F.3d at 1105-08, 1119-20, 1122-24; *Blue Cross*, 113 F. Supp. 2d at 356-57, 359-60.

147. AAP's conduct tracks this pattern. The tobacco defendants assured the public that decades of "independent" research had failed to establish harm, while suppressing contrary evidence. AAP assures parents that the schedule is "fully tested" and "safe," and blocks the studies that would test it, while marginalizing research showing harm. Both enterprises used the apparatus of science to foreclose scientific inquiry.

148. Based on *Philip Morris* and *Blue Cross*, AAP's categorical safety claims, if proven, are actionable mail and wire fraud when used as part of a coordinated enterprise scheme to mislead the public.

V. CLAIMS FOR RELIEF

FIRST CLAIM FOR RELIEF
VIOLATION OF RICO, 18 U.S.C. § 1962(c)

149. Plaintiffs reallege and incorporate by reference paragraphs 1-148

150. Section 1962(c) of RICO provides: "It shall be unlawful for any person employed by or associated with any enterprise engaged in, or the activities of which affect, interstate or foreign commerce, to conduct or participate, directly or indirectly, in the conduct of such enterprise's affairs through a pattern of racketeering activity …."

151. To establish a civil RICO violation, Plaintiffs must prove: (1) an enterprise; (2) defendant's conduct of the enterprise's affairs; (3) through a pattern of racketeering activity; and (4) injury to business or property caused thereby.

A. The Enterprise Exists

152. As detailed in the above (¶¶ 6-10, 50-144), Defendant and other enterprise participants including vaccine manufacturers form an association-in-fact enterprise. An association-in-fact enterprise must have at least three structural features: "a purpose, relationships among those associated with the enterprise, and longevity sufficient to permit these associates to pursue the enterprise's purpose." *Boyle v. United States*, 556 U.S. 938, 946 (2009).

153. The coordinated conduct described in the Factual Background establishes all three features. AAP and the other enterprise members share a common purpose: maximizing vaccine uptake regardless of unresolved safety questions. They pursued this purpose: the Offit Article's deflection "10,000 vaccines" claim that substituted immunogenicity theory for actual safety testing (¶¶ 51-63); blocking IOM-recommended cumulative safety studies for over two decades (¶¶ 64-68); the Red Book pricing and administration standard that makes vaccines the financial backbone of pediatric practice (¶¶ 97-100); enforcement against dissenting physicians through

medical board complaints and hospital credentialing challenges (¶ 34-45); insurance incentive programs that penalize practices failing to meet vaccination targets (¶¶ 94-96); and coordinated "misinformation" campaigns to suppress safety concerns (¶¶ 101-104). This conduct spans more than two decades, thus satisfying *Boyle*'s longevity requirement.

154. These relationships are reinforced by financial ties. Vaccine manufacturers fund AAP through multiple channels, including direct donations via the "Friends of Children Fund"—where Pfizer, Merck, and Sanofi are "President's Circle" donors ($50,000 or more annually) and GlaxoSmithKline is a "Patron" donor—as well as conference sponsorships, educational program funding, and grants for vaccine-related initiatives. *See* American Academy of Pediatrics, Current Partners, https://www.aap.org/en/philanthropy/corporate-and-organizational-partners/current-partners, perma.cc/6X6L-WXKD. It does not appear that AAP publicly discloses aggregate industry funding.

155. AAP serves as the functional equivalent as the Tobacco Institute and Center for Tobacco Research which conducted the cigarette manufacturers' joint public relations and funded "special projects" research, and then conveyed the unified message about the asserted unresolved questions about smoking and cancer. *See* ¶¶ 145-148.

156. For more than sixty years AAP and its enterprise associates have controlled federal vaccine policy through membership on the CDC's Advisory Committee on Immunization Practices. AAP has had a liaison seat from ACIP's founding in 1964. CDC, "History and Evolution of the Advisory Committee on Immunization Practices, United States, 1964–2014," MMWR Oct. 24, 2014. From 1995 until mid-2025, AAP and the CDC harmonized their immunization schedules, operating as a unified voice on vaccine recommendations.

Congressional Research Service, "The Advisory Committee on Immunization Practices (ACIP)," IF12317.

157. On June 9, 2025, HHS Secretary Kennedy removed all seventeen ACIP members. AAP liaisons were subsequently disinvited from ACIP workgroups. AAP has filed suit to restore its position. The six decades of control and institutional coordination satisfy *Boyle*'s "longevity" requirement. The lawsuit by AAP and other members of the enterprise against HHS shows how the enterprise operates.

158. The control was evidenced by the endemic conflicts of interest when the schedule expanded most rapidly. A 2000 House Committee on Government Reform report found that CDC routinely granted conflict-of-interest waivers to ACIP members and that seven of ten members of the rotavirus working group had financial conflicts. U.S. House of Representatives, Committee on Government Reform, "Conflicts of Interest in Vaccine Policy Making," Majority Staff Report, 106th Cong., June 15, 2000. A 2025 JAMA study documented that conflicts among ACIP members peaked at 42.8% in 2000, declining to 5% by 2024. Kanter GP, Mankowitz T & Lurie P, "Conflicts of Interest in Federal Vaccine Advisory Committees," JAMA 2025;334(14):1295-97. It was during this high-conflict of interest era that AAP's Paul Offit served on ACIP (1998-2003) while holding Merck-funded patents on a rotavirus vaccine. It was also the period when AAP argued against safety studies of the cumulative effect (net benefit or harm) of the IOM-recommended safety studies. ¶¶ 60-63.

159. In sum, AAP and vaccine manufacturers constitute an association-in-fact enterprise under 18 U.S.C. § 1961(4): they share a common purpose, maintain ongoing financial and institutional relationships, and have coordinated conduct affecting interstate commerce for more than two decades.

B. AAP Conducts the Enterprise's Affairs

160. AAP directs the enterprise through multiple mechanisms detailed in the Factual Background: publishing the Red Book as 'authoritative' guidance that pediatricians must follow (¶¶ 97-98); maintaining financial pressure through insurance reimbursement structures (¶¶ 94-96); controlling the information 67,000 pediatricians deliver to families and opposing federal reform efforts (¶¶ 87-93, 111-123); and most critically, blocking safety studies while claiming the schedule is "fully tested" (¶¶ 64-77).

C. Through a Pattern of Racketeering Activity

161. Mail and wire fraud occur when one makes material misrepresentations with intent to defraud. 18 U.S.C. §§ 1341, 1343. Each fraudulent statement transmitted interstate constitutes a predicate act.

162. AAP committed dozens of predicate acts from 2002-2025, as detailed in Section I, "The Lies Exposed: AAP's Material Misrepresentations and Omissions of Fact" (¶¶ 105-148). Key examples include: January 2002, publishing Offit's "10,000 vaccines" article in *Pediatrics*, substituting a theoretical calculation about B-cell capacity for actual safety testing (¶¶ 51-62); November 20, 2025, publishing AAP President Susan Kressly's statement that "decades of rigorous research have shown vaccines do not cause autism, one day after the CDC admitted this was "not an evidence-based claim" (¶¶ 138-139); December 5, 2025, further fraudulent claims about the effects of moving the Hep b shot from birth to day 60 to block ACIP reform (¶¶ 112-113).

163. Each misrepresentation was transmitted interstate to AAP's 67,000 members and millions of parents, constituting predicate acts of mail and wire fraud under 18 U.S.C. §§ 1341 and 1343.

164. These acts demonstrate both continuity spanning 24 years and relatedness through common purpose, methods, and victims. *H.J. Inc. v. Northwestern Bell*, 492 U.S. 229, 239 (1989). As in *Philip Morris*, where the enterprise's fraud continued through trial, AAP's December 2025 exaggerations and January 2026 actions demonstrate ongoing racketeering activity, defeating any limitations defense. *Philip Morris*, 566 F.3d at 1134.

D. Causation: AAP's Intended Chain of Reliance

165. AAP designed a coercive system where its fraudulent statements would reach parents through pediatricians. The causation chain operates exactly as intended.

166. A 2025 KFF/Washington Post survey found that 85% of parents trust their child's pediatrician "a great deal" or "a fair amount" for vaccine information—making pediatricians the most trusted source, ranking above local health departments (64%), the CDC (59%), and the FDA (55%). KFF/The Washington Post, "Survey of Parents," Oct. 10, 2025, https://www.kff.org/public-opinion/kff-the-washington-post-survey-of-parents/. *See also* Kempe et al., "Parental Hesitancy About Routine Childhood and Influenza Vaccinations," *Pediatrics* 2020;146(1):e20193852, https://doi.org/10.1542/peds.2019-3852 (parents consistently rank healthcare providers as their most trusted source for vaccine information, with studies showing 74-82% citing their child's doctor as the most influential factor in vaccine decision-making).

167. RICO requires "some direct relation between the injury asserted and the injurious conduct alleged." *Holmes v. Securities Investor Protection Corp.*, 503 U.S. 258, 268 (1992). That standard is satisfied here. AAP publishes false safety claims knowing pediatricians must follow its guidelines or face loss of board certification, insurance participation, and hospital privileges. Pediatricians, economically dependent on vaccine administration and quality bonuses tied to AAP benchmarks, present AAP's claims to parents as medical fact. Parents consent based on

what their pediatricians tell them. Children suffer injuries from the untested schedule, causing families economic harm.

168. The Supreme Court held in *Bridge v. Phoenix Bond & Indemnity Co.*, 553 U.S. 639, 656-58 (2008), that first-party reliance is not an element of RICO claims predicated on mail or wire fraud. A plaintiff can be injured "by reason of" a fraud scheme even without receiving or relying on any misrepresentation. *Id.* at 649. What matters is whether the defendant's conduct proximately caused the injury, not whether the plaintiff relied on anything.

169. The First Circuit applied *Bridge* to pharmaceutical fraud transmitted through prescribing physicians in *Kaiser Found. Health Plan, Inc. v. Pfizer, Inc.*, 712 F.3d 21 (1st Cir. 2013) ("*Kaiser*"). Pfizer made misrepresentations to physicians, who prescribed based on those misrepresentations, injuring the payor that reimbursed for those prescriptions. The circuit court upheld that physician intermediaries do not render causation too remote when the defendant intended the scheme to operate through them. *Id.* at 36-39.

170. The parent Plaintiffs have stronger causation than the *Kaiser* plaintiffs. Pfizer influenced independent physicians through marketing. AAP exercises direct control over pediatricians through board certification, insurance participation requirements, and economic compulsion. Pediatricians who deviate from AAP guidelines face loss of livelihood. *Kaiser* established that influence suffices for proximate cause. This case involves control, which is more than sufficient.

171. As shown in Section D (¶¶ 81-86), vaccine manufacturers have acquired companies treating the side effects their vaccines cause. The enterprise profits from the problem, then profits again from treating it.

E. Concrete Injuries to Business or Property

172. Plaintiffs suffered economic injuries as detailed in ¶¶ 21-22 for Plaintiff Shaw, ¶¶ 26-27 for Plaintiff Nelson, ¶ 33 for Plaintiff Doe, ¶ 42 for Plaintiff Thomas, and ¶¶ 43-44 for Plaintiff Stoller, under *Medical Marijuana, Inc. v. Horn*, 604 U.S. 593 (2025).

173. Defendant violated 18 U.S.C. § 1962(c), causing Plaintiffs damages subject to trebling under 18 U.S.C. § 1964(c).

SECOND CLAIM FOR RELIEF
CONSPIRACY TO VIOLATE RICO (18 U.S.C. § 1962(D))

174. Plaintiffs reallege and incorporate by reference paragraphs 1-173.

175. 18 U.S.C. § 1962(d) provides: "It shall be unlawful for any person to conspire to violate any of the provisions of subsection (a), (b), or (c) of this section."

176. To establish RICO conspiracy, Plaintiffs must prove that Defendant knowingly agreed to participate in the conduct of an enterprise's affairs through a pattern of racketeering activity; here, mail and wire fraud. *Salinas v. United States*, 522 U.S. 52, 65 (1997). The agreement "need not be express, but may be inferred from the defendants' conduct." *United States v. Ruggiero*, 726 F.2d 913, 923 (2d Cir. 1984). "Circumstantial evidence showing a unity of purpose or a common design and understanding among conspirators to commit the crime is sufficient to prove a conspiracy." *United States v. Maloney*, 71 F.3d 645, 652 (7th Cir. 1995).

177. The object of the conspiracy is to maintain and expand vaccine uptake by disseminating false safety assurances though AAP's pediatrician's network while blocking studies that might reveal harm. AAP's knowledge is established by its awareness of the IOM's 2002 and 2013 findings that cumulative safety studies had not been conducted, and its continued dissemination of categorical safety claims despite this knowledge. The co-conspirators are the enterprise participants identified in ¶¶ 6 and 152-159 above.

178. The evidence of agreement is overt coordinated action. AAP and other professional trade groups are presently engaged in joint litigation against HHS to restore the vaccine recommendations the enterprise depends upon (¶¶ 118, 157). This lawsuit is an agreement reduced to a filed complaint. Some of the enterprise participants have identified themselves, aligned their interests in a single legal action, and stated their common purpose: preserving the vaccine schedule that generates their revenue. They have hoisted themselves with their own petard.

179. Additional conduct from which agreement can be inferred includes: six decades of joint participation in ACIP, with AAP holding a liaison seat since 1964 (¶ 156); the 1995 "harmonized" schedule jointly launched by AAP, ACIP, and AAFP that created the unified standard state mandates enforce (¶ 91); annual funding flows from Pfizer, Merck, Sanofi, and GSK through AAP's "Friends of Children Fund" and other channels (¶ 154); Merck's $1.5 million endowment funding the position held by AAP's primary spokesman on vaccine safety (¶ 66); Offit's simultaneous service on ACIP while holding Merck-funded patents and publishing in AAP's journal (¶ 158); synchronized public statements during the December 2025 ACIP deliberations (¶¶ 67, 112); and AAP's 2019 campaign urging tech platforms to suppress vaccine safety content, a campaign that served manufacturers' interests as much as AAP's (¶¶ 101-103).

180. In *Philip Morris*, the court inferred agreement from similar evidence: decades of parallel conduct, joint funding arrangements, and coordinated public statements. 449 F. Supp. 2d at 851-906, *aff'd*, 566 F.3d 1095, 1118 (D.C. Cir. 2009).

181. Plaintiffs suffered injuries detailed above, entitling them to treble damages under 18 U.S.C. § 1964(c).

182. Defendant violated 18 U.S.C. § 1962(d), entitling Plaintiffs to treble damages under 18 U.S.C. § 1964(c).

VI. CONCLUSION

183. For over twenty-five years, the AAP has told parents, physicians, and policymakers that the childhood vaccine schedule is safe, even though no one had ever studied whether vaccines created a net benefit or harm to children. The AAP's sleight-of-hand was to pass-off the *apparatus* of data collection as *proof* of safety. The fraud is that it looked like science: VAERS sounds like surveillance, but is a passive, woefully under-reporting system that was never designed to establish causation. The VSD sounds like a safety monitoring system, but it is just a giant digital filing cabinet.

184. When the IOM twice told the CDC to analyze the files in the filing cabinet, AAP's deflection sounded like ethics, claiming prospective studies with an unvaccinated control group would be unethical, even though the IOM specifically rejected such studies in favor of analysis of existing records. And AAP dismissed as methodologically flawed every study that found unvaccinated children healthier. The strategy was to mischaracterize unanalyzed safety systems as proof of the safety of the vaccine schedule, to sell more vaccines.

185. The AAP's January 2026 conduct strips away any remaining pretense. AAP calls reducing the CDC schedule down to eleven vaccines "dangerous" — one more than California and Massachusetts require. The inconsistency is dispositive. AAP's position is about control and revenue, not childhood safety.

186. AAP claims that recent federal changes to vaccine schedule policy endanger children. The real threat is to member revenue. AAP is presenting these concerns to a

Massachusetts federal court, where they should be recognized for what they are: the latest predicate acts in a quarter-century racketeering enterprise.

VII. PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that upon trial of this action, the Court enter judgment in their favor and against Defendant, and grant the following relief:

Declaratory Relief: A declaration that no studies have established the safety of the entire childhood immunization schedule; that the specific representations and omissions detailed in Section I of this Complaint are materially false and misleading; and that Defendant's broader claims (including that the schedule is "fully tested and proven safe," vaccines are categorically "safe and effective," questioning physicians spread "misinformation," and pediatricians "lose money on vaccines") are predicate acts under RICO.

Injunctive Relief: An injunction requiring Defendant to publish corrective statements in vaccine-related publications (e.g., the Red Book and HealthyChildren.org) disclosing the lack of comprehensive safety testing and insurer incentive programs, and prohibiting further unqualified safety claims without such disclosures.

Damages: Treble damages under 18 U.S.C. § 1964(c) for economic injuries to business or property suffered by Plaintiffs Shaw, Nelson, Doe, Thomas, and Stoller.

Attorneys' Fees and Costs: An award of reasonable attorneys' fees, expert fees, and costs pursuant to 18 U.S.C. § 1964(c), and such other and further relief as the Court deems just and proper.

Dated January 21, 2026

Respectfully submitted,
/s/ Richard Jaffe

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EXHIBIT C

Immunization Safety Review: Multiple Immunizations and Immune Dysfunction

Kathleen Stratton, Christopher B. Wilson and Marie C. McCormick, Editors, Immunization Safety Review Committee, Board on Health Promotion and Disease Prevention

ISBN: 0-309-50866-5, 152 pages, 6 x 9, (2002)

Immunization Safety Review

Multiple Immunizations and Immune Dysfunction

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Knowing is not enough; we must apply.
Willing is not enough; we must do.

—Goethe

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This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the NRC's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

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Ann Bostrom, Ph.D., Georgia Institute of Technology
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Claire-Anne Siegrist, Ph.D., University of Geneva
Brian Ward, M.D., McGill University

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by **Robert Lawrence**, Johns Hopkins Bloomberg School of Public Health, and **Floyd Bloom**, The Scripps Research Institute. Appointed by the National Research Council and Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Foreword

Vaccines are among the greatest public health accomplishments of the past century. In recent years, however, a number of concerns have been raised about the safety of, and need for, certain immunizations. Indeed, immunization safety is a contentious area of public health policy, with discourse around it having become increasingly polarized and exceedingly difficult. The numerous controversies and allegations surrounding immunization safety signify an erosion of public trust in those responsible for vaccine research, development, licensure, schedules, and policy-making. Because vaccines are so widely used—and because state laws require that children be vaccinated to enter daycare and school, in part to protect others—immunization safety concerns should be vigorously pursued in order to restore this trust.

It is in this context that the Institute of Medicine (IOM) was approached more than a year ago by the Centers for Disease Control and Prevention and the National Institutes of Health to convene an independent committee that could provide timely and objective assistance to the Department of Health and Human Services in reviewing emerging immunization-safety concerns.

The IOM was chartered by the National Academy of Sciences in 1970 to serve as an adviser to the federal government on issues affecting the public's health, as well as to act independently in identifying important issues of medical care, research, and education. The IOM thus brings to this mission three decades of experience in conducting independent analyses of significant public health policy issues. In particular, as described in more detail in this report, the IOM has a long history of involvement in vaccine safety. The IOM published its first

major vaccine-safety report in 1977, followed by a subsequent report in 1988; both focused on the safety of polio vaccines. Two subsequent major reports, published in 1991 and 1994, examined the adverse events of childhood vaccines. Since then, the IOM has conducted several smaller studies and workshops focused on various vaccine-safety topics. These studies were all well received by both the public and policy makers, and previous IOM committees on vaccine safety issues have been viewed as objective and credible.

Given the sensitive nature of the present immunization safety review study, the IOM felt it was especially critical to establish strict criteria for committee membership. These criteria prevented participation by anyone with financial ties to vaccine manufacturers or their parent companies, previous service on major vaccine-advisory committees, or prior expert testimony or publications on issues of vaccine safety.

The rationale for imposing these stringent criteria was twofold. First, given growing public concern about vaccine safety and the public scrutiny surrounding this committee's work, it was important to establish standards that would preclude any real or perceived conflict of interest or bias on the part of the committee members. While the committee members all share a belief in the benefits of vaccines to the public health, none of them has any vested interest in any of the vaccine safety issues that will come before them. Second, the IOM wanted to ensure consistency in the committee membership and avoid having members recuse themselves from the deliberations because they had participated in the development or evaluation of a vaccine under study.

Thus, the IOM has convened a distinguished panel of 15 members who possess significant breadth and depth of expertise in a number of fields, including pediatrics, neurology, immunology, internal medicine, infectious diseases, genetics, epidemiology, biostatistics, risk perception and communication, decision analysis, public health, nursing, and ethics. The committee members were chosen because they are leading authorities in their respective fields, are well respected by their colleagues, and have no conflicts of interest. This committee brought a fresh perspective to these critically important issues and approached its charge with impartiality and scientific rigor.

The IOM does not propose the use of the criteria it has laid out above in selecting members for federal vaccine advisory committees. The IOM committee was convened for a very different purpose from the usual federal vaccine advisory committees and, as such, required different standards.

As with all reports from the IOM, the committee's work was reviewed by an independent panel of experts. The purpose of the review process is to enhance the clarity, cogency, and accuracy of the final report and to ensure that the authors and the IOM are creditably represented by the report published in their names. The report review process is overseen by the National Research Council's (NRC) Report Review Committee (RRC), comprised of approximately 30 members of the National Academy of Sciences, National Academy of Engineer-

ing, and IOM. The IOM, in conjunction with the RRC, appoints a panel of reviewers with a diverse set of perspectives on key issues considered in the report. Unlike the selection criteria for committee membership (discussed above), many reviewers will have strong opinions and biases about the report topic. The composition of the review panel is not disclosed to the committee until after the report is approved for release. While the committee must consider and evaluate all comments from reviewers, it is not obligated to change its report in response to the reviewers' comments. The committee must, however, justify its responses to the reviewers' comments to the satisfaction of the RRC's review monitor and the IOM's review coordinator. A report may not be released to the sponsors or the public, nor may its findings be disclosed, until after the review process has been satisfactorily completed and all authors have approved the revised draft.

This report represents the unanimous conclusions and recommendations of that dedicated committee whose members deliberated a critical health issue. The report's conclusions and recommendations should be of value to all concerned about these important matters.

Kenneth I. Shine
President, Institute of Medicine

Acknowledgments

The committee would like to acknowledge the many speakers and attendees at its open meeting held on November 12, 2001, in Seattle. The discussions were informative and helpful. The committee would also like to thank those people who submitted information to the committee through the mail or e-mail. Finally, the committee would like to thank the IOM staff for their dedication to this project. Without their commitment, attention to detail, creativity, sensitivity, and hard work, this project would be unworkable.

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Executive Summary

ABSTRACT

By two years of age, healthy infants in the United States can receive up to 20 vaccinations to protect against 11 diseases. Although most people know that vaccines effectively protect against serious infectious diseases, approximately one-quarter of parents in a recent survey believe that infants get more vaccines than are good for them, and that too many immunizations could overwhelm an infant's immune system. The Immunization Safety Review Committee reviewed the evidence regarding the hypothesis that multiple immunizations increase the risk for immune dysfunction. Specifically, the committee looked at evidence of potential biological mechanisms and at epidemiological evidence for or against causality related to risk for infections, the autoimmune disease type 1 diabetes, and allergic disorders.

There are reasonable theories for how vaccines could cause these effects. However, for allergic disease and type 1 diabetes, the evidence from animal and clinical studies is weak that relevant biological mechanisms operate in humans after receipt of vaccines. The biological mechanisms evidence regarding increased risk for infections is strong. However, the committee found that the epidemiological evidence (i.e., from studies of vaccine-exposed populations and their control groups) favors rejection of a causal relationship between multiple immunizations and increased risk for infections and for type 1 diabetes. The epidemiological evidence regarding risk for allergic disease, particularly asthma, was inadequate to accept or reject a causal relationship.

These immune disorders carry heavy individual and societal burdens, and serious vaccine-preventable disease could increase if parents unnecessarily avoid immunizing their children due to continuing concerns about this issue.

Because vaccines are given to healthy children to protect others in addition to themselves, it is important to understand fully the possible risks of serious adverse consequences of vaccines. Therefore, the committee recommends continued attention in the form of policy analysis, research, and communication strategy development. However, the committee does not recommend a review by national and federal vaccine-related advisory bodies of the licensure or schedule of administration of the vaccines administered to infants in the United States on the basis of concerns about immune dysfunction. See Box ES-1 for a summary of all conclusions and recommendations.

Immunization to protect infants and children from vaccine-preventable diseases is one of the greatest achievements of public health. Immunization is not without risks, however. It is well established, for example, that the oral polio vaccine can on rare occasion cause paralytic polio.

The Immunization Safety Review Committee was established by the Institute of Medicine (IOM) to evaluate the available evidence on a series of immunization safety concerns. While all of the committee members share the view that immunization is generally beneficial, none of them has a vested interest in the specific immunization safety issues that come before the group.

For each hypothesis to be examined, the committee assesses both the scientific evidence and the significance of the issue for society.

> The *scientific* assessment has two components: an examination of the epidemiological and clinical evidence regarding a possible causal relationship between the immunization and the adverse event, and an examination of experimental evidence for any biological mechanism(s) relevant to the hypothesis.
>
> The *significance* assessment addresses such considerations as the burden of the health risks associated with the vaccine-preventable disease and with the adverse event in question, as well as the level of public concern about the safety issue.

In this report, the committee examines the hypothesis that receipt of multiple immunizations adversely affects the developing immune system.

The examination of experimental evidence for biological mechanisms has been referred to in previous reports of this committee (IOM, 2001a, 2001b) and others (IOM, 1991, 1994) as an assessment of "biological plausibility." The committee has noted, however, that the term is a source of confusion on at least two fronts. First, it is associated with a particular set of guidelines (sometimes referred to as the Bradford Hill criteria) for causal inference from epidemiological evidence; and second, readers sometimes regard the term with a degree of certainty or precision the committee never intended. For example, a relationship

between immunization and a particular adverse event may be found to be biologically plausible at the same time that the epidemiological evidence is found to be inadequate to accept or reject a causal relationship.

Given the resulting lack of clarity, the committee believes that the adoption of new terminology and a new approach to its discussions of experimental biological data are warranted. The committee will thus review evidence regarding "biological *mechanisms*" that might be consistent with the proposed relationship between immunization and a given adverse event. This biological assessment section of the report is written distinct from any argument regarding the causality of such relationships.

Beginning with this report, the committee will summarize the biological mechanisms as theoretical only, or as having derived from either experimental evidence in animals or *in vitro* systems or from mechanism-related, biological evidence in humans of response to vaccine or infectious disease antigen. If there is either experimental evidence (e.g., from animals) or evidence in humans for a mechanism, the committee will designate it as weak, moderate, or strong. Though the committee tends to judge biological evidence in humans to be "stronger" than experimental evidence, the strength of the evidence also depends on other factors, such as experimental design and sample size. The conclusions drawn from this review will depend both on evidence and scientific judgment.

UNDER REVIEW

Over the past two decades, the pediatric immunization schedule has grown more complicated. In 1980, infants received immunizations against four diseases (diphtheria, tetanus, pertussis, and polio). Today, a healthy infant immunized in complete accord with the recommended childhood immunization schedule receives up to 15 doses of five vaccines to protect against seven diseases by 6 months of age and up to 20 doses of seven vaccines to protect against 11 diseases by 2 years of age. According to a recent survey, a substantial minority of parents (23–25%) believes that getting too many immunizations weakens a child's immune system and that children get more immunizations than are good for them (Gellin et al., 2000).

The Immunization Safety Review Committee was asked to address the hypothesis that multiple immunizations can adversely affect the developing immune system. One particular concern, for example, is related to increases in the incidence of diseases such as asthma and type 1 diabetes—conditions associated with immune system dysfunctions. Although genetic factors are known to affect the risk of these diseases, increases in their incidence seem more likely to reflect changes in environmental exposures than in the genetic makeup of a population. Immunization has been proposed as one possible adverse environmental modifier of immune function.

To conduct its review, the committee had to establish a clear statement of the question before it, as well as a manageable scope of inquiry. The committee focused on exposure to multiple immunizations during infancy (less than two years of age), a period of active immune system development. The committee included studies of "one vaccine" if it contained antigens against more than one disease or more than one strain of infectious agent. For example, the diphtheria and tetanus toxoids and pertussis vaccine would be considered to represent "multiple immunization." The committee restricted its considerations regarding causality to those vaccines used in the United States.

Because immune system dysfunction is a broad term—adverse outcomes can result from stimulation of harmful immune responses or suppression of beneficial immune responses—the committee had to define it for the purposes of this study. The scope of the committee's inquiry can be summarized in the following three questions:

1. Do multiple immunizations have adverse short-term effects on the developing infant immune system that are reflected in increased susceptibility to heterologous infection (infections other than those targeted by the immunization)?
2. Does exposure to multiple antigens, as administered in vaccines, directly and permanently redirect or skew the immune system toward autoimmunity, as reflected in type 1 diabetes?
3. Does exposure to multiple antigens, as administered in vaccines, directly and permanently redirect or skew the immune system toward allergy, as reflected in asthma?

The committee was unable to address the concern that repeated exposure of a susceptible child to multiple immunizations over the developmental period may also produce atypical or non-specific immune or nervous system injury that could lead to severe disability or death (Fisher, 2001). There are no epidemiological studies that address this. Thus, the committee recognizes with some discomfort that this report addresses only part of the overall set of concerns of some of those most wary about the safety of childhood immunization.

The committee collected information from several sources. At an open scientific meeting in November 2001 (see Appendix C), academic researchers gave presentations on specific scientific issues germane to the topic. All information presented to the committee at that meeting can be viewed on the project website (www.iom.edu/imsafety). In addition, an extensive review was performed of the published, peer-reviewed scientific and medical literature. (see Appendix D).

Autoimmune Diseases

Collectively, diseases of autoimmunity affect 3 to 5 percent of the population in the United States (Jacobson et al., 1997). Autoimmune diseases are mediated by T cell and/or T cell-dependent B cell responses directed against self-

antigens, and the T cell responses in most autoimmune diseases are dominated by interferon-_ producing CD4 T cells, commonly referred to as Th1 T cells (Marrack et al., 2001). An autoimmune process can target individual organs, such as the central nervous system in multiple sclerosis, or can operate throughout the body, as in systemic lupus erythematosus. For this report, the committee focused on type 1a diabetes, which is associated with an autoimmune-mediated loss of insulin-secreting pancreatic cells. (Type 1b refers to diabetes associated with a loss of insulin secretion, for reasons unknown. Many epidemiological studies do not distinguish between these two types.) Type 2 diabetes is not associated with destruction of insulin-secreting cells. Type 1 diabetes has been referred to as "childhood" or insulin-dependent diabetes, while type 2 diabetes has been referred to as "adult-onset" diabetes. However, the onset of either form of the disease can occur at any age.

Worldwide, estimates of the incidence of type 1 diabetes in children under 14 years of age range from 0.1 per 100,000 in parts of China and Venezuela to 36.8 per 100,000 in Sardinia and 36.5 per 100,000 in Finland (Karvonen et al., 2000). As reported by Karvonen and colleagues (2000), estimated incidence for the early 1990s in the United States locations range from 11.7 per 100,000 in Chicago to 17.8 per 100,000 in Allegheny County, Pennsylvania.

Allergic Diseases

Allergy is responsible for a variety of acute and chronic health problems, including anaphylaxis, rhinitis, asthma, and allergic eczema. These conditions reflect an overreaction of the immune system to allergens—normally harmless environmental agents such as pollens, dust mites, insect venom, and certain foods. Under certain circumstances, exposure to an allergen primes the immune system for hypersensitivity reactions involving allergen-specific IgE antibodies and Th2 cells.

The committee focused on allergic asthma. Characteristic symptoms of asthma are episodes of shortness of breath, coughing, wheezing, and chest tightness. These symptoms reflect an acute bronchial hyperresponsiveness to specific allergens and other environmental factors, and a chronic inflammation of the airways (IOM, 2000; Parham, 2000).

The prevalence of asthma has increased in the United States and other countries over the past 30 years (Grant et al., 1999). An international study of asthma in children found that prevalence was higher in more developed countries (Asher and Weiland, 1998). In the United States, the prevalence rates of self-reported asthma rose from 3.1 percent in 1980 to 5.4 percent in 1994, an increase of 74 percent (Mannino et al., 1998). For children aged 0 to 4 years, rates increased by 159 percent during this period (from 2.2 percent to 5.7 percent). Increases in asthma prevalence were seen in all race, sex, age, and regional groups in the United States.

Antigen Load

Central to the concerns about multiple childhood immunizations is whether the recommended schedule overloads an infant's immune system. That is, are there quantitative or qualitative aspects of the antigens to which an infant is exposed through immunization that lead to an inability of the developing immune system to respond appropriately?

Calculations reviewed by the committee (Kollman, 2001; Offit et al., 2002) suggest that the number of antigens contained in the complete set of vaccines that comprise the recommended childhood immunization schedule has actually decreased over the past 20 to 30 years, despite the increased number of vaccines and vaccine doses administered. The removal from the schedule of two vaccines, smallpox and the whole cell pertussis vaccine, accounts for this decrease. Routine use of the smallpox vaccine, which contained approximately 200 distinct and potentially antigenic elements, was discontinued in the United States in 1971. The whole-cell pertussis vaccine was replaced by an acellular vaccine, the first of which was approved by the FDA in 1991. The whole-cell vaccine contained approximately 3,000 distinct and potentially antigenic components, whereas the acellular vaccine contains only 2–5 antigens.

Vaccines added to the immunization schedule over the past 20 years have relatively few antigens. For example, the hepatitis B vaccine contains only one antigen. Therefore, the decrease in vaccine antigens from the removal of smallpox and whole cell pertussis vaccines far exceeds the increase of antigens from the addition of newer vaccines added to the schedule.

Another question is whether infants are capable of responding adequately to the antigens presented by immunization. Although the numbers of different T cell receptors present in human neonates has not been determined directly, their diversity has been shown by several groups to be similar to that of the adults. This is the basis for the notion that human infants have the capacity to respond to the substantial number of foreign molecules (e.g., bacterial antigens) to which they are exposed shortly after birth. This is consistent with the theoretical estimates presented to the committee, which suggest that the capacity of the infant's immune system is at least 1000 times greater than that maximally required to respond to vaccines (Kollman, 2001; Offit et al., 2002).

Over the course of several decades, the antigen load presented to the developing immune system has undergone significant qualitative changes, particularly in the context of the total antigen exposures during infancy and childhood. Approximately a decade ago, researchers interested in the changing epidemiology of several diseases began formulating the "hygiene hypothesis." This hypothesis suggests that the increasingly aseptic environment in which children in developed countries live has led to changes in the development of the immune system, causing an increase in allergic disease (Rook, 2000; Strachan, 2000; Wills-Karp et al., 2001). In keeping with the hygiene hypothesis, factors that

decrease the risk for allergy include the presence of pets, infections through the fecal-oral route, and rural living.

The proposed explanation for an immune system role in these epidemiological observations is that early exposure to infectious diseases and environmental microbes "shapes" the developing immune system toward a Th1[1] cell responsiveness, which is generally considered a protective immune response (i.e., to host defense against intracellular pathogens and allergy). Eliminating these early exposures through hygienic practices and altered behaviors is thought to predispose the immune system toward a Th2[2] cell responsiveness, which is associated with allergy.

The most recent refinement of the hygiene hypothesis includes regulatory cell imbalance (Rook, 2001; Wills-Karp et al., 2001). This Th2-skewing or regulatory cell imbalance, some theorize, is exacerbated by exposure to vaccines, many of which evoke a Th2 response instead of the Th1 response that would be generated by wild-type infections with the diseases that the immunizations prevent.

Not yet clear is the role vaccines may have in directly altering the development of the immune system, or the relative contribution of immunization-related changes in the context of the hygiene hypothesis. Vaccine-induced immune responses may differ from those resulting from wild-type infection because of differences in context, including differences in their timing, either in terms of age at exposure or of the sequence of antigen exposure. Most certainly, the route of exposures—that is, an injection rather than a respiratory or gastrointestinal exposure—is different from what it had been. Under debate is whether that difference in exposure is associated with adverse health outcomes.

In any case, the number of infections prevented by immunization is actually quite small compared with the total number of infections prevented by other hygienic interventions such as clean water, food, and living conditions.

SCIENTIFIC ASSESSMENT

Causality

Heterologous Infection

The committee reviewed several case-control or cohort studies (Black et al., 1991; Burstein and Fleisher, 1994; Davidson, 1991; Griffin et al., 1992; Kristensen et al., 2000) and a randomized controlled trial (Otto et al., 2000). Vaccine

[1] Th1 (h stands for helper) cells travel to the site of infection and secrete cytokines that mainly activate macrophages. Upon activation, macrophages will phagocytose extracellular pathogens and then kill them.

[2] The primary function of Th2 cells is to stimulate B cells to make antibodies which bind to extracellular bacteria and virus particles. Th2 cells work within secondary lymphoid tissue.

exposure varied among the studies but fit the committee's definition of exposure to "multiple immunizations." The studies examined the effects of adding one vaccine to an existing immunization schedule, of one vaccine dose consisting of antigens from more than one infectious agent or strain of virus (e.g., DTP, OPV, or MMR), or of several vaccines received at the same time. Outcome measures in the studies also varied, with the "disease" group including subjects who had a positive culture to invasive bacterial disease, who had symptoms related to infectious diseases, or who had died. Limitations of the studies included a potential health care utilization bias and high dropout rates. Despite these variations and limitations, the overall findings from the studies consistently demonstrated either no effect or a beneficial effect of multiple immunizations on heterologous disease. **Therefore, the committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of heterologous infections.**

Type 1 Diabetes

The committee found five controlled studies (Blom et al., 1991; DeStefano et al., 2001; EURODIAB, 2000; Heijbel et al., 1997; Karvonen et al., 1999) and three ecological studies (Classen, 1996; Hiltunen et al., 1999; Hyoty et al., 1993) that examined this relationship. The studies looked at the effects of adding one vaccine to an existing immunization schedule, of one vaccine dose consisting of antigens from more than one infectious agent or strain of virus (e.g., DTP, OPV, or MMR), or of several vaccines received at the same time. Despite these variations, the overall findings from the studies consistently demonstrated no effect of multiple immunizations on the incidence of type 1a diabetes. **Therefore, the committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of type 1 diabetes.**

Allergic Disease

The committee reviewed five studies that utilized controls (Farooqi and Hopkin, 1998; Hurwitz and Morgenstern, 2000; Kemp et al., 1997; Wickens et al., 2001), including a randomized controlled trial (Nilsson et al., 1998) and one ecological study (Anderson et al., 2001). Outcomes assessed included allergic symptoms (wheezing) and allergic disorders (hay fever and asthma). All the studies examined exposure to DTaP or DTwP, and other vaccines given concurrently, such as MMR and polio vaccines, but no two studies examined exactly the same exposure.

While many of these studies reported elevated odds ratios linking immunizations to some allergic outcome, some of which were statistically significant, methodological weaknesses within individual studies, as well as the pattern of

results across studies diminish the confidence that the observed associations reflect causal relationships. In the two studies that reported a significant positive effect of DTP or tetanus immunization or the pertussis component of DTwP (Farooqi and Hopkin, 1998; Hurwitz and Morgenstern, 2000), potential sampling bias, caused by substantial losses to follow-up or restriction to subjects with regular medical care, could have distorted the relationship between immunization and allergies.

A problem in most of the studies was that the number of unvaccinated children was small, limiting the ability to control for potentially confounding factors, which are numerous and strong for the outcomes of asthma and atopy, and particularly complex when considering risk over an entire childhood. Adequate control of confounding is a serious issue for observational designs, particularly in this domain, as nonimmunized children typically differ on baseline characteristics from immunized children in ways that are not always measurable.

Finally, the findings of the studies, taken as a whole, did not show a consistency of findings that would outweigh the concerns about individual studies. While some studies pointed to the pertussis vaccine as a risk factor for allergic syndromes with no effect of MMR, another found that MMR vaccine was the strongest risk factor. The ecological study indicated a protective DPT effect, and the only randomized study indicated minimal or no effect of pertussis vaccines, with a non-significant reduction in risk from the whole-cell vaccine.

Given the design weaknesses in the observational studies, and a randomized trial study that does not support the risk factor most frequently implicated in the observational studies, **the committee concludes that the epidemiological and clinical evidence is inadequate to accept or reject a causal relationship between multiple immunizations and an increased risk of allergic disease, particularly asthma.**

Biological Mechanisms

Although biological data do not provide an independent basis for evaluating causality, they can help validate epidemiologically based conclusions for or against causal associations; such data can also guide further investigation when epidemiological evidence is inconclusive. The mechanisms considered by the committee represent two possible pathways to adverse outcomes: stimulation of harmful immune responses, or suppression of beneficial immune responses. The stimulation of harmful immune responses involves the mechanisms of molecular mimicry,[3] bystander activation, [4] and nonspecific or polyclonal T-cell and/or B-

[3] Molecular mimicry is the antigenic similarity between a pathogen antigen and a cellular antigen which results in the induction of antibodies or T cells that act against the pathogen but also cross-react with the self antigen (Parham, 2000).

cell activation. The suppression of beneficial immune responses is addressed in terms of the hygiene hypothesis and the prevention of potentially protective infections through immunization.

In theory, molecular mimicry, bystander activation, and impaired immunoregulatory mechanisms might act in an additive or synergistic manner to affect the risk of autoimmunity. There is, however, no experimental evidence for molecular mimicry by any of the vaccines in the current routine childhood immunization schedule to create an antigenic epitope[5] capable of cross-reaction with self epitopes. **Therefore, in the absence of experimental or human evidence regarding molecular mimicry or mercury-induced modification of any vaccine component to create an antigenic epitope capable of cross-reaction with self epitopes as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that these mechanisms are only theoretical.**

There is some evidence of a bystander effect associated with immunization, but this effect is 1) relatively modest compared to those resulting from wild-type infection, 2) most evident to co-administered vaccine antigens rather than other environmental antigens or infections and 3) inconsistently shown. Current vaccines have, on balance, weak or no Th1-inducing activities. BCG appears to demonstrate the principle for co-administered antigens. However, BCG is not used in the U.S., so the relevance for this mechanism in the effects of the U.S. recommended schedule is not demonstrated. Viral vaccines carry some potential for bystander activation, but likely would have a small effect, if it occurs at all. The data on DTaP vaccine indicates that Th1 dominance is not prominent. There is also no evidence in humans that vaccine antigens lead to the pathophysiological disease state. The limited evidence from humans that does exist regards surrogates of the disease process, that is, just some components of the events that would need to take place for the appearance of clinically relevant pathophysiology. **Thus, the committee concludes that there is weak evidence for bystander activation, alone or in concert with molecular mimicry, as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity.**

In the absence of experimental or human evidence regarding loss of protection against a homologous infection as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that

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[4] Bystander activation results when an infection creates environmental conditions that allow the activation of self-reactive T and B cells that are normally held in check. It does not require that antigens of the infectious agent be structurally similar to self-antigens.

[5] An epitope is a molecule's specific antigenic site that is bound by an antibody.

this mechanism is only theoretical. On balance, the current recommended childhood immunization schedule in the United States appears less likely to act as an initiator or facilitator of autoimmunity than the schedule of the past.

On a numerical basis, vaccine-preventable infections represent a minute fraction of the overall infectious and microbial exposure in childhood. For immunization to have an impact on autoimmunity under the hygiene hypothesis, it would be necessary for one or more vaccine-preventable diseases to be particularly important for conditioning immunoregulatory immune responses. The gastrointestinal tract is thought to play a particularly critical role in this process, so it would follow that immunizations that affect infection or colonization of the gut would be good candidates, but none of the childhood vaccines currently in use do so. Data from animal models suggest that no one infection is likely to be key, but rather a global reduction in microbial contact could be a factor.

The theory by which the hygiene hypothesis, originally proposed on the basis of epidemiological data, could explain an increase in incidence of autoimmune (or allergic) disease is substantial, and the biological evidence in support of the hygiene hypothesis is moderate. However, the potential contribution of vaccine-preventable diseases as part of this model is minimal. **Therefore, in the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that this mechanism is only theoretical.**

Considering molecular mimicry, bystander activation, and impaired immunoregulation collectively rather than individually, the committee concludes that there is weak evidence for these mechanisms as means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity.

The biological mechanisms by which immunizations that contain microbial stimuli favor Th1 responses and immunizations containing alum favor Th2 responses are well established. Although the impact of immunization on heterologous allergic responses is unknown, on balance the current routine childhood immunization schedule in the United States is less likely to favor Th1 responses to heterologous antigens and more likely to favor Th2 responses. **The committee concludes that there is weak evidence for bystander activation as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.**

The theory by which the hygiene hypothesis could explain an increase in incidence of allergic diseases is substantial. However, the potential contribution of vaccine-preventable diseases as part of this hypothesis is minimal. **In the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an indi-**

vidual's risk of allergy, the committee concludes that this mechanism is only theoretical. The committee also concludes that there is weak evidence for the existence of any biological mechanisms, collectively or individually, by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.

The committee concludes that there is strong evidence for the existence of biological mechanisms by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk for heterologous infections.

SIGNIFICANCE ASSESSMENT

The committee's assessment of the significance of concerns about possible immune system dysfunctions took several factors into consideration: the burden of the possible adverse outcomes of autoimmune diseases such as type 1 diabetes and allergic diseases such as asthma; indications of the extent of the concern about multiple immunizations; and views regarding the framework for immunization policy-making.

Although parents appear to value immunization, a substantial minority (23-25%) believes that multiple immunizations could be harmful (Gellin et al., 2000). Autoimmune and allergic diseases are common in the United States, after all, and the incidence of these conditions appears to be increasing. As represented by type 1 diabetes and asthma, these conditions are life-threatening if not adequately treated and are associated with substantial health care costs.

A better understanding of parents' perceptions of risk and decisionmaking may be necessary in order to prevent decreases in immunization rates and increases in vaccine-preventable disease. Current approaches to immunization policy-making emphasize epidemiological and economic considerations, but a recent paper suggests that these policies may benefit from greater attention to ethical issues, including personal liberty and equity in allocation of the benefits and burdens of immunization (Feudtner and Marcuse, 2001). **Thus, the committee concludes that concern about multiple immunizations has been, and could continue to be, of societal significance in terms of parental worries, potential health burdens, and future challenges for immunization policy-making.**

RECOMMENDATIONS REGARDING PUBLIC HEALTH RESPONSE

With government and professional recommendations calling for young children to receive increasing numbers of immunizations, it is important to respond to concerns about possible increases in risk of allergic or autoimmune diseases. Although the committee's review points to no causal relationship between multiple immunizations and type 1 diabetes or risk of infection, and the

review is inconclusive for asthma, the biological evidence does provide weak support for increased risk of allergy and autoimmunity and strong support for increased risk of infection (see Table ES-1 for summary). Further study of such associations poses difficult scientific challenges, and relevant epidemiological evidence remains limited. Several important scientific and policy issues, therefore, deserve further public health attention.

Policy Review

The nature of the childhood immunization schedule is likely to change in response to such factors as the development of new vaccines and utilization of novel delivery systems. Changing perceptions of disease risks—derived from antibiotic resistance, threats of bioterrorism, or (re)emerging infectious diseases—could also lead to wider use of existing vaccines not currently included in the immunization schedule. As the array of available vaccines and disease targets expands the current emphasis on universal recommendations and state mandates for vaccine use should be reassessed (Feudtner and Marcuse, 2001). **The committee recommends that state and federal vaccine policymakers consider a broader and more explicit strategy for developing recommendations for the use of vaccines.**

Feudtner and Marcuse (2001) have provided a beginning for such discussion by urging consideration of a range of perspectives (e.g., those of individuals, families, organizations, society) regarding the benefits, risks, and ethical implications of vaccine use and immunization policies. Priorities can be expected to differ among the diverse perspectives, and policymakers must consider how to achieve an equitable balance. These issues require long-term planning and evaluation; a reactive response to the next schedule addition will be much less effective than a proactive assessment and strategy development across-the-board.

As part of this overall effort, the committee encourages an exploration of the merits of accommodating requests for alternative vaccine-dosing schedules and the development of appropriate clinical guidance for any such alternatives. A more flexible schedule might allow for a reduction in the number of vaccines administered at one time. Such a change would respond to some concerns about multiple immunizations; but it would also have disadvantages, such as requiring more health care visits, that might contribute to lower rates of immunization coverage in the population and consequent increases in morbidity and mortality. In addition, such a change would require extensive communication with health-care providers and health plans in order that appropriate immunizations occur and are reimbursed equivalently to those on the “traditional” schedule.

By issuing the recommendation above, the committee does not intend to signal concern about health consequences of the multiple immunizations in the recommended childhood immunization schedule. In fact, **the committee does not recommend a policy review—by the CDC’s Advisory Committee on**

Immunization Practices (ACIP), the American Academy of Pediatrics' Committee on Infectious Diseases, and the American Academy of Family Physicians—of the current recommended childhood immunization schedule on the basis of concerns about immune system dysfunction.

The committee does not recommend a policy review by the Food and Drug Administration's Vaccines and Related Biologic Products Advisory Committee of any currently licensed vaccines on the basis of concerns about immune system dysfunction.

Research

The committee concluded that the findings available from epidemiological sources and consideration of possible biological mechanisms do not at this time warrant specialized studies of possible associations between multiple immunizations and immune system dysfunction. Instead, the committee encourages epidemiological studies on immunization safety conducted within the framework of ongoing research and surveillance programs on allergy, autoimmune disease, and vaccine safety; it also encourages additional basic research on the immune system and on allergy and autoimmune diseases.

The committee emphasizes the need for continuing surveillance of vaccine recipients and possible adverse events. Changes in the immunization schedule may present opportunities to study whether or not the incidence of adverse health outcomes also changes. Several vaccine-related data resources already exist, including the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), and state and local immunization registries. **The committee recommends exploring the feasibility of using existing vaccine surveillance systems, alone or in combination, to study safety questions related to asthma and other important allergic disorders, as well as to study type 1 diabetes and other important autoimmune diseases.** An important component of such research will be the use of uniform standards of observation and evaluation.

In addition, surveillance of autoimmune diseases and allergic disorders should be strengthened. Disease registries and long-term research programs that identify individuals with these diseases, or with known genetic risk factors, could be an efficient means of finding subjects for either retrospective or prospective studies of possible vaccine-related risks. **The committee recommends exploring the use of such cohorts for research on possible vaccine-related disease risks. Furthermore, the committee recommends that disease registries and research programs for autoimmune and allergic disorders routinely collect immunization histories as part of their study protocols.**

Research on the developing human immune system, especially in relation to vaccines, is limited. Studies of animal models are essential to advancing knowledge of the immune system, but those studies have limits because of important

differences between humans and animals. Thus, **the committee recommends continued research on the development of the human infant immune system.**

Genetic factors are known to be an important source of variability in the responses of the human immune system and in the risk of allergic or autoimmune disease. But understanding of the complex interactions among genetic variables, as well as of the interactions between those variables and environmental exposures (including vaccines and wild-type viral and bacterial agents), remains incomplete. **The committee endorses current research efforts aimed at identifying genetic variability in human immune system development and immune system responsiveness as a way to gain a better understanding of genetic susceptibility to vaccine-based adverse events.**

For some autoimmune and allergic disorders, surrogate biological markers of disease or disease risk have been identified. In particular, in individuals at risk for type I diabetes, the development of multiple autoantibodies to GAD65 (glutamic acid decarboxylase), IA-2 (protein tyrosine phosphatase-like molecule), and insulin correlate strongly with later development of overt type I diabetes (Notkins and Lernmark, 2001). However, there are to date no other surrogate markers that have sufficient predictive power to be useful in monitoring risk for other autoimmune diseases in children receiving routine immunizations (Leslie et al., 2001). For allergic disorders, the clinical history of allergic diseases should be collected in follow-up evaluations, and the feasibility of specific tests for atopy considered. In theory, collecting data on known markers in the course of vaccine research and testing would present an opportunity to study the prevalence of such markers before and after vaccination. Similarly, it might also be possible to study whether the prior presence of a marker was associated with differences in the response to a vaccine. **The committee recommends exploring the feasibility of collecting data on surrogate markers for type I diabetes and clinical history of allergic diseases in the vaccine testing and licensing process.** Such might also be useful in vaccine-related studies in high-risk cohorts. **The committee recommends exploring surrogates for type I diabetes and clinical history of allergic diseases in existing cohort studies of variations in the immunization schedule.**

Communication

Along with the increasingly complicated immunization schedule has come a dramatic increase in the complexity of immunization safety issues, and it appears that some people have redefined their conceptions of the related risks and benefits. The focus seems to have shifted from whether children will get a disease if they are not vaccinated to whether children will experience temporary or potentially longer-term adverse events if they *are* vaccinated (McPhilips and Marcuse, 2001).

The committee is not convinced, however, that available reports on such attitudes provide an adequate scientific basis for understanding either these

changes in perception or the groups that are experiencing them. More information is needed in order to develop effective risk-benefit communication strategies on immunization and immunization safety.

A deeper understanding of why and how people make decisions as they do is needed, but relying on impressions, assumptions, or any single research method (e.g., survey, focus group, mental modeling, decision analysis) will be too limited. Therefore, **the committee recommends that an appropriate panel of multidisciplinary experts be convened by the Department of Health and Human Services. It would develop a comprehensive research strategy for knowledge leading to the optimal design and evaluation of vaccine risk-benefit communication approaches.**

SUMMARY

A review of the possible biological mechanisms for any adverse effects of multiple immunization on immune function does not support the hypothesis that the infant immune system is inherently incapable of handling the numbers of antigens presented during routine immunization.

A review of the clinical and epidemiological literature suggests that multiple immunizations do not lead to risk of infection or type 1 diabetes, and that the possible role in the risk of allergy is indeterminate. Meanwhile, the biological evidence that immunization might lead to infection, autoimmune disease, or allergy is more than only theoretical. This literature base is somewhat limited, however, and the concern is great among a significant minority of parents.

Therefore the committee recommends limited but continued public health attention to this issue in terms of exploiting current research efforts. No recommendations for policy change are made, but the committee does recommend considering new frameworks for immunization policy, particularly as the number of licensed vaccines increases.

TABLE ES-1 Biological Mechanisms for the Possible Role of Immunizations in Increasing the Risk of Immune Dysfunction

Adverse Health Outcome	Mechanism	Committee Conclusion About the Weight of the Biological Evidence
Autoimmune disease	Molecular mimicry	Theoretical only
	Bystander effect	Weak
	Loss of protection induced by homologous infection	Theoretical only
	Via the hygiene hypothesis	Theoretical only
	Collective mechanistic possibilities	Weak
Allergic disease	Bystander effect	Weak
	Via the hygiene hypothesis	Theoretical only
	Collective mechanistic possibilities	Weak
Heterologous Infections	Carrier-induced epitope suppression	Strong
	Competition for antigen presentation	

BOX ES-1 Committee Conclusions and Recommendations

SCIENTIFIC ASSESSMENT

Causality Conclusions

The committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of heterologous infections.

The committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of type 1 diabetes.

The committee concludes that the epidemiological and clinical evidence is inadequate to accept or reject a causal relationship between multiple immunizations and an increased risk of allergic disease, particularly asthma.

Biological Mechanisms Conclusions

Autoimmune Disease

In the absence of experimental or human evidence regarding molecular mimicry or mercury-induced modification of any vaccine component to create an antigenic epitope capable of cross-reaction with self epitopes as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that these mechanisms are only theoretical.

The committee concludes that there is weak evidence for bystander activation, alone or in concert with molecular mimicry, as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity.

In the absence of experimental or human evidence regarding loss of protection against a homologous infection as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that this mechanism is only theoretical.

In the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that this mechanism is only theoretical.

Considering molecular mimicry, bystander activation, and impaired immunoregulation collectively rather than individually, the committee concludes that there is weak evidence for these mechanisms as means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity.

Allergic Disease

The committee concludes that there is weak evidence for bystander activation as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.

In the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy, the committee concludes that this mechanism is only theoretical.

The committee concludes that there is weak evidence for the existence of any biological mechanisms, collectively or individually, by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.

Heterologous Infection

The committee concludes that there is strong evidence for the existence of biological mechanisms by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk for heterologous infections.

SIGNIFICANCE ASSESSMENT

Conclusions

The committee concludes that concern about multiple immunizations has been, and could continue to be, of societal significance in terms of parental worries, potential health burdens, and future challenges for immunization policy-making.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review

The committee recommends that state and federal vaccine policymakers consider a broader and more explicit strategy for developing recommendations for the use of vaccines.

The committee does not recommend a policy review—by the CDC's Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics' Committee on Infectious Diseases, and the American Academy of Family Physicians—of the current recommended childhood immunization schedule on the basis of concerns about immune system dysfunction.

The committee does not recommend a policy review by the Food and Drug Administration's Vaccines and Related Biologic Products Advisory Committee of any currently licensed vaccines on the basis of concerns about immune system dysfunction.

Research

Epidemiological Research

The committee recommends exploring the feasibility of using existing vaccine surveillance systems, alone or in combination, to study safety questions related to asthma and other important allergic disorders, as well as to study type 1 diabetes and other important autoimmune diseases.

The committee recommends exploring the use of cohorts for research on possible vaccine-related disease risks. Furthermore, the committee recommends that disease registries and research programs for autoimmune and allergic disorders routinely collect immunization histories as part of their study protocol.

Basic Science and Clinical Research

The committee recommends continued research on the development of the human infant immune system.

The committee endorses current research efforts aimed at identifying genetic variability in human immune system development and immune system responsiveness as a way to gain a better understanding of genetic susceptibility to vaccine-based adverse events.

The committee recommends exploring the feasibility of collecting data on surrogate markers for type I diabetes and clinical history of allergic diseases in the vaccine testing and licensing process.

The committee recommends exploring surrogates for type I diabetes and clinical history of allergic diseases in existing cohort studies of variations in the immunization schedule.

Communication

The committee recommends that an appropriate panel of multidisciplinary experts be convened by the Department of Health and Human Services. It would develop a comprehensive research strategy for knowledge leading to the optimal design and evaluation of vaccine risk-benefit communication approaches.

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Immunization Safety Review: Multiple Immunizations and Immune Dysfunction

Immunization to protect infants and children from vaccine-preventable diseases is one of the greatest achievements of public health. Immunization is not without risks, however. It is well established, for example, that the oral polio vaccine can on rare occasion cause paralytic polio, that some influenza vaccines have been associated with a risk of Guillain-Barré syndrome, and that vaccines sometimes produce anaphylactic shock. Thus public concern about the safety of immunizations has increased. A recent survey suggests that a substantial minority of parents (23–25%) believes that getting too many immunizations weakens a child's immune system and that children get more immunizations than are good for them (Gellin et al., 2000). Given the widespread use of vaccines, state mandates requiring vaccination of children for entry into school or day care, and the importance of ensuring that trust in immunization programs is justified, it is essential that safety concerns receive assiduous attention.

The Immunization Safety Review Committee was established by the Institute of Medicine (IOM) to evaluate the evidence on possible causal associations between immunizations and certain adverse outcomes, and to then present conclusions and recommendations. The committee's mandate also includes assessing the broader significance for society of these immunization safety issues. In this report, the committee examines the hypothesis that receipt of multiple immunizations, as recommended by public health authorities, adversely affects the developing immune system.

THE CHARGE TO THE COMMITTEE

Since the mid-1990s, challenges to the safety of immunizations seem to have gained prominence in public and scientific debate. Given these persistent and growing concerns about immunization safety, the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) recognized the need for an independent, expert group to address immunization safety in a timely and objective manner. The IOM has been involved in such issues since the 1970s. (A brief chronology can be found in Appendix A.) In 1999, as a result of IOM's previous work and its access to independent scientific experts, CDC and NIH began a year of discussions with IOM to develop the Immunization Safety Review project to address vaccine safety issues both existing and emerging.

The Immunization Safety Review Committee is responsible for examining a broad variety of immunization safety concerns. Committee members have expertise in pediatrics, neurology, immunology, internal medicine, infectious diseases, genetics, epidemiology, biostatistics, risk perception and communication, decision analysis, public health, nursing, and ethics. While all the committee members share the view that immunization is generally beneficial, none of them has a vested interest in the specific immunization safety issues that come before the group. Additional discussion of the committee composition can be found in the Foreword written by Dr. Kenneth Shine, President of the IOM.

The committee is charged with examining three immunization safety hypotheses each year during the three-year study period (2001–2003). These hypotheses are selected by the Interagency Vaccine Group (IAG)—made up of officials from the National Vaccine Program Office at the Department of Health and Human Services (DHHS), the National Immunization Program and the National Center for Infectious Diseases at the CDC, the National Institute for Allergy and Infectious Diseases at the NIH, the Department of Defense, the Food and Drug Administration (FDA), the National Vaccine Injury Compensation Program at the Health Resources and Services Administration (HRSA), the Centers for Medicare and Medicaid Services (CMS, formerly the Health Care Financing Administration), and the Agency for International Development. For each topic, the committee reviews relevant literature and submissions by interested parties, and holds an open scientific meeting, followed directly by a one- to two-day closed meeting, to formulate its conclusions and recommendations. The committee's findings are released to the public in a brief consensus report 60–90 days after its meeting.

For each hypothesis to be examined, the committee assesses both the scientific evidence and the significance of the issue for society.

The *scientific* assessment has two components: an examination of the epidemiological and clinical evidence regarding a possible causal relationship

between the vaccine and the adverse event, and an examination of experimental evidence for any biological mechanism(s) relevant to the hypothesis.

The *significance* assessment addresses such considerations as the burden of the health risks associated with the vaccine-preventable disease and with the adverse event in question. Other considerations may include the perceived intensity of public or professional concern, or the feasibility of additional research to help resolve scientific uncertainty regarding causal associations.

The findings of the scientific and significance assessments provide the basis for the committee's recommendations on public health response, which includes immunization policy review, current and future research, and effective communication strategies. There are limits to the committee's charge, however. For example, recommending a change in the licensure, scheduling, or administration of a vaccine would exceed the committee's authority. If it concluded that the scientific evidence or other important factors justified such action, it could recommend convening the appropriate advisory group(s) to examine the question. See Figure 1 for a schematic of the committee's charge.

THE STUDY PROCESS

The committee held an initial organizational meeting in January 2001. CDC and NIH presented the committee's charge at the meeting, and the committee conducted a general review of immunization safety concerns and determined its methodology for assessing causality. This approach would be used for the hypotheses to be considered at subsequent meetings. A website (www.iom.edu/imsafety) and a listserv were created to facilitate communication with the committee and provide public access to information about its work. The committee's conclusions and recommendations in the first two reports, *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism* (IOM, 2001a) and *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders* (IOM, 2001b), are summarized in Appendix B.

To evaluate the hypothesis on multiple immunizations and immune system dysfunction, the committee collected information from several sources. At an open scientific meeting in November 2001 (see Appendix C), academic researchers gave presentations on specific scientific issues germane to the topic. All information presented to the committee at that meeting can be viewed on the project Website (www.iom.edu/imsafety). In addition, an extensive review was performed of the published, peer-reviewed scientific and medical literature (see Appendix D). A reference list of material reviewed by the committee, even if not cited in this report, can be found on its website as well.

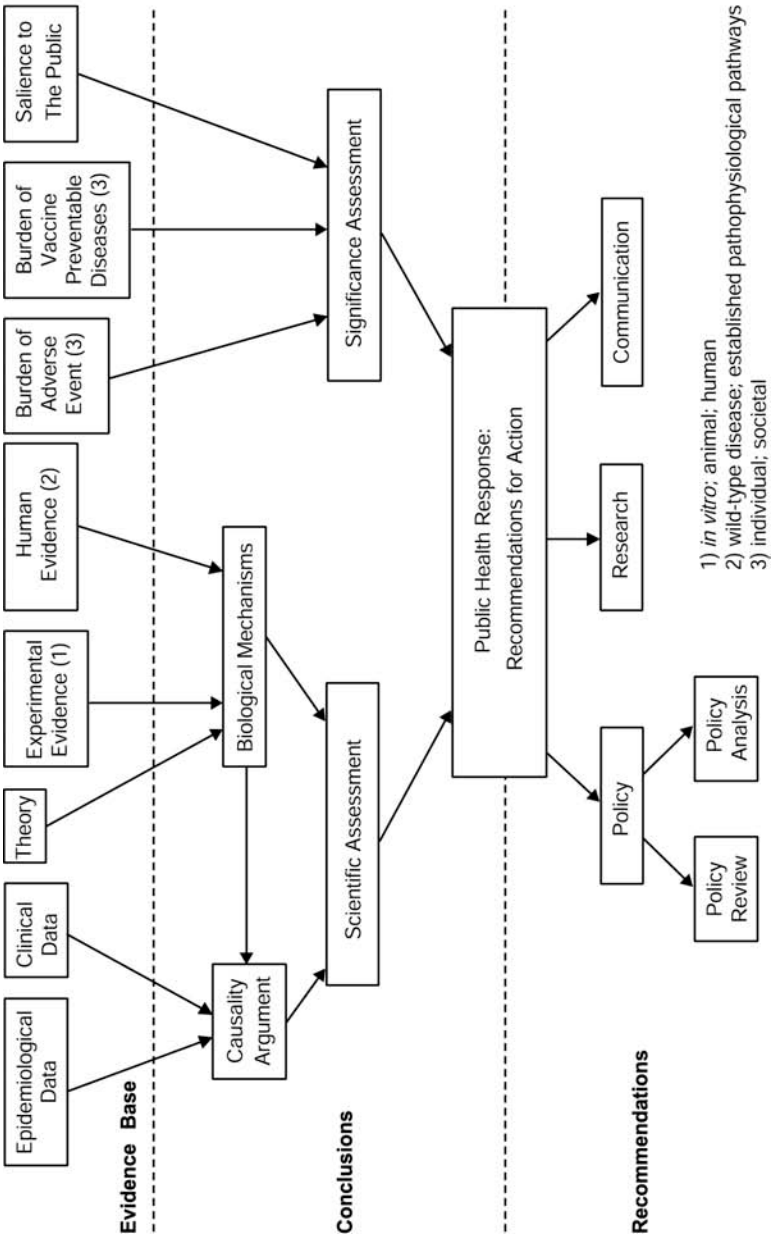


FIGURE 1 Committee Charge

THE FRAMEWORK FOR SCIENTIFIC ASSESSMENT

Causality

The Immunization Safety Review Committee has adopted the framework for assessing causality developed by its predecessors (convened by the IOM in 1991 and 1994) to address questions of immunization safety. The categories of causal conclusions used by the committee are as follows:

1. No evidence
2. Evidence is inadequate to accept or reject a causal relationship
3. Evidence favors rejection of a causal relationship
4. Evidence favors acceptance of a causal relationship
5. Evidence establishes a causal relationship.

Assessments begin from a position of neutrality regarding the specific vaccine safety hypothesis under review. That is, there is no presumption that a specific vaccine (or vaccine component) does or does not cause the adverse event in question. The weight of the available clinical and epidemiological evidence determines whether it is possible to shift from that neutral position to a finding for causality ("the evidence favors acceptance of a causal relationship") or away from causality ("the evidence favors rejection of a causal relationship"). The committee does not conclude that the evidence favors rejecting causality merely if the evidence is inadequate to support causality. Instead, it maintains a neutral position, concluding that the "evidence is inadequate to accept or reject a causal relationship". For some relationships that fall into this category, data are plentiful but the results are conflicting or not strongly convincing. For other relationships that fall into this category, the data specifically addressing the causal relationship are scarce. Some authors of similar assessments use phrases such as "the evidence does not presently support a causal association." The committee believes however that such language does not make the important distinction between evidence that a relationship does not exist (category 3) and evidence that is indeterminate with regard to causality (category 2).

Although there are no firm rules for an amount of or quality of evidence required to support a specific category of causality conclusion, standard epidemiological criteria are used to guide the decision. The strongest category is "establishes causality," which is reserved for those relationships where the causal link is unequivocal, such as with OPV and vaccine-associated paralytic polio, or certain anaphylactic reactions to vaccine administration. The next category is "favors acceptance" of a causal relationship. This is evidence that is strong and generally convincing, although it is not firm enough to be described as unequivocal or established. "Favors rejection" is the strongest category in the negative direction. There is no "establishes no causal relationship" category since it is virtually impossible to prove the absence of a relationship with the same certainty that one can establish the presence of one. Finally, if the evidence

is not reasonably convincing in either the causal or non-causal direction, it is placed in the category "inadequate to accept or reject a causal relationship." Evidence that is sparse, conflicting, of weak quality, or just suggestive falls into this category.

The sources of evidence considered by the committee in its scientific assessment of causality include epidemiological and clinical studies directly addressing the question at hand. That is, the data relate to the effects of the vaccine(s) under review and the specific adverse health outcome(s) under review—in the case of this report, the effects of multiple immunizations on developing immune system function. Epidemiological studies carry the most weight in a causality assessment; these studies measure health-related exposures or outcomes in a defined sample of subjects and make inferences about the nature and strength of associations between exposures and outcomes in the overall population from which the study sample was drawn. Epidemiological studies can be categorized as observational or experimental (clinical trial), and as uncontrolled (descriptive) or controlled (analytic). Among these various study designs, experimental studies generally have the advantage of random assignment to exposures and therefore carry the most weight in assessing causality. Uncontrolled observational studies are important but are generally considered less definitive than controlled studies. In uncontrolled observational studies where observations are made over time, confounding (e.g., changing case definitions and improving case detection) may influence the incidence and prevalence of the adverse outcomes studied.

Case reports and case series are generally inadequate by themselves to establish causality. Despite the limitations of case reports, the causality argument for at least one vaccine-related adverse event (the relationship between vaccines containing tetanus toxoid and Guillain-Barré syndrome) was strengthened most by a single, well-documented case report on recurrence of the adverse event following re-administration of the vaccine, a situation referred to as a "rechallenge" (IOM, 1994).

Biological Mechanisms

Evidence considered in the scientific assessment of biological mechanisms includes human, animal, and *in vitro* studies related to biological or pathophysiological processes by which immunizations could cause immune system dysfunction. This kind of review has been referred to in previous reports of this committee (IOM, 2001a, 2001b) and others (IOM, 1991, 1994) as an assessment of the "biological plausibility" of a causal relationship. The committee has previously described biological plausibility as existing on a spectrum, ranging from not plausible to established. An agreed upon hierarchy of evidence required for assessments of biological plausibility does not exist, nor does an associated terminology (Weed and Hursting, 1998).

The committee has noted, moreover, that the term biological plausibility is a source of confusion on at least two fronts. First, it is associated with guidelines (sometimes referred to as the Bradford Hill criteria) for causal inference from epidemiological evidence (Hill, 1965). In that context, an assessment of the biological plausibility of an association demonstrated by epidemiological analysis is meant to ensure that such an association is consistent with current biological knowledge. Evidence regarding biological plausibility can never prove causality. Therefore, it is also meant to guard against attributions of causality to biologically implausible statistical associations that might result from studies that have not adequately accounted for important variables.

For example, although a strong statistical relationship might exist between a woman's risk of breast cancer and the number of bathrooms in her home, there is no mechanism based on knowledge of cancer biology that could indicate the relationship is causal. Rather, the number of bathrooms is associated with socioeconomic status, which is associated with such factors as diet that can be linked mechanistically to cancer biology. The biological implausibility of an association between the number of bathrooms in a house and the risk of breast cancer weakens the argument for a causal relationship. In other cases, a review of the biological plausibility of an association might add reassurance that the epidemiological findings point toward or reflect causality. Occasionally an epidemiological observation has been explained by a reasonable biological mechanism that, on further investigation, appeared not to be relevant for the pathophysiology.

This committee, however, is often faced with a set of circumstances in which the epidemiological evidence is judged inadequate to accept or reject a causal association between a vaccine exposure and an adverse event of concern. It is then left with the task of examining proposed or conceivable biological mechanisms that might be operating if an epidemiologically sound association *could* be shown between vaccine exposure and an adverse event. Identification of sound mechanisms could influence the development of an appropriate research agenda and give support for policymakers, as decisions frequently must be made in situations of incomplete information regarding causality. Finally, there is often value in understanding and pursuing possible biological mechanisms even if the epidemiological evidence suggests a lack of a causal association. New epidemiological studies could question that existing causality assessment and the biological data would gain prominence in the new assessments. Also, a review of biological data could give support to the negative causality assessment or could cause one to reconsider or pursue the epidemiological findings further.

Second, the committee understands that some readers of its reports are confused by what are perceived as contradictory findings. Although the committee has previously stated that biological plausibility can range across a spectrum, readers sometimes regard the term with a degree of certainty or precision the committee never intended. When other evidence of causality is available, bio-

logical plausibility adds an additional piece of supportive evidence. However, in the absence of other evidence pointing to a causal relationship, use of the term biological plausibility, as ingrained in the language of causal inference, seems to add confusion.

Thus the committee finds that for the purpose of its reports, the lack of clarity in the phrase "biological plausibility" warrants the adoption of new terminology and a new approach to its discussion of biological data. The committee will review evidence regarding "biological mechanisms" that might be consistent with the proposed relationship between a vaccine exposure and given adverse events. This biological assessment section of the report is written distinct from any argument regarding the causality of such relationships. This is not meant to imply that current understanding of biological processes does not shape or guide assessments of causality. In fact, the current thinking of a possible biological explanation for a relationship between immunization and an adverse event will influence some of the important controls used in a good epidemiological analysis. The important consideration of "confounders" in epidemiological studies comes from understanding biological phenomena that could underlie or explain the observed statistical relationship. Only when important confounders are considered can the statistical observation be considered for evidence of causality. However, absent evidence of a statistical association, or convincing clinical evidence, biological mechanisms cannot be invoked to prove causality.

There are three general categories of evidence on biological mechanisms:

Theoretical only: A reasonable mechanism can be hypothesized that is commensurate with scientific knowledge and that does not contradict known physical and biological principles, but it has not been demonstrated in humans or animal models.

Experimental evidence: The evidence can be derived under highly contrived conditions. For example, the results require extensive manipulation of the genetics of an animal system or extreme vaccine antigen exposures *in vivo* or *in vitro* in terms of dose, route, or duration. Other experimental evidence is derived under less contrived conditions. For example, a compelling animal or *in vitro* model exists whereby administration of a vaccine antigen under conditions similar to human use results in a pathological process analogous to a human disease pathology. Experimental evidence often describes effects on just one or a few of the steps in the pathological process required for expression of disease. As more components of the theoretical pathways are shown to operate in reasonable experimental models, the more confident one is that the mechanisms could possibly result in disease in humans.

Evidence that the mechanism results in known disease in humans: For example, a wild-type infection causes the adverse health outcome, or another vaccine has been demonstrated to cause the same adverse outcome by the same or similar mechanism. Data from population-based studies of the effects of the vaccine

administration on the occurrence of the adverse outcomes under review contribute not to the biological mechanisms argument but to the causality argument.

Beginning with this report, the committee will summarize the biological mechanisms as theoretical only, or as having derived from either experimental evidence or mechanism-related evidence in humans. If there is evidence in experimental models or humans for a mechanism, we will designate it as weak, moderate, or strong. Though the committee tends to judge evidence in humans to be "stronger" than experimental evidence from animals or *in vitro* systems, the strength of the evidence also depends on other factors, such as the experimental design and sample size. Obviously, the conclusions drawn from this review will depend both on evidence and scientific judgment. To ensure that its own summary judgment is defensible, the committee intends to be as explicit as possible regarding the strengths and limitations of the biological data.

Published and Unpublished Data

Published reports that have been subjected to a rigorous peer review process carry the most weight in the committee's assessment. Unpublished data and other reports that have not undergone peer review do have value, and they are often considered by the committee; they could be used, for example, in support of a body of published literature with similar findings. If the committee concluded that the unpublished data were well described, had been obtained using sound methodology, and presented very clear results, the committee could report, with sufficient caveats in the discussion, how those data fit with the entire body of published literature. But only in extraordinary circumstances could an unpublished study refute a body of published literature. In general, the committee cannot rely heavily on unpublished data in making its scientific assessments (regarding either causality or biological mechanisms) because they have not been subjected to a rigorous peer review process, and therefore must be interpreted with caution.

The committee acknowledges that its approach differs from the state of the art for evidence-based reviews of clinical practices in medicine, which does not include consideration of unpublished or non-peer-reviewed information or of studies with flawed experimental designs (U.S. Preventive Services Task Force, 1996). However, the Immunization Safety Review Committee was convened specifically to assess topics that are often of immediate and intense concern. In some cases, the committee's review will take place as data are only beginning to emerge. Thus, given the unique nature of this project, the committee thought it was important to review and consider as much information as possible, including unpublished information. The committee did not perform primary or secondary analyses of unpublished data, however. In reviewing unpublished material, the committee applied generally accepted standards for assessing the quality of scientific evidence, as described above. (All unpublished data reviewed by the

committee and cited in this report are available—in the form reviewed by the committee—through the public access files of the National Academies at 202-334-3543 or www.national-academies.org/publicaccess.)

UNDER REVIEW: MULTIPLE IMMUNIZATIONS AND IMMUNE DYSFUNCTION

Over the past two decades, the pediatric immunization schedule has grown more complicated. In 1980, the youngest infants received vaccines against four diseases (diphtheria, tetanus, pertussis, and polio). Today, a healthy child immunized in complete accord with the recommended childhood immunization schedule receives up to 15 doses of five vaccines to protect against seven diseases by 6 months of age and up to 20 doses of seven vaccines to protect against 11 diseases by 2 years of age (see Figure 2). Furthermore, the immunization schedule seems likely to expand in the next decade, with more vaccines for infants and children being developed or considered.

The increase in the number of vaccines and vaccine doses given to children has led to concerns among some about possible adverse effects of individual vaccines or of the aggregate vaccine exposure. One such concern has been prompted by increased incidence of conditions associated with immune system dysfunctions—for example, asthma and type 1 diabetes, often referred to as insulin-dependent diabetes mellitus. Although genetic factors are known to affect the risk of these diseases, increases in their incidence seem more likely to reflect changes in environmental exposures than in the genetic makeup of a population. Increased exposure to vaccines has been proposed as one possible environmental modifier of immune function.

For others, however, the concern is that having to administer many injections in a short period of time could adversely affect the acceptance of the immunization schedule by parents and health care providers, leading to reduced vaccination rates and greater risk of vaccine-preventable disease. Combination vaccine products can mean fewer injections per visit, but, they give little comfort to those who worry about the safety of multiple vaccine exposures. In addition, if adverse effects occur after the receipt of a combination vaccine product it may be difficult to determine which individual vaccine is responsible. Another concern is that development of novel vaccine delivery systems (i.e., nasal sprays and patches) may further complicate the issue of the effects of vaccines on the developing infant immune system.

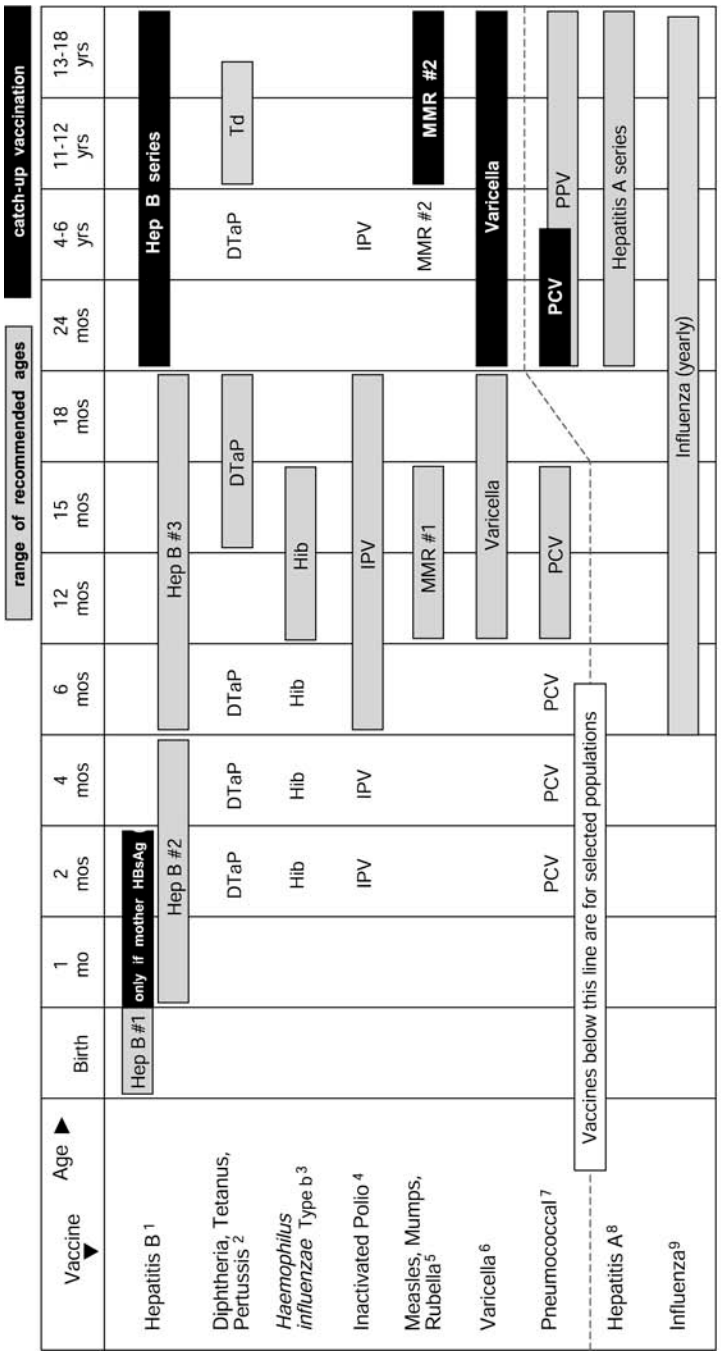
Framing the Question

The Interagency Vaccine Group asked the Immunization Safety Review Committee to address the concern that multiple immunizations can adversely affect

the developing immune system. To conduct its review, the committee had to establish a clear statement of the question before it, as well as a manageable scope of inquiry. Both "multiple immunization" and "immune system dysfunction" must be defined for the purposes of this report. First, multiple immunization has several possible meanings. A single dose of vaccine may present multiple antigens for a single disease (e.g., polio or pneumococcal vaccines) or multiple antigens for multiple diseases (e.g., measles-mumps-rubella [MMR] vaccine). Also, individual doses of several separate vaccines may be administered at a single health care visit. And further "repeat" doses of a single vaccine are administered, alone or with other vaccines, at specified intervals (e.g., 2, 4, and 6 months of age). The committee intended its primary focus to be on exposure to multiple vaccine antigens during infancy and childhood. However, as described in the section below on causality, the literature base is not large, and relevant studies often addressed the effects of incremental exposure differences, such as four vaccines compared to three.

The committee restricted its considerations to those vaccines used in the United States. Thus, data regarding BCG vaccine, which is used against tuberculosis in other countries, did not contribute directly to the committee's causality arguments. (Studies of BCG did, however, help inform the committee's understanding of the biological arguments for and against the hypotheses.) Nor did the committee address possible effects of smallpox vaccine, which has not been used in the United States for 30 years. The committee included studies of "one vaccine" if it contained antigens against more than one disease or more than one strain of infectious agent. For example, the diphtheria and tetanus toxoids and pertussis (DTP) vaccine—whether whole-cell (DTwP) or acellular (DTaP) preparations—would be considered to represent a "multiple immunization," as would the polio vaccines, which contain live or killed viruses against three distinct strains of poliovirus.

Second, immune system dysfunction is a broad term. A brief review of the literature about immunization safety indicates that three types of immune system injury are of concern to vaccine safety advocates: risk of infection, risk of allergic diseases, and risk of autoimmune diseases. These concerns have gained prominence due to a generic consideration of biological mechanisms and due to studies, mostly ecological analyses, that are occasionally salient in the lay and scientific literature. The committee considered two possible pathways to adverse outcomes: stimulation of harmful immune responses or suppression of beneficial immune responses. The committee addressed infections only as distinct from those the vaccines are intended to protect against—referred to as heterologous infection—and in lieu of trying to sweep broad categories of allergic and autoimmune diseases, the committee narrowed its focus to specific conditions. It appeared to the committee that much of the concern, and a large component of the evidentiary base, centered around the allergic disease of asthma and the autoimmune form of diabetes—that is, type 1a diabetes, one of two types of



This schedule indicates the recommended ages for routine administration of currently licensed childhood vaccines, as of December 1, 2001, for children through age 18 years. Any dose not given at the recommended age should be given at any subsequent visit when indicated and feasible. ■ Indicates age groups that warrant special effort to administer those vaccines not previously given. Additional vaccines may be licensed and recommended during the year. Licensed combination vaccines may be used whenever any components of the combination are indicated and the vaccine's other components are not contraindicated. Providers should consult the manufacturers' package inserts for detailed recommendations

FIGURE 2 Recommended Childhood Immunization Schedule, United States, 2002

NOTES

1. Hepatitis B vaccine (Hep B). All infants should receive the first dose of hepatitis B vaccine soon after birth and before hospital discharge; the first dose may also be given by age 2 months if the infant's mother is HBsAg-negative. Only monovalent hepatitis B vaccine can be used for the birth dose. Monovalent or combination vaccine containing Hep B may be used to complete the series; four doses of vaccine may be administered if combination vaccine is used. The second dose should be given at least 4 weeks after the first dose, except for Hib-containing vaccine which cannot be administered before age 6 weeks. The third dose should be given at least 16 weeks after the first dose and at least 8 weeks after the second dose. The last dose in the vaccination series (third or fourth dose) should not be administered before age 6 months.

Infants born to HBsAg-positive mothers should receive hepatitis B vaccine and 0.5 mL hepatitis B immune globulin (HBIG) within 12 hours of birth at separate sites. The second dose is recommended at age 1-2 months and the vaccination series should be completed (third or fourth dose) at age 6 months.

Infants born to mothers whose HBsAg status is unknown should receive the first dose of the hepatitis B vaccine series within 12 hours of birth. Maternal blood should be drawn at the time of delivery to determine the mother's HBsAg status; if the HBsAg test is positive, the infant should receive HBIG as soon as possible (no later than age 1 week).

2. Diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP). The fourth dose of DTaP may be administered as early as age 12 months, provided 6 months have elapsed since the third dose and the child is unlikely to return at age 15-18 months. **Tetanus and diphtheria toxoids (Td)** is recommended at age 11-12 years if at least 5 years have elapsed since the last dose of tetanus and diphtheria toxoid-containing vaccine. Subsequent routine Td boosters are recommended every 10 years.

3. *Haemophilus influenzae* type b (Hib) conjugate vaccine. Three Hib conjugate vaccines are licensed for infant use. If PRP-OMP (PedvaxHIB® or ComVax® [Merck]) is administered at ages 2 and 4 months, a dose at age 6 months is not required. DTaP/Hib combination products should not be used for primary immunization in infants at age 2, 4 or 6 months, but can be used as boosters following any Hib vaccine.

4. Inactivated poliovirus vaccine (IPV). An all-IPV schedule is recommended for routine childhood poliovirus vaccination in the United States. All children should receive four doses of IPV at age 2 months, 4 months, 6-18 months, and 4-6 years.

5. Measles, mumps, and rubella vaccine (MMR). The second dose of MMR is recommended routinely at age 4-6 years but may be administered during any visit, provided at least 4 weeks have elapsed since the first dose and that both doses are administered beginning at or after age 12 months. Those who have not previously received the second dose should complete the schedule by the visit at age 11-12 years.

6. Varicella vaccine. Varicella vaccine is recommended at any visit at or after age 12 months for susceptible children (i.e. those who lack a reliable history of chicken-pox). Susceptible persons aged $\geq$13 years should receive two doses, given at least 4 weeks apart.

7. Pneumococcal vaccine. The heptavalent **pneumococcal conjugate vaccine (PCV)** is recommended for all children aged 2-23 months and for certain children aged 24-59 months. **Pneumococcal polysaccharide vaccine (PPV)** is recommended in addition to PCV for certain high-risk groups. (See CDC, 2000b).

8. Hepatitis A vaccine. Hepatitis A vaccine is recommended for use in selected states and regions, and for certain high-risk groups; consult your local public health authority. (See CDC, 1999c).

9. Influenza vaccine. Influenza vaccine is recommended annually for children age $\geq$6 months with certain risk factors (including but not limited to asthma, cardiac disease, sickle cell disease, HIV and diabetes; (see CDC, 2001d) and can be administered to all others wishing to obtain immunity. Children aged $\leq$12 years should receive vaccine in a dosage appropriate for their age (0.25 mL if age 6-35 months or 0.5 mL if aged $\geq$3 years). Children aged $\leq$8 years who are receiving influenza vaccine for the first time should receive two doses separated by at least 4 weeks.

Additional information about vaccines, vaccine supply, and contraindications for immunization, is available at www.cdc.gov/nip or at the National Immunization Hot-line, 800-232-2522 (English) or 800-232-0233 (Spanish).

what are often referred to as insulin-dependent diabetes mellitus (IDDM). The committee also considered neurological disorders for which the injury is known to be caused by the immune response, including MS and Guillain-Barré syndrome, but did not include these in its causality considerations due to the paucity of epidemiological/clinical information that addresses the possible role of multiple immunizations rather than individual vaccines. In addition, the committee will likely address at least some of these adverse outcomes in subsequent reports.

The scope of the committee's inquiry can be summarized in the following three questions:

1. Do multiple immunizations have adverse short-term effects on the infant immune system that are reflected in increased susceptibility to heterologous infection?
2. Does exposure to multiple antigens, as administered in vaccines, directly and permanently redirect or skew the immune system toward autoimmunity, as reflected in type 1 diabetes?
3. Does exposure to multiple antigens, as administered in vaccines, directly and permanently redirect or skew the immune system toward allergy, as reflected in asthma?

The committee was unable to address the concern of some that repeated exposure of a susceptible or fragile child to multiple vaccines over the developmental period may also produce atypical or nonspecific immune or nervous system injury that could lead to severe disability or death (Fisher, 2001b). Such adverse health outcomes may not be "classical" diseases but variants of diseases. Variants would not necessarily be picked up in epidemiological or clinical investigations that use strict diagnostic criteria. There are no epidemiological studies that address this, either in terms of exposure or outcome. That is, there is no study that compares an unvaccinated control group with children exposed to the complete immunization schedule, nor are there any studies that looked at health outcomes other than those classically defined, such as infections, allergy, or diabetes. Thus the committee recognizes with some discomfort that this report addresses only part of the overall set of concerns of some who are most wary about the safety of childhood vaccines.

Key Features of Immune Response

The immune system of humans and other vertebrates has the capacity both for generalized and specialized responses to organisms, such as bacteria, viruses, and parasites. Generalized responses are produced by mechanisms of innate immunity, while the mechanisms of adaptive immunity generate highly specialized responses to a diverse array of antigens; these are presented by microbes or by products such as vaccines, which may incorporate only specially selected

antigens. The capacity for highly specialized immune responses carries with it the possibility that those responses will be directed against antigens of the body's own cells, the process known as autoimmunity, or against normally harmless environmental materials, such as foods and pollens, a process known as allergy.

Antigen-specific immunity is mediated by T and B lymphocytes (also referred to as T and B cells)[1] and their products. These cells carry antigen-specific receptors on their surface. B lymphocyte receptors, the immunoglobulins (e.g., IgA, IgE, IgG), can potentially react with a wide variety of molecular structures. T lymphocyte receptors recognize short pieces of proteins (peptides) bound to self-major histocompatibility (MHC) molecules, which in humans are referred to as HLA (human leukocyte antigen) molecules. As an individual's T and B cells develop, an enormous diversity of receptors is formed, allowing those cells to recognize and respond to the variety of antigens that might be encountered over a lifetime. This diversity is achieved by a nearly random process of genetic recombination of the genes that encode T- and B-cell receptors. When T and B cells are activated by antigens encountered through infection or vaccines, they multiply and differentiate into effector cells tailored to respond to those antigens. The effector T cells include two types of "helper" cells, designated Th1 and Th2.

During their development and at all stages of their subsequent existence, T and B lymphocytes are "educated" by their environment. Initially, their antigen receptors have no intrinsic bias—that is, they are as likely to recognize antigens from the individual (self antigens) as from a foreign source (e.g., a microbe). As part of the education of T lymphocyte precursors in the thymus, those cells must show that their receptors are capable of reacting with self-peptides bound to self-MHC molecules. Cells that do not react or react very strongly to these self antigens usually die. Cells that react weakly are allowed to mature, leave the thymus, and go to the secondary lymphoid tissues as naïve T cells (na_ve refers to the immune system at birth). This process ensures that T cells have the potential to be useful in that they can react with self-MHC. Similarly, strongly self-reactive B lymphocytes are removed during development.

The censoring of more strongly self-reactive T and B lymphocytes is imperfect, however. As a result, some strongly self-reactive lymphocytes with the potential to produce autoimmunity can be found in the blood and secondary lymphoid tissues of most apparently normal individuals. Usually, these self-reactive T and B lymphocytes do not induce autoimmunity. For the most part, they simply do not encounter self antigens in a context that can trigger lymphocyte activation and expansion. Others are unable to respond even on encounter with self-antigen because they are anergic and/or short-lived cells that will soon die. Even when naïve self-reactive T cells do encounter self antigens, these

[1] The designations of these cells reflect the sites where they mature. T lymphocytes migrate from the bone marrow to mature in the thymus, whereas B lymphocytes mature in the bone marrow.

T cells are held in check in most individuals by counter-regulatory mechanisms, including suppressive cytokines and regulatory (suppressor) T lymphocytes that prevent the self-reactive T (and B) lymphocytes from responding (Ermann and Fathman, 2001; Letterio and Roberts, 1998; Maloy and Powrie, 2001; Moore et al., 2001; Roncarolo and Levings, 2000; Rook et al., 2000; Shevach, 2000; Wills-Karp et al., 2001; Zhang et al., 2001). Self-reactive B lymphocytes are also held in check by the lack of T cell help, without which they are unable to replicate and produce higher affinity antibodies in greater quantities.

In some individuals, however, these regulatory processes fail, allowing self-reactive T and B cells to replicate, differentiate into effector cells, and cause autoimmunity—which is likely to be a multistep process. A common initial event may be the proliferation and differentiation of naïve self-reactive T (and in some cases B) cells into effector/memory cells. Thereafter, other mechanisms may further amplify the T cell response sufficiently to produce, sustain, or trigger a relapse of clinical autoimmune disease. There may also be cases where mixed Th1 and Th2 T cell responses can mediate autoimmunity (Benoist and Mathis, 2001; Marrack et al., 2001).

Genetic factors have been shown, through a substantial body of data from both human studies and animal models, to play a critical role in determining risk for autoimmunity. In some rare disorders, single-gene defects are uniformly associated with the development of autoimmunity.[2] However, the vast majority of human autoimmune diseases appear to be complex traits in which multiple genetic factors determine disease susceptibility and environmental factors determine whether disease develops (Ermann and Fathmann, 2001; Robles and Eisenbarth, 2001; Wanstrat and Wakeland, 2001). Familiar examples of such diseases include type 1a diabetes mellitus, systemic lupus erythematosus (SLE), and multiple sclerosis (MS) (Noseworthy et al., 2000; Robles and Eisenbarth, 2001; Steinman, 2001; Wakeland et al., 2001; Wanstrat and Wakeland, 2001; Wucherpfennig and Eisenbarth, 2001).

Considerable progress has been made in identifying genetic factors that determine risk for autoimmune disorders. One major risk factor—common to type 1a diabetes, SLE, MS, and many other autoimmune diseases—is related to the MHC/HLA locus, which encodes the molecules that bind and present antigenic peptides to T lymphocytes. Genetic differences among individuals—in the ability of their MHC molecules to bind specific antigenic peptides in such a way that a portion of the peptide (the epitope[3]) is recognized by their T lymph o-cytes—influences the differences among individuals in the generation of T

[2] Examples include two rare forms of polyendocrine autoimmunity (Aaltonen and Bjorses, 1999; Bennett et al., 2001; Wildin et al., 2001) and the autoimmune lymphoproliferative syndrome (Jackson and Puck, 1999). Similarly, more than 90 percent of individuals with a genetic absence of the complement protein C1q will develop systemic lupus erythematosus (Wanstrat and Wakeland, 2001).

[3] Epitope is a "portion of an antigenic molecule that is bound by an antibody or gives rise to the MHC-binding peptide that is recognized by a T-cell receptor" (Parham, 2000).

lymphocytes able to respond to self or foreign antigenic peptides. The other genes that confer risk for autoimmune disease are less completely characterized, but the best candidates are genes that regulate the amplitude and quality of the immune response or that affect the generation of specific antigenic epitopes.

Atopy or allergy refers to diseases resulting from IgE-associated immune responses to innocuous environmental substances, such as certain foods or pollens. Allergic individuals have a hereditary predisposition to mount IgE responses when they encounter such substances, which are referred to as allergens, and they develop "atopic" (allergic) diseases such as asthma. This predisposition results in part from a bias favoring the generation of Th2 T cell responses to allergens, which produce the cytokines IL-4, IL-5, and IL-13 that favor the production of IgG4 and IgE antibodies by B cells and are implicated in allergic types of inflammation. By contrast, non-allergic individuals either do not mount an immune response to environmental allergens or mount a Th1 T cell response, which cells produce interferon-γ (IFN-_) and favors the production of IgG1 antibodies. Multiple genetic factors appear to involved in the predisposition to atopy, but these are at present incompletely understood.

In humans, the immune system begins development in early gestation. Although the human fetus has the potential to respond to foreign antigens by midgestation, exposure is very limited and the immune system is often referred to as naïve at birth. Active immunity in the neonate includes B and T cell responses, although the responses are not identical to those of older children. Infants' B cell responses to T cell-independent antigens, such as polysaccharide antigens, is less vigorous than in adults. Thus, pure polysaccharides (including unconjugated *H. influenzae* and *S. pneumoniae* polysaccharides) do not induce an effective antibody response in children under approximately 2 years of age. However, if these polysaccharides are conjugated (linked) to protein antigens, they become T cell-dependent and induce protective antibody responses even in young infants. The effectiveness of such vaccines reflects the substantial maturity of T cell and T cell-dependent B cell responses, and the diverse repertoire of antigens that can be recognized by T cell and B cell receptors in the human infant. There are certain functional differences compared to adult T cells, including the apparent tendency in favor of Th2 responses, which differences appear to reflect in large part the naïve status of the neonatal immune system and lack of exposure to bacteria and other microbes, which encourage Th1 responses, prior to birth (reviewed in English et al., 2001; Lewis and Wilson, 2001; Prescott et al., 1998; Siegrist, 2001).

Antigen Exposure Through Vaccines

Central to the safety concerns about multiple childhood immunizations is the question of whether the increasingly complex recommended schedule of immunizations overloads a child's immune system. That is, have there been quantitative or qualitative changes in the antigens to which a child is exposed through

vaccines that lead to an inability of the immune system to respond appropriately? A related question involves the "hygiene hypothesis." These two issues are reviewed here, prior to the review of evidence regarding possible adverse health effects—specifically infection, autoimmune disease, or allergy—of multiple immunizations on the developing immune system.

A vaccine directed against a single disease can contain one antigen or can contain multiple antigens, each of which can have multiple epitopes. For example, the polio vaccine has always been directed against three strains of poliovirus. The pneumococcal polysaccharide vaccine (recommended for children older than 24 months of age and for adults) contains antigens for 23 distinct strains of pneumococcal bacteria, and the pneumococcal polysaccharide-protein conjugate vaccine (for children between 2 and 23 months of age) contains antigens for seven distinct strains of pneumococcal bacteria. With other vaccine products, such as the DTaP vaccine or the MMR vaccine, a single inoculation (or "shot") is directed against several different diseases. Some vaccines are much simpler. For example, the vaccine directed against the hepatitis B virus contains only one protein antigen.

Quantitative Considerations

Calculations presented to the committee (Kollman, 2001; Offit et al., 2002) suggest that the number of antigens contained in the complete set of vaccines that comprise the recommended childhood immunization schedule has decreased over the past 20 to 30 years, despite the increased number of vaccines and vaccine doses administered. The removal of two vaccines from the schedule account for this decrease. First, routine use of the smallpox vaccine was discontinued in the United States in 1971; the World Health Assembly certified the elimination of wild-type smallpox in May 1980 (CDC, 2001c). The smallpox vaccine contained approximately 200 distinct and potentially antigenic elements. Second, the DTwP vaccine—the whole-cell pertussis (wP) vaccine generally given in combination with diphtheria (D) and tetanus (T)—was replaced by an acellular vaccine DTaP, the first of which was approved by the FDA in 1991. The whole-cell vaccine contained approximately 3,000 distinct and potentially antigenic components, whereas the acellular vaccine contains only 2–5 antigens. As of 1997, the acellular pertussis vaccine is the vaccine of choice in the United States, although the whole-cell preparation is still used elsewhere.

The vaccines added to the immunization schedule over the past 20 years have relatively few antigens. For example, the hepatitis B vaccine, a genetically engineered product, contains only one antigen, and the *Haemophilus influenzae* type b (Hib) vaccine contains only two. The varicella vaccine, a live viral vaccine, contains approximately 70 antigens (see Table 1). Thus, with the elimination of smallpox vaccine and the changeover to the acellular pertussis vaccine, the total number of immunogenic proteins or polysaccharides in childhood

vaccines has decreased to a level well below that of the vaccines given widely even as recently as 1980 (Kollman, 2001; Offit et al., 2002).

Certain caveats must be made regarding these calculations. First, they rely on counting numbers of unique molecules (e.g., proteins) in smallpox and whole cell *B. pertussis* vaccines—some of which may not be antigenic and others of which contain multiple epitopes to which the immune system responds. The calculations also do not address the effects of changes in the presence or absence of contaminating proteins. For example, the use of antibiotics, growth media, animal proteins, or carrier proteins could alter these preliminary calculations. In addition, there is no attempt to consider inter- or intra-manufacturer differences in vaccine preparations.

The other side of the quantitative question regarding antigen load is whether infants are capable of responding adequately to the antigens presented by vaccines. Adult humans have a T cell receptor repertoire (the numbers of unique T cell receptors and thus the number of different epitopes to which the T cells of an individual could respond) of ~2.5 x 10^7 (Arstila et al., 1999). Although the numbers of different T cell receptors present in human neonates has not been determined directly, their diversity has been shown by several groups to be similar to that of adults. Thus, the range of different epitopes that human neonates can recognize is almost certainly >10^7. The diversity of antigens to which B cells can make specific antibodies is thought to be even greater, and although there are some qualitative differences from adults, it appears that the overall diversity of antigens to which B cells can respond is similar to adults by 6–8 weeks of age in humans (English et al., 2001; reviewed in Lewis and Wilson, 2000; Marolleau, 1998). This is the basis

TABLE 1 Number of Immunogenic Proteins and Polysaccharides Contained in Vaccines Over the Past 40 Years

1960		1980		2000	
Vaccine	Protein	Vaccine	Protein	Vaccine	Protein
Smallpox	~200	Diphtheria	1	Diphtheria	1
Diphtheria	1	Tetanus	1	Tetanus	1
Tetanus	1	WC-Pertussis	~3000	AC-Pertussis	2–5
WC-Pertussis	~3000	Polio	15	Polio	15
		Measles	10	Measles	10
Polio	15	Mumps	9	Mumps	9
		Rubella	5	Rubella	5
Total	**~3217**			Hib	2
		Total	**~3041**	Varicella	69
				Pneumococcus	8
				Hepatitis B	1
				Total	**123–126**

SOURCE: Adapted from Offit et al., 2002
NOTE: WC-Pertussis = whole cell pertussis, AC = acellular pertussis

for the notion that human infants have the capacity to respond to the substantial number of foreign molecules (e.g., bacterial antigens) to which they are exposed shortly after birth. This is consistent with the theoretical estimates presented to the committee, which suggest that the capacity of the infant's immune system is at least 1000 times greater than that maximally required to respond to vaccines (Kollman, 2001; Offit et al., 2002).

It is the judgment of several scientific groups, including the Immunization Safety Review Committee, that the antigen load of the recommended childhood immunization schedule has decreased, not increased, in the last 20 years or so and that the infant immune system has an adequate capacity to respond to that number of antigens.

Qualitative Considerations

In considering whether the additional exposure to vaccine antigens might "overwhelm" the infant immune system, reference has been made to the fact that the fetus moves from a sterile environment in the womb into the birth canal and outside world that is coinhabited by an almost infinite array of microorganisms (IOM, 1994). Within hours, the newborn's skin and upper respiratory and intestinal tracts are colonized by a variety of bacteria and fungi, and exposure to viruses begins. Thus, the baseline exposure to microbial antigens by an infant is very large.

The normal infant develops a "commensal" relationship with these bacteria and fungi, almost always without preceding expression of overt disease—a sort of truce between the host and microbe that allows the microbe to colonize but not invade. During this process, the immune system is stimulated by these exposures, as illustrated by the presence of detectable antibody and lymphocyte responses to organism-specific antigens. Antibodies against the common pathogens *H. influenzae* and pneumococci has also been demonstrated in infants not recognized to have had disease caused by these bacteria (Anderson et al., 1972; Gray et al., 1981; Sell et al., 1973). Moreover, genetic immunodeficiency diseases represent "experiments of nature" that show that abnormality of any single component of the host defense system, including antibody and lymphocyte function, can result in serious, often lethal disease caused by pathogens or by one or another of the commensal organisms. Thus a vigorous immune response is required to protect the human infant against infection by a broad variety of organisms that have the potential to cause disease, and the infant must be able to mount this response consistently and repeatedly. Within this context, it seems unlikely that immunizations constitute a significant departure from the magnitude of the antigenic challenges endured under natural circumstances by any normal infant.

Over the course of several decades, the antigen load presented to the developing immune system has undergone significant qualitative changes,

particularly in the context of the total antigen exposures during infancy and childhood. Approximately a decade ago, researchers interested in the changing epidemiology of several diseases began formulating the "hygiene hypothesis," which has generated an extensive descriptive and research literature (e.g., Rook, 2000; Wills-Karp et al., 2001). Fundamentally, the hygiene hypothesis suggests that the increasingly aseptic environment in which children in developed countries are reared has led to changes in the development, or maturation, of the infant immune system. Many ecological analyses correlate the rise of allergic and autoimmune diseases in many parts of the world with increased economic development (Rook and Stanford, 1998). Epidemiological literature in support of the hygiene hypothesis includes findings of a negative correlation between risk for allergic diseases and a host of factors that would increase a child's exposure to bacteria and other infectious agents. These risk factors include, for example, the number of older siblings, the presence of pets, infections through the fecal-oral route, and rural living. Changes other than in hygienic behavior, such as increases in environmental pollutants, have also occurred in the developed world and may contribute to the changing epidemiology of some diseases.

The proposed explanation for an immune system role in these epidemiological observations is that early exposure to infectious diseases and environmental microbes "shapes" the developing immune system toward a Th1-cell responsiveness, which is generally considered a protective immune response (i.e., to host defense against intracellular pathogens and allergy). Eliminating these early exposures through hygienic practices and altered behaviors is thought to predispose the immune system toward a Th2 cell responsiveness, which is associated with allergy. This "skewing" or "biasing" of the immune system as a result of the elimination of many kinds of antigen exposures, some theorize (Rook, 2001), is exacerbated by exposure to vaccines, many of which evoke a Th2 response instead of the Th1 response that would be generated by wild-type infections with the diseases that the vaccines prevent. The most recent refinement of the biological mechanisms proposed to explain the hygiene hypothesis looks beyond the idea of a simple Th1-Th2 imbalance into the realm of regulatory cell imbalance (Rook, 2001; Wills-Karp et al., 2001). Under this scenario, a major contributor to altered immune responses is a decrease in T regulator cells, along with the alteration in T effector cells (Th1 or Th2).

Not yet clear is the role immunizations may have in directly altering development of the immune system, or the relative contribution of vaccine-related changes in the context of the hygiene hypothesis. Vaccine-induced immune responses may, however, differ from those resulting from wild-type infection because of differences in context, including differences in their timing, either in terms of age at exposure or of the sequence of antigen exposure. For example, through immunization, many American children currently mount a simultaneous immune response to diphtheria, tetanus, pertussis, hepatitis B, *Haemophilus influenzae* type b, and three strains of poliovirus three times during the first 6

months of life. It is unlikely that the timing of this vaccine-induced immune response would have been mimicked under conditions of nonvaccination.

In any case, the number of infections prevented by vaccines is actually quite small compared with the total number of infections prevented by other hygienic interventions, such as clean water, food, and living conditions. And, although it is true that the developing immune system is frequently bombarded with many antigens at one time, most of the antigens do not pose a threat inherent to the infant. Most certainly, the route of antigen exposures through vaccines—that is, an injection rather than a respiratory or gastrointestinal exposure—is different than what occurs in wild-type infection.

Actually, the history of vaccine development shows that the immune response to a vaccine is sometimes devastatingly different from the response to wild-type infection. Early experience with killed-virus vaccines directed against measles and respiratory syncytial virus (RSV) saw the appearance of atypical and virulent disease in vaccinated individuals that were subsequently infected with wild-type virus.

In the 1960s, some children developed an atypical form of measles after receiving the killed measles virus vaccine (Fulginiti and Helfer, 1980). Atypical measles is described as a delayed, severe hypersensitivity reaction (Krause et al., 1978; Redd et al., 1999). Symptoms of high fever, headache, abdominal pain, myalgia, and cough (Redd et al., 1999) are followed in 48–72 hours by the appearance of a maculopapular, pruritic rash on the extremities that spreads inward toward the trunk and may become vesicular, purpuric, or petechial (Brodsky, 1972). Patients become severely ill during the first few days of illness, but atypical measles is self-limited and resolves in 7–14 days (Brodsky, 1972).There was only one report of a possible fatality among cases seen in the 1960s following use of the inactivated measles vaccine (Redd et al., 1999).

Children with atypical measles were found to lack the antibody to the measles virus F protein, which is responsible for the virus's hemolytic and cell fusion properties (Annunziato et al., 1982; Redd et al., 1999). In contrast, the H, or hemagglutin protein, the other measles virus surface protein, was found in the sera of the ill patients. This indicated that children given the killed-virus vaccine formed antibody against the H protein even though they did not do so against the F protein (Annunziato et al., 1982). There was also a suggestion of an exaggerated cellular immune response to measles antigens in patients (Redd et al., 1999), although more recent studies in rhesus monkeys suggest that the induction of humoral and CD4 T cell-mediated immunity but not cytotoxic T cells directed against viral antigens may be an important factor in the adverse response to subsequent infection with wild-type virus which resulted in the production of extremely high levels of circulating antibody (Polack et al., 1999; Redd et al., 1999). Years after being vaccinated with killed virus, patients who contracted measles were still developing a clinical illness that, aside from the

initial symptoms, was quite different from regular measles (Annunziato et al., 1982).

A similar effect was seen when a vaccine against RSV infection—the leading cause of lower respiratory tract illness among infants and children—was tested. Susceptible children were vaccinated with a concentrated, formalin-inactivated, adjuvant-enhanced vaccine. Children who received this vaccine initially developed high levels of neutralizing and complement-fixing antibody. However, upon exposure to wild-type RSV, they developed more severe infections than unvaccinated children did (CDC, 2000a; IOM, 1985). Thus, the experimental RSV vaccine was never used clinically.

Atypical measles syndrome and the severe RSV infections are two disturbing consequences of immunization. These two examples resulted from an incomplete understanding of the immune system's response to the live and killed form of these viruses. Thus, it is clear that the response to vaccines cannot be predicted, even with caution and reserve and therefore should be assessed carefully.

Autoimmune and Allergic Diseases

Autoimmune Disease

Collectively, diseases of autoimmunity affect 3 to 5 percent of the population in the United States. (Jacobson et al., 1997).Autoimmune diseases are mediated by T cell and/or T cell-dependent B cell responses directed against self-antigens, and the T cell responses in most autoimmune diseases are dominated by interferon-_ producing CD4 T cells, commonly referred to as Th1 T cells (Marrack et al., 2001). An autoimmune process can target individual organs, such as the brain and spinal cord in multiple sclerosis, or can operate throughout the body, as in systemic lupus erythematosus. For this report, the committee focused on the autoimmune form of diabetes, referred to as type 1a diabetes. Type 1b refers to diabetes associated with an idiopathic loss of insulin secretion. Type 2 diabetes is not associated with destruction of insulin-secreting pancreatic islet cells. Type 1 diabetes has frequently been referred to as "childhood" or insulin-dependent diabetes, while type 2 diabetes has been referred to as "adult-onset" diabetes. It is now recognized that onset of either form of diabetes can occur at any age.

Type 1a diabetes results from the immunological destruction of pancreatic islet ß cells (Atkinson and Eisenbarth, 2001). (The destruction of the islet cells in type 1b diabetes is idiopathic). The beta cells produce insulin, which the body requires to process glucose. Symptoms of type 1 (a and b) diabetes include increased thirst and urination, constant hunger, weight loss, blurred vision, and extreme fatigue. Once diagnosed, the condition can be treated with regular injection of supplemental insulin, but various long-term complications (e.g., diabetic retinopathy, kidney failure, vascular disease) are common. The

development of clinical disease is preceded by an asymptomatic period of progressive islet destruction that may last for many years. As understanding of type 1a diabetes increases, the preclinical period may provide a window for interventions that can delay or prevent clinical onset (Knip, 1997).

The etiology of type 1a diabetes and other autoimmune diseases is multifactorial, involving genetics and environmental exposures. Genetic susceptibility, arising from combinations of multiple genetic factors, appears to be a necessary but not sufficient risk factor for the disease. Monozygotic twins of persons with type 1a diabetes are at increased risk compared with other family members, but as few as 23 percent of these twins developed the disease in one report (Abiru and Eisenbarth, 2000). Although the disease can cluster in families, more than 80 percent of type 1 diabetes cases are reported to occur in persons with no family history of the disease (Dorman et al., 1995). Certain genetic factors may also provide protection from type 1 diabetes.

Environmental factors are thought to serve as triggers or promoters of the autoimmune process in genetically susceptible individuals. In particular, dietary and viral exposures have been suspected in type 1 diabetes. Some studies found that early exposure to cow's milk was associated with increased risk (Gerstein, 1994), as was breastfeeding for less than 3 months (Gerstein, 1994). Newer prospective studies, however, have found no association with these factors (Graves et al., 1999; Hummel et al., 2000; Norris et al., 1996). Congenital rubella syndrome (CRS) shows a clear association with type 1 diabetes, with about 20 percent of CRS patients in the United States also having diabetes (Menser et al., 1978; Rubinstein et al., 1982). Studies of Coxsackie B virus infections have produced conflicting evidence regarding their possible contribution to type 1 diabetes (Robles and Eisenbarth, 2001). Atkinson and Eisenbarth (2001) described a model of progression to clinical disease that depends not on exposure to a single triggering environmental agent but rather on the cumulative effect of various exposures over time.

Worldwide, estimates of the incidence of type 1 diabetes[4] in children under 14 years of age range from 0.1 per 100,000 in parts of China and Venezuela to 36.8 per 100,000 in Sardinia and 36.5 per 100,000 in Finland (Karvonen et al., 2000). As reported by Karvonen and colleagues (2000), estimated incidence for the early 1990s for United States locations range from 11.7 per 100,000 in Chicago to 17.8 per 100,000 in Allegheny County, Pennsylvania. In most populations, incidence is highest in the oldest age group (10–14 years). The disease is also diagnosed in adults, but incidence data are limited. Data from Rochester, Minnesota, for 1945–1969 suggest an incidence rate of 9.2 per 100,000 among persons age 20 and older (Melton et al., 1983).

Rates have generally been lower in more tropical countries and higher in populations of European origin. These patterns may be related to differences

[4] Most population-based studies do not distinguish between types 1a and 1b diabetes.

among racial and ethnic groups in the distribution of genetic risk factors or to the differences in exposure to environmental factors (Atkinson and Eisenbarth, 2001). In any case, the worldwide incidence of type 1 diabetes appears to be increasing 3% a year, and the rate of increase is greatest where incidence has been low (Onkamo et al., 1999). Data from Europe also indicate that incidence is increasing more rapidly among the youngest children (ages 0–4 years) (EURODIAB, 2000).

Allergy

Allergy is responsible for a variety of acute and chronic health problems, including anaphylaxis and allergic rhinitis, asthma, and eczema. These conditions reflect an overreaction of the immune system to allergens—normally harmless environmental agents such as pollens, dust mites, insect venom, and certain foods—that can be encountered through inhalation, ingestion, injection, or skin contact. Under certain circumstances, exposure to an allergen primes the immune system for hypersensitivity reactions involving allergen-specific IgE antibodies and Th2 cells.

The committee focused its attention on allergic asthma for this report. Characteristic symptoms of asthma are episodes of shortness of breath, coughing, wheezing, and chest tightness. These symptoms reflect an acute bronchial hyperresponsiveness to specific allergens and other environmental factors, and a chronic inflammation of the airways (Busse and Lemanske, 2001; IOM, 2000; Kay, 2001; Parham, 2000). The acute response involves activation of mast cells in the lower airways and their release of histamine, cytokines, and other molecules. These mast-cell mediators induce accumulation of fluid, secretion of mucus, and contraction of the smooth muscle around the airways. A “late phase” response includes persistent or recurrent bronchial constriction and infiltration of airway tissue by inflammatory cells. The inflammation can produce temporary or permanent tissue damage.

Exposures to allergens and other environmental factors are known to induce new episodes of asthma when the disease is established, but the underlying factors that account for the development of this type of hyperresponsiveness are not fully understood. Several genetic factors may combine in various ways to establish susceptibility, but they remain poorly defined (Barnes, 2000; Kay, 2001). Environmental exposures may also influence the development of asthma, but current evidence is mixed for exposure such as cockroach allergens or cat dander (e.g., IOM, 2000; Lau et al., 2000; Litonjua et al., 2001; Peat et al., 1993). The presence of older siblings or attendance at day-care (factors that may be markers for the nature or timing of certain exposures) has shown protective effects (Ball et al., 2000). Early exposure to certain viral infections also has shown protective effects (Illi et al., 2001; Openshaw and Hewitt, 2000), but some

respiratory infections have been associated with increased risks (Nafstad et al., 2000), as has early exposure to antibiotics (Droste et al., 2000).

The prevalence of asthma has increased in the United States and other countries over the past 30 years (Grant et al., 1999). An international study of asthma in children found that prevalence was higher in more developed countries (Asher and Weiland, 1998). In the United States, the prevalence rates of self-reported asthma rose from 3.1 percent in 1980 to 5.4 percent in 1994, an increase of 74 percent (Mannino et al., 1998). For children age 0–4 years, rates increased by 159 percent during this period (from 2.2% to 5.7%). Increases in asthma prevalence were seen in all race, sex, age, and regional groups in the United States. No national estimates of the incidence of new asthma cases in the United States are available.

SCIENTIFIC ASSESSMENT

Causality

As has been specified, the committee's review of the safety of multiple immunizations focused on three possible adverse outcomes: heterologous infections; autoimmune disease in the form of type 1a diabetes; and allergy, especially asthma. For each of these outcomes, the epidemiological evidence is summarized (in the text and in accompanying Tables 2, 3, and 4) and the committee's conclusion regarding causality is presented. The search strategies used to identify relevant published reports are described in Appendix D.

Heterologous Infections

Controlled Epidemiological Studies

Guinea-Bissau. Kristensen and colleagues (2000) studied the relationship between vaccination and childhood survival in a population of 8,752 children born to mothers participating in a longitudinal mortality study in Guinea-Bissau. Recommended childhood vaccines in Guinea-Bissau include BCG, OPV, DTP, and measles. Vaccination status was determined by inspection of immunization cards kept by the children's parents. Children were excluded if the card could not be examined, which was the case for more than a third of children.

Vaccine exposure for BCG, OPV, and DTP was assessed during a first visit when children were 0–6 months of age. Mortality was assessed at a subsequent visit approximately 6 months later. For surviving children, vaccination status, including measles vaccine exposure as well as that of BCG, OPV, and DTP, was updated. Mortality was assessed again at a third visit, approximately 6 months after the second visit.

A Cox proportional hazards model was used to calculate the mortality ratio for vaccinated and unvaccinated children. The overall mortality for any vaccine was nonsignificant (RR = 0.74, 95% CI 0.53–1.03). Receipt of BCG vaccine was associated with lower mortality (adjusted RR = 0.55, 95% CI 0.36–0.85), as was measles vaccine (adjusted RR = 0.48, 95% CI 0.27–0.87). The mortality ratio for one dose of DTP vaccine versus none was 1.84 (95% CI 1.10–3.10), but the ratio for two to three doses was not significantly elevated (RR = 1.38, 95% CI 0.73–2.61). The pattern was similar for OPV, with an elevated mortality ratio for one dose (RR = 1.81, 95% CI 1.07–3.05), and nonsignificant ratio for two to three doses (RR = 1.39, 95% CI 0.73–2.64).

The authors conclude that receipt of BCG and measles vaccines may have a protective effect against mortality, while receipt of a single dose of DTP and polio vaccines may carry a higher mortality risk compared with receiving no vaccinations. The results also suggest that DTP vaccine may negate the positive effects associated with BCG vaccine.

However, the interpretation of these findings warrants caution. The vaccination status of some children was unclear and more than a third of the children did not have records available. Many children may have been underimmunized, contributing to the increased mortality rates and reflecting limited access to health care. Vaccinated children were also more likely to receive health care than unvaccinated children, which may mean that getting vaccinated is associated with access to or use of other interventions that improve survival. Mothers of children vaccinated with DTP were younger than mothers of children vaccinated with BCG or measles vaccine, which means maternal age may have contributed to infant mortality risk. The adjustment procedure for potential confounders was also unclear. For the United States, the findings regarding BCG vaccine are not relevant since the vaccine is not routinely used in this country.

United States-Boston. In a case-control study, Burstein and Fleischer (1994) examined the relationship between vaccination and the risk of occult bacteremia. Cases and controls were patients treated in the emergency department at Children's Hospital in Boston between November 1987 and December 1990. Cases were 54 children age 3 to 36 months who participated in a multicenter antibiotic study. Pathogens isolated from these children included *S. pneumoniae, E. coli, S. aureus, H. influenzae,* or *Salmonella spp*. The 108 controls were matched to cases according to age. Each case had two controls. One control group included febrile nonbacteremic children. The other group included nonfebrile children who were treated for symptoms not related to infectious diseases. Vaccination history, including DTwP, was obtained from medical records.

The authors found no significant difference between cases and controls for time since last vaccination of any type, or for time since last DTwP vaccination. Limitations of this study included weak statistical power. It was also unclear which vaccines, other than DTwP, the children received.

United States-Tennessee. Griffin and others (1992) examined the ass o-ciation between DTwP immunization and the risk of invasive bacterial infection. The incidence of invasive bacterial diseases (*H. influenzae*, *N meningitidis*, *Streptococcus pneumoniae*, group B *Streptococcus*, or *Listeria monocytogenes*) was measured in a cohort of 64,591 children who received at least one dose of DTwP vaccine through any of the four largest Tennessee county health clinics from 1986 to 1987. Based on surveillance data, 158 children diagnosed with invasive bacterial infection after receiving DTwP vaccine were identified in this cohort. Using a Poisson regression model and controlling for age, the relative risk for infections during the early post-immunization periods (0–7, 8–14, 15–28 days) compared with the later period (29 or more days) was nonsignificant. The authors concluded that there was no increase in the risk for invasive bacterial infection following receipt of DTwP vaccine, especially during the early post-immunization period. Interpretation of the study is limited by the lack of an unvaccinated comparison group. In addition, the analysis was limited to cases of serious culture-confirmed infections.

United States-Kaiser Permanente Northern California. In a case-control study, Black and colleagues (1991) examined the relationship between vaccination and the risk of heterologous invasive bacterial disease. Cases and controls were identified from member records in the Kaiser Permanente Medical Care Program of Northern California. As cases, 223 children between 1 month and 2 years of age who were diagnosed with invasive bacterial disease (*Pneumococcus*, *H. influenzae*, *E. coli*, and *Meningococcus*) between 1986 and 1988. Invasive bacterial disease status was identified from a computerized microbiology laboratory database. The 446 controls were matched according to age, sex, zip code, and length of plan membership. For cases, all vaccines received within three months prior to disease onset were identified through medical chart review. For matched controls, the date of diagnosis for the corresponding case was the reference date used to obtain vaccination histories. Children had received one or more of the following vaccines: DTP, OPV, and MMR.

A conditional logistic regression model was used to estimate the effect of recent immunization on disease; odds ratios were calculated from the regression results for each vaccine. A separate analysis controlled for the effect of well care visits and day care attendance (information available for 72 percent of the subjects). Odds ratios were calculated for separate time intervals from date of vaccine receipt to date of disease diagnosis: 0–7 days, 8–30 days, 31–60 days, and 61–90 days. Receipt of individual vaccines was associated with a lower risk of disease in all time intervals, with significant effects for DTP at any interval after 7 days and for OPV at 8–30 days and 31–60 days. After adjustment for day-care attendance and well-care visits, however, no individual vaccine had a significant effect on risk of disease. But there was a significant protective effect in the adjusted analysis from the receipt of any vaccine within 30 days (OR = 0.26, 95% CI 0.09–0.76) or 90 days (OR = 0.31, 95% CI 0.13–0.73).

The authors conclude that vaccines do not increase the risk for invasive bacterial disease and that they may provide a protective effect against disease, especially within 3 months after vaccination. However, children who received well care visits were also less likely to develop invasive bacterial disease than those who did not receive them. A health care effect may account for the observed protection of vaccines against heterologous invasive bacterial disease.

United States-Alaska. In a two-part study, Davidson and colleagues (1991) examined risk of disease following receipt of DTwP vaccine among Alaskan Native children. They first conducted a case-control study to examine the risk of invasive bacterial disease. The 186 cases were children 2 to 24 months old who received at least one DTwP vaccine and were identified through surveillance reports for *H. influenzae* type b and *S. pneumoniae* diseases. There were 186 controls matched according to age, sex, residence, and number of DTwP vaccines received. The time interval between last DTwP vaccination and date of disease diagnosis (the reference date for controls) was obtained. There were no significant differences in DTwP vaccine intervals for Hib disease cases. For *S. pneumoniae* disease, significantly more cases had been immunized 31–60 days earlier (OR = 3.3, 95% CI 1.1–10.0), but differences were not significant for shorter or longer intervals. The authors conclude that there was no clear association between the timing of DTwP vaccination and risk of invasive bacterial disease. The authors note that a possible explanation for the lack of difference observed in the study is overmatching. Overmatching is where cases and controls closely resemble each other on factors related to the exposure of interest. In this study, matching based on the number of DTP vaccines received may have resulted in the lack of difference in the timing of DTwP immunization between cases and controls. However, the authors observed that matching according to the number of DTP vaccines was necessary and reduced potential confounders such as those related to health status.

Subjects in the second part of the study included 104 cases and controls from the earlier part who had complete medical records available. Cases and controls were combined to compare the occurrence of any illnesses within 30 days before and after receipt of DTwP vaccine. Comparisons were made for the occurrence of any illness, any infectious disease, otitis media, other respiratory infections, temperature greater than 38°C, or hospitalization. There was a higher incidence of any illness during the 30 days prior to DTP vaccination than in the 30 days following vaccination (53% versus 43%, p = .004). There were no significant differences between the pre- and post-vaccination periods for the other indicators of illness. The authors again conclude that DTwP vaccination does not increase the risk of other illnesses. The authors note that the higher frequency of disease in the pre-DTP group compared to the post-DTP group may have resulted from a “well-child effect,” whereby immunization of children with illnesses was postponed until they were well.

Randomized Controlled Trial

Germany. Otto and colleagues (2000) examined differences between vaccinated and unvaccinated children in the risk of morbidity associated with infectious diseases. A total of 662 children, born between January 1995 and December 1996, were randomized to receive their first vaccine (against diphtheria, pertussis, tetanus, *Haemophilus influenzae type B,* and poliomyelitis) at either 60 days or 90 days after birth.[5] Children were observed during the third month of life, beginning at the sixth day after vaccine receipt. Mothers kept a daily journal and recorded any occurrence of symptoms. Morbidity was assessed in terms of the incidence of coughing, signs of rhinitis, restlessness, vomiting, rash, pain, poor food or fluid intake, fever, and respiratory embarrassment.

A total of 166 children were excluded from the analysis, mostly because of missed vaccination. The authors observed a significant ($p < 0.01$) increase in vomiting, cough, rhinitis, restlessness, rash, and pain in the unvaccinated group compared with the vaccinated group. Hospitalization was more frequent among unvaccinated children ($n = 4$) than vaccinated children ($n = 1$). The authors concluded that children who received vaccinations during the third month of life did not demonstrate an increased risk of infectious-disease symptoms and may experience some protective effect from vaccination. Study limitations included observer bias in that the mothers, who were responsible for monitoring morbidity, were not blinded as to vaccination status. The high exclusion and dropout rate (39% versus 11% in the unvaccinated group), especially in the vaccinated group, may also effect interpretation of the study results.

Other Studies

The committee reviewed additional articles that reported adverse events after receipt of multiple immunizations. These studies helped inform the committee's assessment of risk for heterologous infection but did not contribute to the causality argument. Most of these articles reported on randomized controlled trials that primarily investigated the safety, efficacy, and/or immunogenicity of various vaccines. They did not specifically examine the incidence of heterologous infections in children post-immunization, compare the incidence of such infections between different exposure groups, or report statistical analyses from which to make inferences or extrapolations related to heterologous infections. The articles reviewed are briefly summarized below.

Shinefield and colleagues (1999) examined the safety and immunogenicity in infants of a heptavalent pneumococcal CRM_{197} conjugate vaccine administered concurrently with DTwP, Hib, and OPV vaccines. Hepatitis B vaccine was

[5] In Greiswald, Germany, immunization recommendations call for children to receive their first vaccine during the third month of life. Children participating in the study received their vaccines on either the first day (60 days after birth) or the 30th day of the third month (90 days after birth), complying with the recommended immunization schedule.

administered concurrently or at least two weeks earlier or later. Children received DTaP vaccine at a later stage of the study. The authors reported on adverse events observed following immunization. In the study, 302 infants age 2 months were randomized to receive the pneumococcal vaccine or meningococcal Group C conjugate vaccine. During the study, 12 emergency room visits occurred within 30 days of any vaccine dose. These visits were for croup, otitis, febrile illness, and urinary tract infection, but none were considered vaccine-related. Following the primary doses of vaccines, eight children were hospitalized, two within 30 days after vaccination. Following the booster doses, there were four emergency department cases (of viral illness, otitis media [two cases], and burn) and four hospitalizations (pneumonia, otitis media, elective surgery, asthma, and cough). The authors did not believe that these events were vaccine-related.

Olin and others (1997) compared the efficacy of three types of DTaP vaccine to the DTwP vaccine used in the United Kingdom. A sample of close to 83,000 infants age 2–3 months were randomized to different DTP vaccine exposures and also given Hib and IPV vaccines. The authors reported on adverse events following vaccine receipt. Those that may have involved heterologous infections included two deaths from pneumonia within 4–7 days of a trial vaccine dose, 20 cases of invasive bacterial infections, and one case of suspected encephalitis

Afari and colleagues (1996) examined the immunogenicity and reactogenicity of two types of DTaP vaccine (a freeze-dried, heat-stable product and a liquid product) and DTwP vaccine. Of the 403 infants who were studied, 136 were randomized to receive the freeze-dried DTaP, 130 to receive liquid DTaP product, and 137 to receive DTwP. The authors reported that three children who received the freeze-dried vaccine died of measles or malaria, two children who received liquid DTaP died of malaria or diarrheal disease, and two children who received DTwP died of multiple boils or malaria. Differences in mortality rates between either DTaP group and the DTwP group were not statistically significant.

Simondon and colleagues (1996) compared the safety and immunogenicity of DTaP and DTwP vaccines in a randomized clinical trial involving 286 Senegalese infants. Children also received BCG and IPV during the study. Six deaths occurred within 2 months after vaccination. On the basis of verbal autopsies, the four deaths in the DTwP group were attributed to diarrhea, malaria, and pneumonia. The two deaths in the DTaP group were attributed to meningitis and diarrhea. The authors suggested caution in drawing conclusions regarding the number and causes of deaths in the study. The infant mortality rate in the study region is high, and verbal autopsies are an imprecise means of determining cause of death.

Riordan and colleagues (1995) reported two cases of bacterial meningitis after receipt of MMR vaccine. Fever and rash occurred in two children, age 12 months and 13 months, within 4 days after MMR vaccine, and were initially attributed to the vaccine. After diagnostic tests, both children were found to have

a high level of C-reactive protein and were diagnosed with a bacterial infection. Meningococcal infection was confirmed in one case and suspected in the other. The authors noted that the median age of children admitted to their hospital with meningococcal disease is 14 months.

Avendano and colleagues (1993) evaluated the safety and immunogenicity of a Hib vaccine made with purified polyribosylribitol phosphate conjugated to tetanus toxoid (PRP-T). The 287 infants in the study were randomized to receive either the Hib vaccine combined in a single injection with DTP, separate injections of Hib vaccine and DTP, or separate injections of DTP and a placebo. The one death during the study, resulting from pneumonia and sepsis, occurred 38 days after the second dose of combined DTP and PRP-T. Cultures obtained from the infant were positive for *Streptococcus pneumoniae*.

Chazono and colleagues (1991) described the side effects following use of DTaP vaccine in Japan and compared that experience with the side effects reported in a Phase III trial of the acellular pertussis vaccine component in Sweden in 1986. Pediatricians in four health centers in Japan collected information on the number of children diagnosed with any infectious diseases after receiving DTaP vaccine, as well as information on cases of pertussis or abnormal reactions such as febrile seizures. Information was obtained from medical charts or from parents or guardians contacted by telephone or mail. Of the 940 infants for whom information was available, three children had an infectious disease (one case each of measles, mumps, and varicella). The authors contrasted their findings with those from the Phase III acellular pertussis trial in Sweden, where three deaths from severe invasive bacterial infection (i.e., Hib, pneumococcal, and meningococcal infections) occurred among 1,385 children.

Ruuskanen and colleagues (1980) examined antibody responses and adverse reactions following receipt of inactivated polio vaccine. Children in the study received 2 doses of IPV as well as 4 doses of DTP between the ages of 3 months and 24 months. Information on reactions following receipt of IPV was obtained from questionnaires returned by parents of 225 of 380 children in the study. Fever (greater than or equal to 37.5°C) was reported for about 17 percent of children and was clinically significant (greater than or equal to 38.5°C) in 5 percent of the children. Fevers usually began the same day as vaccination and lasted up to 2 days. In a few children (exact number unspecified), fevers started 6 or more days following vaccination. The authors believed that these fevers were caused by infection, and not vaccination, although the basis for their belief was not stated.

Causality Argument

The committee reviewed several case-control or cohort studies (Black et al., 1991; Burstein and Fleisher, 1994; Davidson et al., 1991; Griffin et al., 1992; Kristensen et al., 2000) and a randomized controlled trial (Otto et al., 2000) (see

Table 2). Vaccine exposure varied among the studies but fit the committee's definition of exposure to "multiple immunizations." The studies examined the effects of the addition of one vaccine to an existing immunization schedule, of one vaccine consisting of antigens from more than one infectious agent or strain of virus (e.g., DTP, OPV, or MMR), or of several vaccines received at the same time. Outcome measures in the studies also varied, with the "disease" group including subjects who had a positive culture to invasive bacterial disease, who had symptoms related to infectious diseases, or who had died. Limitations of the studies included a potential health care utilization bias and high dropout rates. Despite these variations and limitations, the overall findings from the studies consistently demonstrated either no effect or a beneficial effect of multiple immunizations on heterologous disease. **Therefore, the committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of heterologous infections.**

Autoimmune Disease: Type 1 Diabetes

Uncontrolled Observational Studies

An ecological analysis by Hyoty and colleagues (1993) and an update by Hiltunen et al. (1999) examined the incidence of type 1 diabetes before and after introduction of MMR vaccine in Finland in 1982. Periodic mumps epidemics had been suggested as a contributing factor in the incidence of Type 1 diabetes, and the introduction of MMR vaccine resulted in almost complete disappearance of mumps. Data on the incidence of type 1 diabetes among children ages 0–14 years was obtained from a national registry for the years 1966–1996. The authors found a continuing increase in the incidence of diabetes over the period, especially among children ages 0–4 years and 5–9 years, but no cohort effect associated with the introduction of MMR vaccine was observed. The authors concluded that neither wild-type mumps nor MMR vaccine were related to the continuing increase in diabetes.

In a letter reporting on an ecological analysis, Classen (1996) examined IDDM incidence in children born before and after the introduction of a hepatitis B immunization program in New Zealand in 1988. At the time, children in New Zealand were also routinely immunized with DTP, MMR, and OPV vaccines. Exposure was based on birth year, and diabetes cases were identified through the diabetes registry in Christchurch. The author reported an increase in average annual incidence of diabetes after introduction of hepatitis B vaccine, although no control was made for the general secular trend of increasing diabetes incidence rates. The incidence rate for 1982–1987 was 11.2 cases per 100,000 per year, and the rate increased to 18.2 cases per 100,000 per year for 1989–1991. The authors proposed a possible link between the hepatitis B vaccine, and the timing of its

administration, and the rising incidence of type 1 diabetes, but the ecological nature of the study limits the ability to make inferences about causation.

Controlled Epidemiological Studies

Vaccine Safety Datalink. In a case-control study, DeStefano and co l-leagues (2001) examined the association between childhood vaccines and the risk of developing type 1 diabetes. Data for both cases and controls were obtained from the four health maintenance organizations (HMOs) that participate in CDC's Vaccine Safety Datalink project. The cases were 252 children diagnosed with type 1 diabetes and the 768 controls were matched to individual cases on HMO, sex, date of birth (within 7 days), and length of health plan enrollment. For each case, vaccination history prior to the date of diabetes diagnosis was gathered from a medical chart review. The same reference date was used to obtain vaccination histories for the matched controls.

The vaccines evaluated included DTaP, DTwP, MMR, varicella, Hib, and hepatitis B. Oral polio vaccine was not included in the analysis because so few children had not received it (one case and three controls). Also tested was the effect of the timing of the first hepatitis B vaccine (never vaccinated; birth to 14 days, 15 to 55 days, or 56 or more days). In addition, the effect of differences in the schedule of Hib immunization (one dose at 21 to 27 months of age versus 3 doses in the first 8 months plus a fourth dose at 12 to 18 months) was examined.

On the basis of a conditional logistic regression model stratified by the matching variables, the odds ratio for each of the vaccines was nonsignificant. However, after adjusting for race/ethnicity and family history of type 1 diabetes, the odds ratio for whole-cell pertussis was 0.23 (95% CI 0.06–0.93). The highest adjusted odds ratio was for MMR (1.43, 95% CI 0.71–2.86) but was not statistically significant. Variations in the timing of hepatitis B vaccine produced no significant differences in the risk of type 1 diabetes. Similarly, there were no significant differences among various Hib immunization schedules. However, the ability to compare the different Hib schedules was limited, since only a few children received either no Hib vaccine or received one dose at 21 to 27 months. The authors concluded that neither the receipt of routine childhood vaccines nor the timing of certain vaccines was associated with an increased risk of type 1 diabetes.

EURODIAB. In a case-control study, a group examined infections and vaccinations as risk factors for type 1 diabetes (EURODIAB, 2000). Cases and controls were identified through seven European centers, each of which operates a population-based diabetes registry. As cases, there were 900 children with diabetes onset before age 15. The 2,302 controls were matched to the cases by age distribution. Vaccination history was obtained from parents through interviews or questionnaires and validated by official sources or entries in child health records held by the parent. Vaccines received included BCG, polio, tetanus, diphtheria, pertussis, rubella, measles, mumps, and Hib.

The odds ratios for all nine vaccines were nonsignificant using either a Mantel Haenszel analysis stratified by center, or a logistic regression analysis with adjustment for center, age group, breast feeding, birth weight, maternal age, jaundice at birth, asthma, and vitamin D supplementation. There was no evidence, the authors concluded, that vaccinations increase the risk of type 1 diabetes. The study may have been compromised by ascertainment bias. About 75% of responders had validated vaccination records available. Validation was based on either a review of official records or on parental recall of exact vaccination dates, even if the investigator did not see a record. The latter may have contributed to imprecision in assigning vaccine status.

Finland. Karvonen and colleagues (1999a) studied the relationship between multiple vaccines and type 1 diabetes by examining the effect of adding Hib vaccine to the routine childhood immunization schedule. Incidence of type 1 diabetes was compared in cohorts of Finnish children born before or after a Hib vaccine efficacy trial and followed for 10 years. One cohort of 128,936 children was born between October 1983 and September 1985, prior to the Hib vaccine trial and thus was not exposed to the vaccine. Children born between October 1985 and August 1987 participated in the Hib vaccine efficacy trial. These children were divided into two cohorts: 59,238 children who were born on odd days were vaccinated with Hib at 3, 4, 6, and 14 to 18 months; 57,114 children born on even days were vaccinated at 24 months only. All children were assumed to have received BCG, diphtheria-tetanus-pertussis, polio, and measles-mumps-rubella vaccines. Newly diagnosed cases of diabetes among all three cohorts were ascertained from a national hospital discharge registry (1983–1986) or a nationwide prospective childhood diabetes registry (1987–1997).

There was no significant difference in the risk of diabetes by age 10 between the children who did not receive the Hib vaccine and children who were vaccinated at 24 months of age. Similarly, no difference in risk was found between the children first vaccinated at 3 months of age and those vaccinated at 24 months. For each of the comparisons, the relative risk was near 1.0. The authors concluded that neither the addition of Hib vaccine to the immunization schedule nor the timing of Hib vaccine increased the risk of type 1 diabetes in children. Estimates of both vaccine exposure and diabetes cases were based on aggregate data from three cohorts and from the population as a whole. Thus, interpreting the results at the level of the individual is difficult.

Sweden. Heijbel and colleagues (1997) examined the effect of pertussis vaccination in infancy on the risk of developing type 1 diabetes. Cumulative incidence of type 1 diabetes at ages 0 to 12 years was compared in cohorts of children born before or after the pertussis vaccine was removed from the routine immunization schedule in Sweden. Specifically, cohorts of children born in 1977 (96,057 children) and in 1978 (93,248 children) received pertussis vaccine

TABLE 2 Evidence Table: Controlled Epidemiological Studies—Vaccines and Heterologous Infections

Citation	Design	Population	Exposure Measure	Outcome Measure	Results	Comment	Contributions to Causality
Kristensen et al. (2000)	Cohort; two visits required	8,752 children born to women participating in a longitudinal mortality study (Guinea-Bissau)	Vaccine status by inspection of immunization card. Vaccines included BCG, polio, diphtheria-tetanus-pertussis,* and measles vaccines	Mortality by parental report	**RR (95% CI) mortality** Any vaccine = 0.74 (0.53–1.03) BCG = 0.55 (0.36–0.85) Measles = 0.48 (0.27–0.87) DTP = 1.84 (1.10–3.10) Polio = 1.81 (1.07–3.05)	vaccination status unclear; records not available for more than one-third; vaccinated children more likely to receive health care; maternal age differences in cohorts; adjustment for potential confounds not clear; DTP may negate the positive effect of BCG	weak evidence relevant to causality; favors beneficial effect of measles and BCG and negative effect of DTP in country with a high infant mortality of uncertain relevance to U.S.; BCG data not relevant to U.S.
Otto et al. (2000)	Randomized controlled trial comparing vaccinated and unvaccinated children	662 children born between Jan 1995 to Dec 1996 at a single hospital; 166 children excluded from final analysis (most missed vaccination) (Germany)	Vaccinated: 1st vaccination (diphtheria, pertussis,* tetanus, (ital.)*Haemophilus influenzae type B*, and poliomyelitis) 60 days after birth Unvaccinated: 1st vaccination at 90 days after birth	Any "Unspecific morbidity" from parental diary on days 66 to 90 after birth. Unspecific morbidity = coughing, signs of rhinitis, restlessness, vomiting, rash, pain, poor	Vomiting, cough, rhinitis, restlessness, rash, pain more common in unvaccinated group (all $p < 0.01$); 4 hospitalizations in unvaccinated group vs. 1 in vaccinated group	Not blinded; drop out/exclusion rate 25%, disproportionately in early-vaccination group	Weak evidence relevant to causality; favors no effect or beneficial effect of vaccines

Burstein & Fleischer (1994)	Case-control	54 case children, age 3–36 months, participating in multicenter antibiotic study and 108 age-matched controls (United States)	Vaccination history, including DTwP, obtained from medical records. Hib not yet available for these children	food/fluid intake, fever and respiratory embarrassment	Children with occult bacterimia: *S. pneumoniae, E. coli, S. aureus, H. influenzae,* or *Salmonella spp*	Difference between cases and controls NS ($p > 0.05$) Interval (days) since last Vaccine Cases = 128.8 +/- 111.5 Febrile = 154.9 +/- 99.6 Trauma = 163.0 +/- 157.8 Interval (days) since last DTwP vaccine Cases = 161.5 +/- 134 Febrile = 188.8 +/- 128.8 Trauma = 184.1 +/- 172.1	Specific vaccines, other than DTwP, administered to children are unknown.; weak statistical power	Weak evidence relevant to causality; favors no effect of vaccines or of DTwP vaccine
Griffin et al. (1992)	Cohort	64,591 children immunized through Tennessee county health clinics	At least one DTP vaccination in 1986 or 1987; exposure based on information in linked TN immunization-birth certificate database	Invasive bacterial infections (*H. influenzae, N. meningitidis, Streptococcus pneumoniae, group B Streptococcus,* or *Listeria monocytogenes*. in children 72 mos. or younger, from surveillance of hospital infection control	**Age-adjusted RR (95% CI)** Of all invasive bacterial infections by days since DTP immunization Comparing early post-immunization periods (0–7, 8–14, 15–28 days) to later period (29+ days): 0–7 days: 1.0 (0.5–2.0) 8–14 days: 0.8 (0.4–1.7) 15–28 days: 1.2 (0.7–1.9)	No unvaccinated comparison group; analysis limited to cases of serious culture-confirmed cases	Weak evidence relevant to causality; favors no effect of DTP vaccine

Continued

Continued

Black et al. (1991)	Case-control	223 cases of invasive bacterial disease in children between 1 month and 2 years from 1986 to 1988; 446 controls matched on age, sex, zip code, duration of plan membership (U.S.Kaiser Permanente)	Immunization by record review; diphtheria-tetanus-pertussis,* measles-mumps-rubella, and oral polio immunization within 3 months of disease onset during first 2 years of life	Invasive bacterial disease status identified from a computerized microbiology laboratory database *Pneumococcus, H .influenzae, E. coli, Meningococcus* among diseases identified	**Unadjusted OR (95% CI)** Within 8–30 days DTP = 0.37 (0.10–1.41) OPV = 0.13 (0.02–1.11) MMR = 0.16 (0.01–2.33) Any = 0.29 (0.09–0.95) Within 61–90 days DTP = 0.31 (0.04–2.50) Any = 0.21 (0.03–1.63) **Adjusted OR (95% CI),** any vaccine (DTP, OPV, MMR), adjusted for day-care attendance and well-care child visits Within 30 days = 0.26 (0.09–0.76) Within 90 days = 0.31 (0.13–0.73)	No demonstration of an increased risk for invasive bacterial disease following immunization with DTP, MMR, and OPV	Weak evidence relevant to causality; favors no effect or beneficial effect
Davidson et al. (1991)	Case-control	study #1 186 cases of invasive bacterial disease; 186 controls matched on age, sex, residence, number DTwP immunizations (US-Alaska natives)	Exposure to DTwP† vaccination determined from public health immunization records and computerized Indian Health Service medical records.	Cases with invasive bacterial disease, specifically, *H. influenzae* type b or *S. pneumoniae*, detected through active and passive surveillance reports	**ORs (95% CI)** < 3 day interval Hib disease = 1.0 (0.05–20.9) 31–60 day interval Hib disease = 1.0 (0.5–2.0) Sp = 3.3 (1.1–10.0) Total = 1.4 (0.8–2.5) > 120 interval days Hib disease 1.0 (0.5–2.2) Sp 0.3 (0.08–1.0) Total = 0.7 (0.3–1.3)	potential for over matching; well child effect likely	Weak evidence relevant to causality; favors no effect of DTwP vaccine

Davidson et al. (1991)	Cohort	study #2 (subset of study #1) 104 cases for whom all medical records were available (U.S.-Alaska natives)	Exposure to DTwP† vaccination determined from public health immunization records and computerized Indian Health Service medical records	Occurrence of all illness during the 30-day period before and after DTwP administration. Categories include: any illness; any infectious disease; otitis media; other respiratory infections; temperature > 38°C; and hospitalization	For all illness, 53% of all children had illnesses during 30 days before DTwP immunization and 43% had illnesses during 30 days after DTwP immunization (p = .004); Other illness categories were non-significant; any infectious disease (p = .084); otitis media (p = .501); other respiratory infections (p = 0.285); temp > 38°C (p = .724); hospitalization (p = .424)	potential for over matching	Weak evidence relevant to causality; favors no effect of DTwP vaccine

BCG = Bacille Calmette-Guerin vaccine
MMR = measles-mumps-rubella vaccine
DTaP = diphtheria-tetanus-acellular pertussis
DTwP = diphtheria-tetanus-whole-cell pertussis
Hep B = hepatitis B vaccine
Hib = *Haemophilus influenzae b* vaccine
OPV = oral polio virus
HMO: health maintenance organization
NS = not significant
CI = confidence interval
OR = odds ratio
RR = relative risk

*These studies do not specify whether acellular or whole-cell pertussis vaccine was administered. It is assumed that whole-cell pertussis vaccine was administered to children in these studies.
†Diphtheria-tetanus-whole cell pertussis vaccine

through DTP vaccinations. Children born in 1980 (97,064 children) and in 1981 (94,065 children) received DT vaccine.

Rates of exposure to DT or DTP vaccine were assessed from yearly vaccination reports of child health care centers. Estimates of pertussis vaccine exposure among children born in 1980 or 1981 were based on reports of vaccine doses released. Data from the national diabetes registry were used to determine the cumulative incidence of type 1 diabetes in each birth cohort. No difference was found in the cumulative type 1 diabetes incidence for any of the birth cohorts. The population-level immunization data limits ability to make extrapolations at the individual level.

In another study in Sweden, Blom and colleagues (1991) used a case-control approach to examine infections and vaccinations as possible risk factors for type 1 diabetes. A total of 339 children age 0 to 14 years and newly diagnosed with diabetes from September 1985 through August 1986 were identified from the Swedish childhood diabetes register. The study included 528 controls matched on age, sex, and county, who were identified from the Swedish population register. Vaccination histories in the two groups were collected from local child health care centers and school health units. The vaccines received by these children included BCG, smallpox, DTP, DT, tetanus, polio, MMR, measles, mumps, and rubella. Similar proportions of children in both the case and control groups had received each of these vaccines.

The odds ratios for risk of type 1 diabetes for individual vaccines (or combination products) were nonsignificant. The odds ratio for measles vaccine alone was 0.74 (95% CI 0.55–1.00), but when the measles-mumps-rubella and/or measles vaccine was considered, the odds ratio suggested a significant reduction in risk (OR = 0.69, 95% CI 0.48–0.98). The authors concluded that the evidence did not support an increased risk of type 1 diabetes after vaccination and that the measles vaccine may have a protective effect against type 1 diabetes. The study was well conducted, but the number of cases of diabetes was small, so that the study may have been under-powered to detect significant differences in the 13 categories of vaccination examined. Power calculations for Type II errors were not provided. The isolated finding of a possible protective effect (just at the 0.05 level of statistical significance) of the measles vaccine is difficult to interpret given the multiple comparisons made in the analysis.

Other Studies

The committee reviewed additional studies examining the relationship between diabetes and BCG or smallpox vaccination (Classen and Classen, 1996, 1997, 1999; Dahlquist and Gothefors, 1995; Parent et al., 1997). But because these vaccines are not routinely administered to children in the United States, the studies were not considered directly relevant to the committee's task.

Causality Argument

The committee found five controlled studies (Blom et al., 1991; DeStefano et al., 2001; EURODIAB, 2000; Heijbel et al., 1997; Karvonen et al., 1999a) (Table 3) and three ecological studies (Classen, 1996; Hiltunen et al., 1999; Hyoty et al., 1993) that studied this relationship. The studies looked at the effects of the addition of one vaccine to an existing immunization schedule, of one vaccine consisting of antigens from more than one infectious agent or strain of virus (e.g., DTP, OPV, or MMR), or of several vaccines received at the same time. Despite these variations, the overall findings from the studies consistently demonstrated no effect of multiple immunizations on the incidence of type 1 diabetes. **Therefore, the committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of type 1 diabetes.**

Allergic Disease

Uncontrolled Observational (Ecological) Study

Anderson and colleagues (2001) examined the relationship between immunization and allergic disease by comparing trends in immunization rates with the prevalence of allergic disease symptoms. Allergy data, specifically for asthma, allergic rhinoconjunctivitis, and atopic eczema, were obtained for children ages 6 to 7 years and 13 to 14 years from centers participating in the International Study of Asthma and Allergies in Childhood (ISAAC). Those data were compared with national and local immunization rates for BCG, DTP, and measles.

For children age 6 to 7 years, allergy data were obtained from 91 centers, with a median of 2,996 children per center (range 1,104–6,533). Local immunization rates were available for 57 centers. Allergy data for children age 13 to 14 years were available from 154 centers with a median of 2,064 children (range = 1,046–11,400); 92 centers had local immunization data.

In the 13- to 14-year-old age group, the authors observed a significant negative association (rank correlations, $p < .05$, adjusted for socioeconomic factors) between local DTP rates and wheezing (-0.53, 95% CI, -1.49, 0.43), rhinoconjunctivitis (-0.60, -1.02, -0.19), and atopic eczema (-0.27, -0.76, 0.21). For measles vaccine, significant negative correlations were found for rhinoconjunctivitis (-0.47, -.98, 0.04) and atopic eczema (-0.42, -0.98, 0.13). No associations were observed for children age 6 to 7 years. The authors concluded that DTP vaccines are not risk factors for allergic disease at the population level. However, the authors noted that because immunization data were available only at the population level, associations at the individual level could not be excluded.

TABLE 3 Evidence Table: Controlled Epidemiological Studies—Vaccines and Type 1 Diabetes

Citation	Design	Population	Exposure Measure	Outcome Measure	Results	Comment	Contribution to Causality Argument
DeStefano et al. (2001)	Case-control	252 children from 4 HMOs that participate in Vaccine Safety Datalink project of the CDC along with their 768 matched controls (United States)	From chart review: vaccine exposure prior to diabetes incidence date: DTaP, DTwP, measles-mumps-rubella, varicella; Hib, HepB; Timing of Hep B (never vaccinated; birth to 4 days, 15 to 55 days, and GTE 56 days); Hib schedule (3 doses in first 8 mos + 4th dose at 12–18 mos vs. 1 dose at 21–27 months)	Cases in HMO registries with ICD-9 diagnosis of type 1 diabetes	**Adjusted OR (95% CI):** Vaccines and Type I diabetes Hep B = 0.73 (0.45–1.19) Hib = 1.23 (0.53–2.89) whole-cell pertussis = 0.23 (0.06–0.93) acellular pertussis = 1.12 (0.63–1.99) MMR = 1.43 (0.71–2.86) Varicella = 1.02 (0.61–1.71) Hep B timing and risk of type 1 diabetes 0–14 d = 0.66 (0.27–1.59) 15-55 d = 0.65 (0.21–2.0) ≥ 56 d = 0.74 (0.45–1.21) Hib schedule and risk of type 1 diabetes: 1 dose only at 21–27 mo: 0.45 (0.15–1.30) Other schedules = 0.71 (0.41–1.24) Not vaccinated = 0.64 (0.22–1.81)	Limited ability in comparing Hib schedules since only a few children received no Hib or only 1 dose at 21–27 months	Weak evidence relevant to causality. Favors no effect of specific vaccine or the timing of Hepatitis B and Hib.
EURODIAB Study Group (2000)	Case-control	900 cases with diabetes and 2302 controls matched on age	Vaccination history by interview or questionnaire; Vaccines included BCG, polio,	Diabetes cases from a population-based register	**Adjusted OR (95% CI)** BCG = 0.83 (0.57–1.20) Polio = 1.20 (0.57–2.52) Tetanus = 1.56 (0.73–3.33)	Ascertainment bias	Weak evidence relevant to causality; Favors no effect

		from 7 European centers with population-based diabetes registers	tetanus, diphtheria, pertussis,* rubella, measles, mumps, and Hib	of childhood onset diabetes			of any vaccine
Karvonen et al. (1999a)	Cohort	10-year follow-up of three cohorts of Finnish children: Cohort 1 = 128,936 (born 1983–1985); Cohort 2 = 59,238 Cohort 3 = 57,114 (born 1985–1987), assignment to cohort 2 or 3 based on odd (2) or even (3) day of birth	3 Vaccine exposure cohorts: 1) born before Hib availability; 2) participating in Hib efficacy trial, vaccination at 3, 4, 6, and 14–18 months; and 3) Hib at 24 months only Children assumed to also have received BCG, diphtheria-tetanus-pertussis,* polio, and measles-mumps-rubella vaccines	New IDDM cases in each cohort, reported in nationwide hospital disease registry (1983-1986) or nationwide prospective childhood diabetes registry (post-1987)	Diphtheria = 1.27 (0.63–2.56) Pertussis = 0.83 (0.63–1.09) Rubella = 1.27 (0.93–1.72) Measles = 1.10 (0.84–1.42) Mumps = 1.03 (0.82–1.30) Hib = 0.75 (0.30–0.92) **RR of diabetes by age 10 (P-value) :** Cohort 3 vs. Cohort 1 = 1.01 (p = 0.228) Cohort 2 vs. Cohort 3 = 1.06 (p = 0.545)	Vaccine exposure and diabetes cases based on aggregate data from three cohorts and from population. Interpretation at level of individual is difficult	Weak evidence relevant to causality. Favors no effect of adding Hib to the vaccine schedule
Heijbel et al. (1997)	Cohort	Birth cohorts of Swedish children with and without routine pertussis vaccination for the following years: 1977 (n = 96,057), 1978 (n =	Exposure to diphtheria-tetanus or diphtheria-tetanus-pertussis* determined from yearly vaccination reports from child health centers. Pertussis vaccine exposure based on reported released doses of vaccines	Cumulative incidence of IDDM to age 12 in each birth cohort, determined from national registry	No difference in cumulative IDDM incidence in birth cohorts	Immunization data population-only. Not known if children received other vaccines besides DT or DTP. No statistical analysis	Weak evidence relevant to causality. Favors no effect of pertussis vaccine

Blom et al. (1991)	Case-control	93,248), 1980 (n = 97,064), and 1981 (94,065)	Children ages 0–14: 339 cases (newly diagnosed diabetes); 528 controls (matched on age, sex, county) (Sweden)	Vaccination history from local child health care centers, school health units. Vaccines included BCG, smallpox, diphtheria-tetanus-pertussis,* diphtheria-tetanus, tetanus, polio, measles-mumps-rubella, measles, mumps, and rubella.	Diabetes cases identified from national registry	**Odds ratios (95% CI)** BCG = 1.04 (0.77–1.40) Smallpox = 1.07 (0.77–1.49) DTP = 0.94 (0.70–1.28) DT = 0.96 (0.71–1.30) Tetanus = 0.96 (0.70–1.31) Polio = 1.04 (0.17–6.25) MMR = 0.95 (0.71–1.28) Mumps = 1.75 (0.54–5.70) Rubella = 1.24 (0.41–3.73) Measles 0.74 (0.5–1.00) MMR and/or measles -0.69 (0.48–0.98). MMR and/or mumps -0.95 (0.70–1.27). MMR and/or rubella- 0.95 (0.71–1.28)	Small number of cases with diabetes; power calculations for type II were not provided; protective effect of measles difficult to interpret due to multiple comparisons made in analysis	Weak evidence relevant to causality. Favors no effect for most vaccines, beneficial effect for MMR and/or measles vaccine

BCG = Bacille Calmette-Guerin vaccine
CI = confidence interval
DTaP = diphtheria-tetanus-acellular pertussis
DTwP = diphtheria-tetanus-whole-cell pertussis
Hep B = hepatitis B vaccine
Hib = *Haemophilus influenzae b vaccine*
MMR = measles-mumps-rubella vaccine
HMO: health maintenance organization
NS = not significant
OR = odds ratio
RR = relative risk

*These studies do not specify acellular or whole-cell pertussis vaccine. It is assumed that whole-cell pertussis vaccine is being administered to children in these studies.

Controlled Observational Studies

Wellington, New Zealand. Wickens and colleagues (2001) studied p o-tential risk factors for asthma in a case-control study of children age7 to 9 years. Cases were 233 children selected from the Wellington, New Zealand, arm of ISAAC who currently had asthma. Controls were 241 children who never had asthma or asthma-like symptoms. Information on demographics and risk factors for asthma, such as parental smoking history, was collected through interviews with parents. Vaccination histories were gathered from the medical records of study participants. Vaccines to which case and control children were exposed included DTP, DT, hepatitis B, polio, MMR, measles, and BCG.

Odds ratios were individually calculated for the following vaccine categories: DPT, DT or DPT, hepatitis B, polio, measles or MMR, MMR, and BCG. Only a few children were unvaccinated (no DTP = 38; no polio = 25; no MMR = 333), and children in the unvaccinated group may have been misclassified, as some of their vaccination records were missing. In an univariate analysis, the asthma odds ratios for most vaccine exposures were non-significant. For MMR, however, the odds ratio was 1.62 (95% CI 1.06–2.47), though for measles or MMR combined the risk for asthma was not significantly increased (OR = 1.52, 95% CI 0.89–2.58). In a multivariate analysis, the association between asthma and MMR vaccine was nonsignificant (OR = 1.43, 95% CI 0.85–2.41). The authors suggested that the significant univariate association observed between MMR vaccination and asthma was confounded by measles infection and polio vaccination and concluded that there was no association between vaccination and asthma, commenting that the (non-significant) elevated odds ratios could be due to selection bias, exposure misclassification or multiple comparisons.

United States. Hurwitz and Morgenstern (2000) examined the association between vaccination and allergies (as well as allergy-related respiratory symptoms) among children and adolescents, using data collected between 1988 and 1994 for the third National Health and Nutrition Examination Survey. For 13,944 infants, children, and adolescents ages 2 months through 16 years, information was gathered regarding DTP or tetanus vaccination, lifetime history of physician-diagnosed allergy (asthma or hay fever), and allergy symptoms in the past 12 months. Children's parents or guardians answered the survey.

Of the 13,944 subjects, 284 children reported no receipt of DTP or tetanus immunization and were classified as unvaccinated. Subjects with missing data (n = 332) were excluded from the analysis. Adjusted odds ratios were calculated for nine different definitions of allergy related symptoms in the vaccinated and unvaccinated groups. Three closely related outcomes were statistically significant: allergy-related symptoms in the past 12 months (adjusted OR = 1.63, 95% CI 1.05–2.4), any lifetime allergy history or 12-month allergy symptoms (OR = 1.7, 95% CI 1.1–2.6), and nose and eye symptoms (OR = 2.2, 95% CI 1.3–3.7).

Odds ratios for asthma, severe allergic reactions, sinus problems, and wheezing ranged from 1.2 to 2.0 and were not statistically significant. The prevalence of atopy as determined by skin testing with 10 environmental allergens was similar in the two groups (49% and 51%). The authors concluded that DTP and tetanus vaccination increases the risk of clinical allergy but not atopy in children and adolescents. The authors noted several limitations. Subjects excluded from the analysis were more likely to have risk factors related to being unvaccinated than subjects included in the analysis. Excluded subjects were also more likely to have allergies than unvaccinated subjects. These limitations may have biased the estimated effects towards a positive effect. The authors' reanalysis of the data, assuming that the excluded subjects were all unvaccinated, lowered the estimated effects. The limitations reported by the authors included the cross-sectional design, self-reported vaccination status and allergy symptoms, use of proxy respondents, missing data on 2.4% of subjects, small number of unvaccinated subjects (2% of the population), lack of clinical information about the clinical nature of symptoms, recall bias, selection bias for care-seeking behavior, and unmeasured confounding. To this could be added the very limited ability to control for confounders due to the small numbers of subjects in the unvaccinated groups, particularly when analyses were restricted to children over 5 years of age, when the number of unvaccinated children for different outcomes ranged between 1 and 8, and the inclusion of children under two years of age, in whom allergic symptoms are difficult to separate from infectious ones.

United Kingdom. Farooqi and Hopkin (1998) examined the relationship between childhood infections and subsequent allergic disorders, along with other potential risk factors, such as immunizations. Of the 3,062 children born between 1975 and 1984 and seen at a general medical practice in the United Kingdom, 1,934 children (63% of original cohort) who remained registered at the practice and who had complete immunization records were included in the study. Information was obtained from medical records and a regional child health database on vaccines received (i.e., diphtheria-tetanus-whole-cell pertussis/diphtheria-tetanus, polio, and measles) and diagnoses of allergic diseases such as hay fever and asthma.

A higher proportion of children with allergic disease received pertussis vaccine, which showed a statistically significant association with allergy, asthma, and hay fever. The unadjusted odds ratio for DTP immunization (either complete or incomplete course) and allergy was 1.57 (95% CI 1.28–1.96); for asthma, the odds ratio was 1.44 (95% CI 1.17–1.85); and for hay fever, the odds ratio was 1.56 (95% CI 1.21–2.02). A multiple logistic regression analysis showed pertussis immunization statistically associated with allergic disease (OR = 1.76, 95% CI 1.39–2.23), along with maternal atopy (OR = 2.0, 95% CI 1.5–2.7) and antibiotic treatment in the first two years of life (OR = 2.1, 95% CI 1.6–2.6). The authors concluded that whole-cell pertussis vaccination significantly increased the odds of developing asthma, and they noted as well that the

association persisted when children with a history of allergic disease prior to immunization were excluded from the analysis. The authors also noted the possibility of health care-seeking bias in their results, but they found no difference between vaccinated and unvaccinated children in the number of health care visits. However, the removal of 36 percent of potential subjects who were no longer registered at the practice, and their exclusion from the study suggests a potential health care seeking bias in the sampled population. Because of this bias, interpretation of the study's findings warrants caution.

Christchurch, New Zealand. Kemp and others (1997) examined the r elationship between immunization and allergic disease in infants. Data on vaccines received, asthma, and allergic diseases were collected for 1,265 children born in 1977 and participating in a New Zealand health study. Children in this health study were expected to have received DTP and polio vaccines at ages 3 and 5 months and measles vaccine at 12 to 15 months. Information on vaccines and the occurrence of asthma and/or allergic diseases (including rhinitis) at ages up to 5, 10, and 16 years was obtained from parents' medical diaries and physicians' records, plus additional inquiries directed to parents. Of the children in the study, 23 did not receive either DTP or polio vaccine at the scheduled age and were classified as "nonvaccinated."

For children age 0 to 10 years, a greater proportion in the immunized group reported asthma episodes, asthma consults, and allergy consults, compared with children in the nonvaccinated group, for whom there were no reports of asthma or consultations for asthma or allergy. Because no events occurred in the nonvaccinated group, the relative risk was infinite (95% CI 1.03–infinity). For children age 11 to 16 years, among whom 5 allergic and asthma consultations/episodes occurred in the nonvaccinated group, the relative risks for vaccinated children (2.7 to 5.6) were not significant. No association was seen between measles vaccine and risk of asthma episodes in children age 0 to 10 years (OR 1.0, 95% CI 0.9–1.1). Minimal effect of potential confounders was seen when each were considered singly in multivariate models, and the unvaccinated children differed from vaccinated children in ways that should have put them at higher risk for asthma-related symptoms (e.g., lower SES, more parental smoking, more family history of allergy, more pet ownership). The authors concluded that infant immunization for DTP and polio may increase the risk of developing asthma in childhood. But limitations of the study, including the small number of unvaccinated children, the marginal significance of the results (with high sensitivity to a change of even one subject in the unvaccinated group), the potential for a health care utilization bias, and difficulty in adjusting for confounders (due to the small number of unvaccinated children), warrant caution in interpreting these findings.

Controlled Clinical Trials

Sweden. Nilsson and others (1998) studied the development of allergic disease during a randomized controlled trial of pertussis vaccines in Sweden (Gustafsson et al., 1996). A total of 669 children were randomized to one of four exposure groups: 2-component DTaP, 5-component DTaP, DTwP, or DT (control). As part of the recommended immunization schedule in Sweden, children were also given inactivated polio and Hib vaccines two or more weeks later or at the same time. Parent questionnaires, clinical findings, and medical record information provided data on diagnoses of bronchial asthma, atopic dermatitis, allergic rhinoconjunctivitis, urticaria, and food allergy. Children were followed from ages 2 months to 2.5 years.

Cumulative incidence of allergic disease at age 2.5 years in the three pertussis vaccine groups was similar to that in the DT group after adjusting for family history of allergy. Among children whose parents had no history of allergic disease, those who received DTwP were estimated to have an 8% relative reduction in risk (one-sided 95% CI = 28% increase) of allergic disease compared with the control group, which had a predicted risk of 22.5%. The combined DTaP group had an estimated 10% relative increase in risk (one-sided 95% CI = 41% increase). When both parents had a history of allergy, DTwP was associated with a 6% relative reduction in risk (one-sided 95% CI = 18% increase) and DTaP with a 8% relative increase in risk (one-sided 95% CI = 27% increase). With the authors' one-tailed test for increased risk, they calculated that with the size of the sample, they had approximately 80% power to detect a 50% increase in risk, roughly the magnitude reported in some other studies. Differences between the DTwP and DTaP groups were not significant. Interestingly, subsequent asthma was elevated over two-fold ($p = 0.03$) by the development of clinical pertussis, which occurred in 14.5% of unimmunized and 4.4% of immunized children, although the authors raised the possibility that this could partly be due to transient bronchial hyperreactivity after whooping cough.

This study had a nonstandard technique of calculating confidence limits, so the upper limits on the relative risk increase may not be directly compared to those of other studies. Although they used a logistic regression model for analysis, which would ordinarily generate odds ratios (and attendant Is) for the risk of asthma due to various immunizations, they appeared (not described) to use the regression model to estimate absolute risks, and calculate relative risk estimates based on these fitted absolute risks. It is also not clear how upper confidence limits on these relative risks were calculated. In addition, their use of one-sided upper limits for the relative risk would be lower than the more conventional two-sided limits by roughly 4–8 percentage points (e.g., 34% [two-sided] vs. 28% [one sided]). The combination of these two factors makes the upper confidence limits reported in this study somewhat difficult to interpret and to compare to other studies, which used odds ratios. For example, the one-sided upper

limit of a 28% relative risk increase reported by these authors for whole cell vaccine (over a baseline risk of 22.5%) corresponds approximately to a two-sided upper limit of a 50% increase in the odds of asthma.

The authors concluded that there was no evidence supporting an increase in allergic disease after pertussis immunization of the magnitude reported in some other studies, and if there was any increased risk, they thought it was most likely to be associated with the acellular pertussis vaccines. However, limitations included wide confidence intervals restriction to symptom development before 2.5 years of age, the unclear and nonstandard statistical approach, and the focus only on the pertussis component of the immunization schedule. Strengths included the randomized, prospective design and small (<5%) loss to follow-up.

Causality Argument

The committee reviewed five studies that utilized controls (Farooqi and Hopkin, 1998; Hurwitz and Morgenstern, 2000; Kemp et al., 1997; Wickens et al., 2001), including a randomized controlled trial (Nilsson et al., 1998) (see Table 4) and one ecological study (Anderson et al., 2001). Outcomes assessed included allergic symptoms (wheezing) and allergic disorders (hay fever and asthma). All the studies examined exposure to DTaP or DTwP, and other vaccines given concurrently, such as MMR and polio vaccines, but no two studies examined exactly the same exposure.

While many of these studies reported elevated odds ratios linking immunizations to some allergic outcome, some of which were statistically significant, methodological weaknesses within individual studies, as well as the pattern of results across studies diminish the confidence that the observed associations reflect causal relationships. In the two studies that reported a significant positive effect of DTP or tetanus immunization or the pertussis component of DTwP (Farooqi and Hopkin, 1998; Hurwitz and Morgenstern, 2000), potential sampling bias, caused by substantial losses to follow-up or restriction to subjects with regular medical care, could have distorted the relationship between immunization and allergies.

A problem in most of the studies was that the number of unvaccinated children was small, limiting the ability to control for potentially confounding factors, which are numerous and strong for the outcomes of asthma and atopy, and particularly complex when considering risk over an entire childhood. Adequate control of confounding is a serious issue for observational designs, particularly in this domain, as nonimmunized children typically differ on baseline characteristics from immunized children in ways that are not always measurable. Control can be compromised by imperfect and possibly biased confounder and outcome measurement introduced by retrospective, unblinded review of records or parental report of outcomes or exposures that occurred in the past.

TABLE 4 Evidence Table: Controlled Epidemiological Studies—Vaccines and Allergic Disorders

Citation	Design	Population	Vaccines	Outcome Measures	Results	Comment	Contribution to Causality Argument
Wickens et al. (2001)	Case-control	233 cases with wheezing or asthma; 241 controls; ages 7–9 years (New Zealand)	DTP,* DT, polio, MMR, measles, BCG, HepB from medical records	Wheezing or asthma in last 12 months by proxy or self-report	**Unadjusted ORs (95% CI):** DTP = 1.51 (0.77–2.97) DT/DTP = 1.43 (0.69–2.96) HepB = 0.72 (0.50–1.06) Polio = 2.11 (0.90–4.90) Measles/MMR = 1.52 (0.89–2.58) MMR = 1.62 (1.06–2.47) BCG = 1.23 (0.41–3.72) **Adjusted ORs (95% CI)** HepB = 0.66 (0.42–1.05) Polio = 2.48 (0.83–7.41) MMR = 1.43 (0.85–2.41)	Potential selection bias, exposure misclassification, or multiple comparisons	weak evidence relevant to causality; favors no effect of any vaccine
Hurwitz & Morgenstern (2000)	cross-sectional survey (NHANES III)	13,944 infants and children ages 2 months through 16 years (United States)	DTP* or tetanus, by proxy (information obtained from children's parent or guardian)	history of physician-diagnosed asthma, hay fever; self-report of allergic reactions by proxy; atopy by skin testing with 10 allergens	**Estimated Crude ORs (95% CI)/Adjusted ORs (95% CI) of DTP or tetanus vaccination on following** Asthma = 2.20 (0.70–6.84)/ 2.00 (0.59–6.74) Hay fever = 1.21 (0.21–6.83)/ 0.82 (0.16–4.35) Severe allergic reaction = 2.11 (9.42–10.45)/ 1.50 (0.33–6.89) Any allergy/allergic reaction = 2.11 (0.81–5.49)/ 1.66 (0.67–4.14) Sinusitis/sinus problems = 2.16 (0.77–6.06)/ 1.81 (0.69–4.71) Wheezing/whistling = 1.03 (0.68–1.57)/ 1.23 (0.78–1.95) Nose & eye symptoms = 2.44	Study limitations included the following: cross-sectional design, recall bias; missing data on 2.4% of unvaccinated subjects; small number of unvaccinated children; lack of clinical information; selection bias for care-seeking behavior; unmeasured confounding; limited ability to control for con-	weak evidence relevant to causality; favors effect of DTP or tetanus vaccine on clinical history of allergic disorder but no effect on atopy defined by skin test reactivity

Citation	Design	Population	Vaccines	Outcome Measures	Results	Comment	Contribution to Causality Argument
					(1.57–3.78)/ 2.22 (1.30–3.77) Any allergy-related respiratory symptom (past 12 mos) = 1.68 (1.09–2.59)/1.63 (1.05–2.54) Any lifetime allergy history/12 mo. Symptoms = 1.79 (1.16–2.76)/1.69 (1.10–2.59)	founders	
Farooqi & Hopkin (1998)	Cohort	1934 patients born in 1975–1984 (United Kingdom)	DTwP/DT, polio, measles immunization from regional Child Health database	Clinical diagnosis of allergic disorder (eczema, hay fever, or asthma).	**Unadjusted OR for DTwP immunization (either complete or incomplete course) (95% CI)** Allergy = 1.57 (1.28–1.95); Asthma = 1.44 (1.17–1.85), Hay fever = 1.56 (1.21–2.02). **Multiple logistic regression: pertussis immunization** Allergic disorders = 1.76 (1.39–2.23)	Potential health care-seeking bias; exclusion of 36% of potential subjects.	Weak evidence relevant to causality. Favors effect of pertussis component of DTwP
Nilsson et al. (1998)	Randomized controlled trial	669 children participating in pertussis vaccine trial (Sweden)	Randomization to DTaP (2- or 5-component), DTwP, and DT given at 2 months. All children were given Hib and inactivated polio virus. Children followed for 2.5 years	Diagnosis based on questionaires, clinical findings, and information on medical records for bronchial asthma, atopic dermatitis, allergic rhinitis, urticaria, and food	**Estimated increase in risk:** No parental history of allergic disease (one-sided 95% CI): DTwP = 8% reduction (28% increase) DTaP = 10% increase (41% increase) Both parents had history of allergic disease DTwP = 6% reduction (18% increase) DTaP = 8% increase (27% increase)	Differences non-significant; one-tailed analysis; wide confidence intervals; restriction to development before 2.5 years of age, and focus only on pertussis component of immunization schedule.	Weak evidence relevant to causality. Favors no effect of DTaP

Citation	Design	Population	Vaccines	Outcome Measures	Results	Comment	Contribution to Causality Argument
				allergy			
Kemp et al. (1997)	cohort	1,265 children born in 1977; followed through age 16 years (New Zealand)	DTP,* polio, measles by proxy	asthma, other allergic diseases by diary or questionnaire by proxy, and by medical records	**Risk ratios** for asthma episodes, asthma consults, and allergy consults for immunized children ages 0–10 years were infinite (95% CI 1.03–infinity) because no events occurred in non-immunized group; **Risk ratios** (95% CI), age 0.16 yrs; Asthma episodes: 2.9 (0.8–23.6) Asthma consults: 2.7 (0.7–22.3) Allergy consults: 5.6 (1.0–222.6) **Risk ratios** for asthma episodes age 0–10 and measles vaccination: 1.0 (0.9–1.1)	weaknesses in study design include small number of unvaccinated children, marginal significance of results, potential for health care utilization bias; difficulty in adjusting for confounders (due to small number of unvaccinated)	weak evidence relevant to causality; favors no effect of any vaccine.

BCG = Bacille Calmette-Guerin vaccine
DTaP = diphtheria-tetanus-acellular pertussis
DTwP = diphtheria-tetanus-whole-cell pertussis
Hep B = hepatitis B vaccine
Hib = *Haemophilus influenzae b vaccine*
MMR = measles-mumps-rubella vaccine
HMO: health maintenance organization
NS = not significant
OR = odds ratio
RR = relative risk
CI = confidence interval

*These studies do not specify acellular or whole-cell pertussis vaccine. It is assumed that whole-cell pertussis vaccine is being administered to children in these studies.

Finally, the findings of the studies, taken as a whole, did not show a consistency of findings that would outweigh the concerns about individual studies. While some studies pointed to the pertussis vaccine as a risk factor for allergic syndromes with no effect of MMR, another found that MMR vaccine was the strongest risk factor. The ecological study indicated a protective DPT effect, and the only randomized study indicated minimal or no effect of pertussis vaccines, with a non-significant reduction in risk from the whole-cell vaccine.

Given the design weaknesses in the observational studies, with effect sizes and modest degrees of statistical significance that are not robust to probable biases, and a randomized trial study that does not support the risk factor most frequently implicated in the observational studies, **the committee concludes that the epidemiological and clinical evidence is inadequate to accept or reject a causal relationship between multiple immunization and an increased risk of allergic disease, particularly asthma.**

Biological Mechanisms

Although biological data do not provide an independent basis for evaluating causality they can help validate epidemiologically based conclusions for or against causal associations; such data can also guide further investigation when epidemiological evidence is inconclusive.

This section discusses evidence regarding immune system responses and mechanisms by which multiple immunizations might be related to autoimmunity, allergy, or risk for infection. The mechanisms considered represent two possible pathways to adverse outcomes: stimulation of harmful immune responses, or suppression of beneficial immune responses. The stimulation of harmful immune responses is discussed in terms of the mechanisms of molecular mimicry, bystander activation, and nonspecific or polyclonal T-cell activation. The possible suppression of beneficial immune responses is addressed in terms of the hygiene hypothesis and the prevention of potentially protective infections through immunization. The discussion includes consideration not only of exposure to vaccine antigens but also of exposure to vaccine adjuvants and of injection as the principal route.

Issues related to autoimmunity are considered first, in an extensive discussion beginning with autoimmune injury related to wild-type infection. This relationship is important to understand because vaccines are intended to act as surrogates for wild-type infection and so might be expected to pose similar risks for harmful autoimmune responses. Inherent in the hypothesis that multiple vaccines predispose to autoimmunity or allergy is an effect, in genetically predisposed individuals, of the vaccines on the developing immune system that somehow increases the risk of such immune disorders at some later time, from childhood to adulthood. Thus, the effect would not be detectably associated in time with the receipt of the immunizations. Allergy is considered next, with the primary focus

being the mechanisms by which vaccine exposure might affect susceptibility (see Figure 3). The discussions in both cases considers the possibility of either stimulation of harmful responses or suppression of beneficial ones.

Multiple Immunizations and Autoimmunity

Proposed Mechanisms for Induction of Autoimmunity Through Infection

Infection can induce immune-mediated tissue injury. In most cases, this injury is short-lived and resolves as the immune system eliminates active infection. The injury is a consequence of the immune response to the foreign invader, and when the invader is eliminated, the damaging immune process ceases. In some diseases, however, infection appears to induce an injurious immune response directed, at least in part, against self antigens. Nevertheless, true autoimmune injury must be distinguished from immune-mediated injury resulting from persistent but undetected infection. If the infectious agent was not detected, ongoing immune-mediated responses to that agent and the resulting injury of host tissues could be interpreted as autoimmunity, when in fact the immune response was directed against the foreign microbe and not against self.

Two major mechanisms—molecular mimicry and bystander activation—are proposed to account for the activation of self-reactive T and B cells and the induction of autoimmunity by infection (Albert and Inman, 1999; Bach and Chatenoud, 2001; Benoist and Mathis, 2001; Davidson and Diamond, 2001; Marrack et al., 2001; Regner and Lambert, 2001; Rose, 2001; Singh, 2000; Wucherpfennig, 2001; Zinkernagel, 2001).

Also described below is the possible link between infection and autoimmunity through the mechanism of nonspecific or polyclonal T cell activation. The evidence regarding the possibility that these mechanisms actually contribute to autoimmune diseases is discussed in a later section.

Molecular mimicry. An antigenic epitope from a microbe that is structurally similar to (mimics) an epitope of a self-molecule has the potential to trigger the activation of self-reactive, naïve T or B lymphocytes. Once activated, self-reactive T cells could expand in number and mature into effector (memory) T cells that have a lower threshold for activation by self antigens. These cells would also gain the ability to migrate to specific tissues, produce additional mediators/cytokines, and to mediate injury on contact with cross-reacting self antigens. In addition, they would gain the potential to help B cells that are responding either to the same antigen as the T cells or to other self-antigens that are physically linked to it.

Bystander activation. Bystander activation results when an infection creates environmental conditions that allow the activation of self-reactive T and B

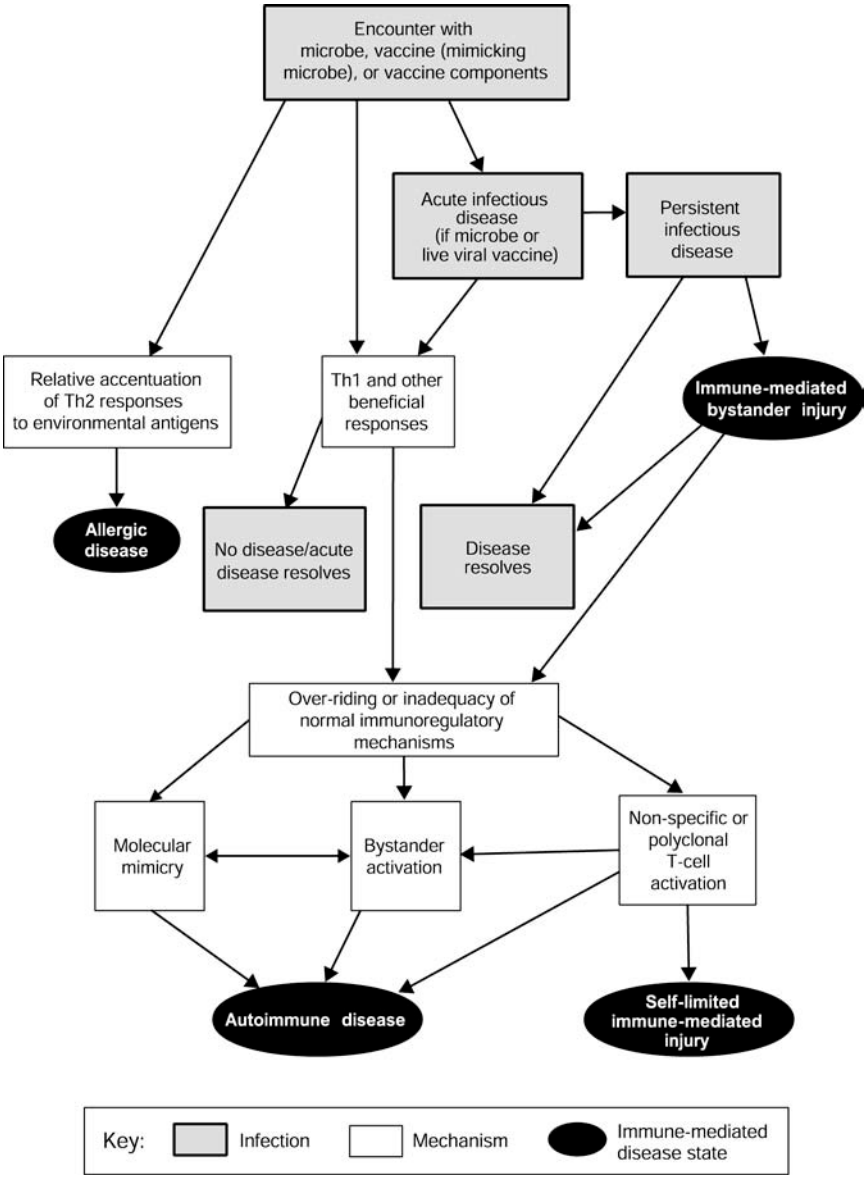


FIGURE 3 Theoretical Basis for Immunization-induced Immune Dysfunction

cells that are normally held in check. It does not require that antigens of the infectious agent be structurally similar to self-antigens. Bystander activation may be mediated in part by infection-induced death of host cells, which results in the release of greater amounts of self peptides or in the generation of novel self-peptides (i.e., novel or cryptic epitopes not normally found in the absence of the infection). As part of this process, molecules derived from the microbes (and perhaps also from the necrotic host cells—e.g., heat-shock proteins) would stimulate other components of the immune system.

In particular, antigen presenting cells (i.e., dendritic cells) gain an increased abundance of self peptide/MHC complexes and costimulatory molecules (e.g., B7 molecules) and produce cytokines, including interleukin 12 (IL-12) and tumor necrosis factor (TNF). Collectively, these changes can allow the activation of naïve self-reactive T cells that are induced to differentiate into Th1 effector T cells, which play a central role in most forms of human autoimmunity (reviewed in Bach and Chatenoud, 2001; Marrack et al., 2001; Martin et al., 2001; Parham, 2000; Robles and Eisenbarth, 2001; Singh, 2000; Wills-Karp et al., 2001). In turn, these self-reactive Th1 T cells would be available to provide help to self-reactive B cells, responding either to the same antigen as the T cells or to other antigens that are physically linked to them.

Nonspecific or polyclonal T cell activation. It is also possible that infections could activate a variety of T or B lymphocytes that would otherwise respond only to certain antigens. This non-antigen-specific response is referred to as a polyclonal or oligoclonal response. For example, toxins produced by *Streptococcus pyogenes* and *Staphylococcus aureus* can act as superantigens, binding both to T cell receptors and to MHC molecules and activating a substantial fraction (greater than 5 percent) of the total T cells of an individual. This overactivation of the immune system leads to the acute "toxic-shock" syndromes associated with the toxin-producing strains of these bacteria. Another example is polyclonal B cell activation following Epstein-Barr virus (EBV) infection and capable of enhancing autoimmune reactions. These nonspecific immune responses are usually self-limited, however, and resolve as the infection is cleared.

If self-reactive T cells are activated by a nonspecific immune response, they can induce autoimmunity. Superantigen-induced activation normally ends in the programmed death (apoptosis) of the activated cells, terminating the response. However, other microbial products, like endotoxin, that trigger the innate immune response can enhance the survival of superantigen-activated T cells (Vella et al., 1995, 1997), and could—in the context of genetic differences in mechanisms controlling the death of activated T cells—prolong the survival of self-reactive T cells, in theory allowing them to mediate self-injury.

Examples of Molecular Mimicry and Bystander Activation in Autoimmunity

The processes of molecular mimicry and bystander activation are not mutually exclusive. These mechanisms may act in synergy or at different stages in the initiation and progression of autoimmunity. Mimicry can be thought of as an initiator, because it triggers the initial activation of cross-reactive T cells, which then replicate and differentiate into effector T cells with a lower threshold for activation by self-antigens. The bystander activation of antigen presenting cells facilitates further replication of these T cells and their differentiation into Th1 T cells and also facilitates their recruitment to the target tissue.

Bystander effects are almost certainly essential for molecular mimicry to succeed in overcoming normal regulatory mechanisms (see Figure 3). Through a process referred to as epitope spreading, the initial activation by an infection of cross-reactive T cells that react to a single self-antigen may play a critical role in facilitating, in a bystander-like manner, the activation of T cells that recognize other self antigens. Thus, even after the infection has resolved and cross-reactive T cells are no longer stimulated by foreign antigens, the autoimmune process would be perpetuated and amplified by self-reactive T cells. These mechanisms have been delineated in animal models, which provide illustrative examples:

Herpes simplex-induced keratitis. In some strains of mice, acute herpes simplex virus infection of the cornea is followed by the development of autoimmune corneal injury (keratitis) (Benoist and Mathis, 2001; Panoutsakaopoulou et al., 2001; Zhao et al., 1998). Genetic factors, including MHC type, account for the differences in susceptibility between strains of mice. In susceptible mice, the development of keratitis depends on the presence of a specific viral antigen, which triggers the generation of T cells that are cross-reactive with a self-protein. These activated, cross-reactive T cells migrate via the blood back to the cornea, where they induce the keratitis.

Infection at sites other than the cornea does not induce the disease, even though cross-reactive T cells are generated. This most likely reflects the need for multiple non-antigen-specific bystander effects of the viral infection. For example, injury to the cornea releases cross-reactive self-peptides that help amplify the number of self-reactive T cells that mature into injurious Th1 effector T cells. The injury to the cornea also triggers the production of inflammatory cytokines that recruit antigen presenting cells and T cells to the infected eye, where the T cells are activated and produce keratitis. (In humans, a similar bystander process likely accounts for trauma-induced sympathetic ophthalmia, in which injury of one eye leads to an autoimmune attack against both the injured and uninjured eye (Chan and Mochizuki, 1999).

Consistent with an important role for non-antigen-specific or bystander effects in herpes simplex-induced keratitis is the ability to induce the disease with mutant strains of herpes simplex virus that lack the cross-reactive epitope. But keratitis can be induced by these mutant strains only if the numbers of

potentially self-reactive T cells have been artificially increased. Simply increasing the number of T cells is not sufficient, however; local infection or injury to the eye is necessary to initiate the disease process.

Experimental allergic encephalomyelitis. Experimental allergic e ncephalomyelitis (EAE) is a demyelinating disorder induced in rodents by immunization with myelin extracts, proteins, or peptides found in myelin (Goverman et al., 1997; Zamvil and Steinman, 1990).[6] Although EAE is one of two commonly used models of MS, it may more accurately model post-infectious acute disseminated encephalomyelitis (ADEM). As with most autoimmune disorders, only some strains of mice are susceptible to EAE, and susceptibility is determined in part by the MHC type. Molecular mimicry is not involved in EAE, since the auto-antigen is the inducing agent.

To induce this disorder, mice are immunized with myelin protein or peptides in a potent adjuvant. The adjuvant must not only increase the persistence of the antigen, but must stimulate antigen-presenting cells to more effectively present these peptides and to produce cytokines, including IL-12, that induce the formation of Th1 T cells that in turn can migrate to the central nervous system and produce injury.

The most commonly used adjuvant in animal studies is complete Freund's adjuvant, which contains dead mycobacteria in a water-in-oil emulsion. Heat-killed whole *Bordetella pertussis* or pertussis toxin can also be use as an adjuvant in this model (Blankenhorn et al., 2000; Goverman et al., 1997; Jee and Matsumoto, 2001; Zamvil and Steinman, 1990). It is the presence of dead mycobacteria that makes Freund's adjuvant effective. Multiple components of the mycobacteria (including those of their membranes and DNA) trigger the innate immune response via Toll-like receptors (Akira et al., 2001; Medzhitov and Janeway, 2000), causing the maturation of antigen presenting cells and the production of IL-12 and other potent cytokines. The inclusion in the initial immunization not only of complete Freund's adjuvant but of biologically active pertussis toxin is common and increases the frequency of clinical disease. The pertussis toxin probably acts as adjuvant and enhances the ability of the T cells to migrate into the central nervous system (Goverman et al., 1997).

Once the demyelinating process has been initiated, exacerbations can be induced by bystander mechanisms alone with the administration of IL-12 or microbial agonists (endotoxin, dsRNA [double-stranded RNA], and bacterial DNA) that stimulate the production of IL-12 and activate other aspects of the innate immune response (Constantinescu et al., 1998; Goverman et al., 1997; Segal et al., 1997).

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[6] For historical reasons this process is called allergic rather than autoimmune encephalomyelitis. But the injury in this disease is mediated by Th1 T cells, not Th2 T cells and IgE antibodies, which are the mediators of allergic diseases.

Human Inflammatory and Autoimmune Conditions Induced by Infection

Various specific infections are associated with the development of self-injury. For many of these infections, there is considerable evidence that the injury is caused, at least in part, by autoimmunity and is not simply a consequence of the immune response to the infectious agent. For example, group A streptococcal infection in humans is clearly linked to the induction of rheumatic fever. Inflammation also occurs in the skin and joints, but the major disability results from injury to the heart or, in the case of Syndenham's chorea and perhaps pediatric autoimmune neuropsychiatric disorders (PANDAS), to the brain (Marrack et al., 2001; Perlmutter et al., 1998; Wucherpfennig, 2001). Human (and mouse) antibodies to certain streptococcal M proteins cross-react with cardiac myosin and can injure cardiac muscle cells in culture, suggesting that molecular mimicry is a factor. However, it is not certain that these antibodies are the cause of the clinical damage observed following infection, nor is there clear evidence that infection leads to the generation of antibodies or T cells that are truly self-reactive rather than cross-reactive. That is, there is no clear evidence of epitope spreading and autoimmunity that persists after infection is eradicated.

Other examples in humans of infection-induced acute inflammatory injury that appears to be autoimmune in nature include Guillain-Barré syndrome, ADEM, reactive arthritis, and herpes simplex keratitis (IOM, 1991, 1994; Marrack et al., 2001; Stuve and Zamvil, 1999; Wucherpfennig, 2001). Guillain-Barré syndrome is most strongly associated with *Campylobacter jejuni* infection, which may account for up to 30 percent of cases (McCarthy and Giesecke, 2001). It has also been associated with a variety of other, mostly viral, infections. ADEM has been associated with measles and mumps virus infections (IOM, 1994). In these conditions, the injurious immune and inflammatory response resolves over time once the infection is eradicated. The damage produced during the period of active infection may, however, result in death or persistent disability, and injury may be re-induced by recurrent infection with the inciting agent. Nonetheless, the resolution of active immune-mediated injury suggests that the loss of self-tolerance is not permanent, and the precise contribution of the various mechanisms cited remains uncertain.

Arguably the strongest evidence for true persistent autoimmunity induced by a specific infectious agent in humans is chronic Lyme disease arthritis. In this disease, there is clear evidence of genetic predisposition (linked to HLA type). A putative molecular mimic has been identified, with bacterial OspA (outer surface protein A) as a mimic of human LFA-1 (lymphocyte function-associated antigen). The disease persists in the absence of any evidence of persistent infection, and cross-reactive T cells are present in increased numbers in the joints of these patients (reviewed in Benoist and Mathis, 2001; Wucherpfennig, 2001).

As noted above, there is also strong evidence for a causal association between congenital rubella infection and type 1a diabetes: approximately 20

percent of individuals with congenital rubella develop diabetes by adulthood (Robles and Eisenbarth, 2001). The pathogenesis of diabetes in these cases shares many features with typical type 1a diabetes. The similar preponderance of HLA class II alleles and the presence of T cells reactive to GAD65 (glutamic acid decarboxylase) peptides (Ou et al., 1999; Robles and Eisenbarth, 2001) suggests that the disease results, at least in part, from congenital rubella-induced autoimmunity. By contrast, there is no evidence for a similar link between acquired rubella infection after birth and type 1 diabetes.

With the exception of chronic Lyme arthritis and congenital rubella-induced diabetes, the role of infection and of specific infectious agents in the induction or exacerbation of the major chronic autoimmune diseases in humans— including type 1a diabetes, MS, systemic lupus erythematosus, and rheumatoid arthritis—is uncertain. A number of associations have been made (see Table 5), but findings across studies have not been consistent and experimental evidence to support a causal link is currently lacking (Benoist and Mathis, 2001; Marrack et al., 2001; Wucherpfennig, 2001). It is worth noting, however, that of the possible mechanisms by which infection might contribute to autoimmunity, only molecular mimicry requires a specific association between an infectious agent and autoimmunity. The evidence that more than one infectious agent can trigger the onset of reactive arthritis and demyelinating neurological diseases is consistent with the notion that bystander effects may be a common feature of infection-induced autoimmune injury. Also, the evidence that a given T cell may be able to recognize multiple peptide-MHC complexes (Marrack et al. 2001; Wucherpfennig, 2001) means it is clearly possible that the proliferation of T cells that are cross-reactive with self-antigens might be induced by more than one infectious agent.

Vaccine-Preventable Diseases and the Possibility of Vaccine-Induced Autoimmunity

The discussion above provided examples and a mechanistic framework from which to consider infection-induced immunological injury and autoimmunity. If the vaccine acts as a surrogate for the infectious disease it is designed to prevent, it might trigger the same type of immune-mediated injury as the infection itself. In previous reviews by the IOM and others (Chen, RT et al., 2001; IOM, 1991, 1994), the plausibility of this notion, and the evidence for or against causation in response to individual vaccines, were reviewed. A causal relationship between a vaccine and an autoimmune disorder was found for MMR and thrombocytopenia, OPV and Guillain-Barré Syndrome (GBS), and tetanus-containing vaccines and GBS. In addition, some types of influenza vaccine are associated with GBS and rubella with arthritis. Vaccinia is associated with acute disseminated encephalomyelitis. None of these findings, however, assessed the risk of autoimmune disease secondary to a “skewing” of immune response

TABLE 5 Putative Examples of Molecular Mimicry in Human Autoimmune Disorders with Proposed Cross-Reactive Autoantigens and Infection-Derived Antigens

Disease	**Organ/ Autoantigen**	**Infection/ Antigen**	**Cross reaction on:**
Lyme arthritis	Joints/LFA-1	*Borrelia burgdorferi*/ Osp A	T cells
Rheumatoid arthritis	Joints/Hsp60	Mycobacteria/ Hsp65	T cells
Multiple sclerosis	Brain/Myelin basic protein	Papillomavirus/ L2	T cells
Type I diabetes	Pancreatic ß-cells/GAD	Coxsackie B/ P2-C	T cells
Stiff man syndrome	GABA-ergic neurons/GAD	hCMV/DNA binding protein	T cells
Primary biliary cirrhosis	Bile duct/pyrdeH complex	*E.coli*/PDC-E2	T cells
Rheumatoid arthritis	Joints/DRB1*0401	*E.coli*/DNAJ/ EBV/gp110	T cells/Antibody
Multiple sclerosis	Brain/Myelin basic protein	EBV/capsid	T cells/Antibody
Myocarditis	Heart/myosin	Chlamydia/60kD protein	T cells/Antibody
Rheumatic fever	Heart/cardiac myosin/heart valves/kidney/ CNS	Streptococci/ M protein b	Antibody
Chagas disease	Heart/ß-1 adren-ergic receptor	*Trypanosoma cruzi*/ribosomal protein	Antibody
Myasthenia gravis	Muscle/ acetylcholine receptor	Herpes simplex/gpD	Antibody
Guillain-Barré syndrome	Peripheral nerve gangliosides	*Campylobacter jejuni* LPS	Antibody

Source: Adapted from Marrack et al., 2001; Wucherpfennig, 2001

caused by multiple immunizations early in life. These studies do provide epidemiological evidence for a causal link between certain vaccines and immune-mediated injury and disease. However, in several cases in which the infection itself is known to trigger immune-mediated diseases (examples are measles, mumps, rubella, *Borrelia burgdorferi* infections), a causal link between immunization against the infection and the disease has not been established.

Assessment of Biological Mechanisms by Which Multiple Immunizations Might Contribute to Autoimmunity

As discussed previously, the total number of different vaccines and vaccine doses administered to children in the first years of life has increased substantially over the past 20 years in the United States. However, the number of individual proteins or polysaccharide antigens administered has declined from a peak of more than 3,000 in the early 1990s to about 130 with the current immunization schedule. By comparison, a single bacterial infection (e.g., *H. influenzae* or group A streptococcus) results in exposure to many more antigens, of which 50 or more induce B or T cell responses (Cunningham, 2000; Halsey, 2001). Thus, the number of antigens in current vaccines resembles the number to which the immune system responds in the physiological context of an infection. Nonetheless, the overall content and context of vaccine administration has changed because of changes in the number of vaccines administered, their timing, the nature and formulation of the vaccines, and the main vaccination route.

The current vaccine formulations and immunization schedule have been shown to induce protection or concentrations of antibody responses sufficient to mediate protection (Blackwelder, 1995; Halsey, 2001). In some cases, achieving protective efficacy has required modification of the amounts of individual components in multivalent or combination vaccines, such as the trivalent polio virus vaccines and the MMR vaccine. The need for such modifications is consistent with the notion that prior or simultaneous infection, or immunization with multiple vaccines or antigens, can influence the magnitude and quality of the immune response to individual antigens (Chen, HD et al., 2001; Gomez et al., 1997; Insel, 1995; IOM, 2001a; Selin et al., 1998, 1999; Vekemans et al., 2001).

That factors related to infection and immunization can affect immune responses raises the theoretical possibility that changes to vaccine formulations or the vaccine schedule might also alter the potential for vaccines to induce, facilitate, or amplify immune-mediated injury or autoimmunity. Theoretically, concomitant or sequential administration of multiple vaccines could have several possible effects, alone or in combination. Molecular mimicry might be enhanced through an additive or synergistic mechanism in which more than one vaccine induces cross-reactive T cells. Another possibility might be the generation of cryptic or novel epitopes that are not found when vaccines are given separately. In addition, the nature or magnitude of bystander effects might be altered.

Molecular mimicry. Molecular mimicry appears to be a mechanism by which Lyme disease causes rheumatoid arthritis. This constitutes evidence for a biological mechanism by which the OspA Lyme vaccine (which is not recommended for routine use, seen in Figure 2) could possibly induce immune-mediated injury. It remains theoretically possible that molecular mimicry occurs in response to other vaccines but that the extent of the immune response induced has been insufficient to induce clinically evident disease. If this were the case, the addition of new vaccines that also induced cross-reactive immune responses might initiate injury and epitope spreading sufficient to result in clinically manifest autoimmunity.

The following example illustrates this hypothetical possibility. In post-infectious encephalitis, a rare but known complication of measles virus infection, the injury appears to be mediated by infection-induced expansion and entry into the nervous system of T cells directed against myelin basic protein (also a target antigen in MS) (Johnson, 1987; Liebert, 1997). Whether this reflects a cross-reactive immune response induced by measles virus or a bystander effect, or both, is uncertain. If measles vaccine (or another vaccine) weakly stimulated T cells cross-reactive with myelin basic protein and were co-inoculated with a second vaccine that also weakly stimulated such cross-reactive T cells, clinically apparent autoimmunity might result from their combined effects, even though it might not result from use of either vaccine alone.

A related theoretical mechanism is altered molecular mimicry. Ingestion of high amounts of inorganic mercury or methylmercury can induce an autoimmune disease in genetically susceptible strains of mice and rats. This effect appears to reflect the modification by mercury of self-proteins—laminin in the rat and fibrallarin in the mouse (Hultman and Nielsen, 2001; Pollard et al., 2000). These modified self-molecules are perceived as foreign by the host, inducing a T and B cell response that may spread to include a response to the native (unmodified) self-protein. At very high concentrations of mercury a polyclonal B cell response is induced, but the basis for this is not known. Mercury-induced immune injury (hypersensitivity) has also been described in some humans, but it is infrequent and the mechanisms are less clearly defined than in the rodent models (Enestrom and Hultman, 1995; Griem and Gleichman, 1995; Pollard and Hultman, 1997).

It is theoretically possible that administration of ethyl mercury-containing vaccines along with vaccines not previously given at the same time (and in the same extremity/site) could result in a mercury-induced modification of a constituent of the coadministered vaccine, creating an antigenic epitope capable of cross-reaction with self epitopes that might activate T cells cross-reactive to self proteins. No experimental evidence is available to support this effect, however. Moreover, the concentrations of mercury required to induce autoimmunity in rodents (blood levels of mercury commonly >100 μg/ml) (Hultman and Nielsen, 2001) are markedly greater than those theoretically achievable through infant

immunization, even before the mercury-containing preservative thimerosal was removed from routine childhood vaccines (Ball, 2001).

In the absence of experimental or human evidence regarding molecular mimicry or mercury-induced modification of any vaccine component to create an antigenic epitope capable of cross-reaction with self epitopes as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that these mechanisms are only theoretical.

Bystander effects. Pathogenic microbes causing vaccine-preventable human diseases are acquired at mucosal surfaces, where they sufficiently evade the innate immunity of local mucosa so that they can replicate, locally or at other sites, before antigen-specific immune responses are induced. Most vaccines, however, are administered by injection. Vaccines are also complex biological products that may contain, in addition to the immunogenic microbial components, alum, stabilizers, small amounts of components carried forward from the preparation of the microbial antigens (e.g., bovine serum, egg or human cellular constituents), and, until recently, the preservative thimerosal. Theoretically, the mechanism of acquisition of vaccine antigens—by injection rather than the mucosal route—or the presence of alum or microbial constituents with adjuvant properties, could alter the quality or magnitude of the immune response compared with a wild-type infection and thereby favor the development of an autoimmune response.

Injection versus mucosal exposure. In principle, bypassing the mucosal surfaces through injection eliminates the mucosal immune response and induces solely systemic immunity. The most obvious consequence is that mucosal antibody responses leading to the production of secretory IgA are absent or less robust following vaccine injection than with wild-type infection (reviewed in Nagler-Anderson, 2001; Neutra et al., 2001). Also in principle, the circulation pattern of the memory T and B lymphocytes induced by an injected vaccine may also differ, as they would be unlikely to home to mucosal-associated lymphoid tissues. This effect does not appear to be critical to protection from disease for which vaccines are currently in use. It may, however, limit the extent to which mucosal colonization and transmission of pathogens are reduced, particularly for polio virus, which is acquired via the intestinal mucosa.

Shifting the primary site of antigen delivery from a mucosal surface to an extremity could, in theory, bypass immunoregulatory mechanisms, such as the production of immunoregulatory cytokines (transforming growth factor-β [TGF-β] or IL-10) and local regulatory T cells, that might modulate or attenuate the immune response and thereby impede the activation of potentially self-reactive cells capable of inducing autoimmunity (Maloy and Powrie, 2001; Neutra et al., 2001; Wills-Karp et al., 2001). There is, however, no experimental evidence that this occurs for current vaccines. Vaccines, in contrast to the infections they are designed to prevent, are instead a less potent stimulus of the immune response.

(The immune response to tetanus and diphtheria toxins presented by their vaccines is an exception. Tetanus and diphtheria are diseases of toxin production rather than invasive infection; such minute amounts of toxin are produced during infection that the immune response is not effectively stimulated.) Thus the bystander effects of vaccines on the systemic immune responses, which in theory might induce autoimmunity, are less robust than those resulting from wild-type infection.

Coadministration of vaccines. Another theoretical possibility is that c o-administration of multiple vaccines (particularly if given in the same extremity so that they would drain to the same regional lymph nodes) might produce an additive bystander effect, augmenting the magnitude or altering the quality of the response to the individual vaccine components. Such an effect is consistent with the findings by Ota et al. that BCG, a live mycobacterial vaccine, augmented the magnitude of the T cell response to other coadministered vaccines (Ota et al., 2002). This effect could also potentially increase the risk for activation of self-reactive T cells (Marchant et al., 1999; Vekemans et al., 2001). However, although BCG induced a potent Th1-type response to mycobacterial antigens, it promoted the production of both Th1- and Th2-type cytokines in response to unrelated vaccines. Thus, BCG is likely to impact immune response to unrelated antigens in early life through its influence on the maturation of dendritic cells, and not by shifting Th2 responses towards Th1 (Ota et al., 2002).

A reciprocal inhibitory effect of BCG vaccine on Th2 responses and allergic disease has been proposed on the basis of animal studies and ecological studies in humans (Aaby et al., 2000; Erb et al., 1998; Herz et al., 1998; Shirakawa et al., 1997), but the data regarding this effect in humans are conflicting (Alm et al., 1997; Gruber et al., 2001a; Strachan, 2000; Wills-Karp et al., 2001). In human infants in The Gambia, BCG induced a strong Th1 T cell response to mycobacterial antigens (Marchant et al., 1999; Vekemans et al., 2001) and enhanced the magnitude of the response to coadministered vaccine antigens (e.g., hepatitis B, tetanus toxoid), but the Th1–Th2 balance of the T cell response to these coadministered vaccines was not affected (Ota et al., 2002). Similarly, prior BCG immunization showed no effect on the development of IgE antibodies (an index of Th2 dependent responses) to tetanus and diphtheria toxoids following subsequent immunization with DT or DTP (Gruber et al., 2001b). Other vaccines that induce IFN-_ responses in human infants to the homologous disease antigens (i.e., live viral vaccines) (Arvin et al., 2001; Gans et al., 2001) are theoretically capable of enhancing a bystander Th1 response to heterologous antigens. The potency of these vaccines is almost certainly less than that of BCG, suggesting that if such an effect were to occur, it would likely be minor.

Th1 versus Th2 response. Autoimmunity is generally associated with Th1 responses, whereas allergy is associated with Th2 responses. DTwP vaccine includes whole formalin-inactivated *B. pertussis* cells, which contain endotoxin and bacterial cell membrane structures that activate the innate immune system

and favor a Th1 response and production of IgG1 antibodies (but not IgG4 antibodies). The vaccine also contains inactivated pertussis toxin and alum, which are adjuvants that favor a Th2 response and production of IgE and IgG4 antibodies (reviewed in Gruber et al., 2001). Some human studies have been interpreted as showing that DTwP, and pertussis infection itself, induced the development of IgE antibodies to vaccine antigens and might have a similar effect on responses to environmental antigens, thereby predisposing to allergy and presumably impeding risk of autoimmunity (Farooqi and Hopkin, 1998; Nilsson et al., 1998; Odelram et al., 1994; Odent et al., 1994; Pershagen, 2000).

More recent studies suggest that the antibody responses to tetanus and diphtheria antigens in children given DTwP vaccine are similar for IgG but signifycantly lower for IgE and IgG4 (a correlate in humans of Th2 responses) when compared with responses in children given DT vaccine (Gruber et al., 2001b). There was no significant effect on IgE antibody response to environmental antigens, suggesting that DTwP may shift the Th1–Th2 balance modestly in the Th1 direction, but only for coadministered antigens (Gruber et al., 2001a). The relative contribution of alum to the Th1–Th2 balance in response to immunization with DT seems to be minor, as the amounts of IgE induced in those given DT with or without alum were similar in one study (Mark et al., 1995). It is important to note, such results do not necessarily mean this would apply to all of the other vaccines in which alum is employed as an adjuvant (e.g., hepatitis B, various conjugate vaccines).

These studies, in which the outcome measure was IgE antibodies, parallel the findings of T-cell responses in infants with pertussis infection or in those who have received DTwP: the T cell response is dominated by the Th1 cytokine interferon-γ, with very weak production of Th2 cytokines, such as IL-5. Conversely, DTaP, which contains acellular pertussis antigens, including inactivated pertussis toxin, but not the Th1-inducing components of *B. pertussis* whole cells, induces a mixed Th1–Th2 response. The Th2 response is more prominent and persistent in children with a family history of allergy (Ausiello et al., 1997; Rowe et al., 2001; Ryan et al., 1997a, 1997b, 1998).

Thus there is some evidence of a bystander effect associated with vaccines, but this effect is relatively modest, most evident with coadministered vaccine antigens rather than other environmental antigens or infections, and inconsistently shown. Current vaccines have, on balance, weak or no Th1-inducing activities. BCG appears to demonstrate the principle for co-administered antigens. However, BCG is not used in the United States, so the relevance for this mechanism in the effects of the U.S. recommended schedule is not demonstrated. Viral vaccines carry some potential for bystander activation, but likely would have a small effect, if it occurs at all. The data on DTaP vaccine indicates that Th1 dominance is not prominent. There is also no evidence in humans that vaccine antigens lead to the pathophysiological disease state. The limited evidence from humans that does exist regards surrogates of the disease process, that is, just

some components of the events that would need to take place for the appearance of clinically relevant pathophysiology. Given the dominant Th1 nature of type 1 diabetes, MS, and most other autoimmune diseases, the prediction is that even if multiple immunizations had a cumulative bystander effect on potentially autoreactive T cells, the current vaccine program would be biased against the generation of Th1-dominated responses. And it is noted that this bias would be stronger now than at any time in the past.

The committee concludes that there is weak evidence for bystander activation, alone or in concert with molecular mimicry, as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity. Moreover, the current routine childhood immunization schedule in the United States appears even less likely to act as an initiator or facilitator of autoimmunity than in the past.

Multiple Immunizations and Infectious Diseases That Protect from Autoimmunity

The mechanisms described above posit that immunizations play a direct role in the initiation or amplification of autoimmune processes. An alternative hypothesis is that immunizations increase the risk of autoimmunity by preventing infectious diseases that have protective effects. The theoretical deleterious effect might be specific to the infection prevented by the vaccine (a homologous effect), or result from a non-antigen-specific effect on the overall nature of the immune response (a heterologous effect). In either case, the notion is that a heretofore protective effect of infection has been lost by immunization.

Homologous effects. The nature of a homologous effect can be illustrated by changes in the epidemiology of poliomyelitis, although this example does not involve autoimmune disease or vaccine-induced effects. The poliomyelitis epidemics that commenced in developed countries near the end of the 19th century are thought to have followed improvements in hygiene that postponed exposure to the virus beyond infancy (Plotkin and Orenstein, 1999; Wilson and Marcuse, 2001). Previously, wild-type poliovirus exposure most commonly occurred in infancy, at a time when passive maternally derived antibody provided partial protection. Thus, a child was first exposed under conditions in which acute paralytic disease was blocked but infection sufficient to immunize against disease on subsequent encounters resulted. Improved hygiene is believed to have reduced circulation of wild-type poliovirus sufficiently to delay exposure in many children until after passively acquired antibody was lost and they were fully susceptible. Further, reduced circulation of wild-type poliovirus would be predicted to result in lower levels of maternal antibody because of less frequent boosting, so that the magnitude of passive antibody transferred and duration of passive protection would be shorter (Zinkernagel, 2001). An immunization program might also be expected to leave infants more susceptible if

vaccine-induced immunity did not induce protective levels of passive maternal antibody and herd immunity sufficient to reduce wild-type virus spread. This potential problem was overcome by actively immunizing infants.

A similar situation may apply to other vaccine-preventable diseases. In the case of measles, mumps, and rubella, the amount of passively-acquired antibody in infants born to mothers whose immunity is due to vaccination is less than and falls more quickly than in infants born to mothers whose immunity is due to wild-type virus infection. As a result, the age at which immunization induces protective antibody responses to measles is younger now than before the widespread use of MMR vaccine (Gans et al., 2001; Redd et al., 1999).

For loss of homologous protection that results from multiple immunizations to be a factor in autoimmunity, a vaccine-preventable infection must cause autoimmune disease. The relative risk will also be affected by the extent to which wild-type infection still occurs in the community; herd immunity will reduce the risk of infection and therefore increase the risk of autoimmune disease. Of the vaccine-preventable diseases, only congenital rubella, which has been noted as inducing type 1 diabetes in about 20 percent of affected individuals, has been causally linked with a chronic autoimmune disorder. Mumps virus infection has been linked to type 1 diabetes in rare cases (IOM, 1994), but causality has not been established. Even though waning of immunity following immunization may delay the age of onset of vaccine-preventable infections, and thus may be a factor in the chronic rubella viral arthritis in adolescent females, there is no evidence that waning immunity and delayed infection increases the potential for induction or acceleration of type 1 diabetes by wild-type rubella or mumps virus. Furthermore, the incidence of type 1 diabetes has increased most in children in the youngest age group (age 0–4 years) (Karvonen et al., 1999b; Podar et al., 2001), arguing against waning immunity as the basis for the increased incidence. The same theoretical considerations apply to the vaccine-preventable diseases that are capable of inducing acute neurological autoimmune injury, including ADEM and Guillain-Barré syndrome.

In the absence of experimental or human evidence regarding loss of protection against a homologous infection as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that this mechanism is only theoretical.

Heterologous effects and the hygiene hypothesis. Possible heterologous effects of vaccination on autoimmunity can be considered in the context of the larger theoretical construct of the hygiene hypothesis, introduced earlier in the report. As noted previously, this hypothesis was first developed as a model to explain the rising increase in asthma and allergic diseases in the developed world (Strachan, 2000), and has been broadened recently to address the apparently

parallel increase in certain autoimmune diseases, including type 1 diabetes and MS (Rook, 2000; Rook and Stanford, 1998; reviewed in Wills-Karp et al., 2001).

The hygiene hypothesis. The hygiene hypothesis is based on the notion that the human immune system (and that of other mammals) evolved in concert with constant exposure to a diverse and changing array of nonpathogenic environmental and commensal microbes, as well as under the persistent threat of lethal infectious diseases caused by microbial pathogens. This microbial exposure is thought to have conditioned the human immune system to respond vigorously to pathogenic microbes but not to harmless environmental antigens (allergens), normal microbial flora and environmental commensals, or self-antigens. Because birth is associated with a rapid switch from a sterile environment to a microbe-rich environment, to which the immune system must learn to respond properly, a component of the hypothesis is that the immune system may be particularly dependent on receiving appropriate conditioning through microbial exposure in early childhood.

During the past century, the developed world has seen improvements in hygiene, the development of effective immunizations, and the advent of antibiotics. These changes have altered the relationships between humans and microbes and, by inference, the challenges that the immune system must meet to provide protection from infection. The magnitude of the change in these relationships over the past century is arguably greater than the total change over all previous millennia of human existence.

The original hygiene hypothesis, developed as a model to explain the rising incidence of asthma and allergy, relied on the then recently elucidated Th1–Th2 paradigm that describes the ability of T cells to differentiate into cells with divergent effector functions. Th1 T cells produce interferon-γ and mediate or regulate cellular immunity and protection against viruses, bacteria, and invasive protozoans. Th2 T cells produce IL-4, IL-5, and IL-13, induce B cells to secrete IgE antibodies, and promote the development of eosinophils, which together mediate allergy and immunity to worms or helminthic parasites. As noted above, a number of microbial components stimulate cells of the innate immune system to produce IL-12 and other cytokines that cause T cells to differentiate into Th1 T cells and inhibit the development of Th2 T cells.

The logic of the hygiene hypothesis is that constant microbial exposure has a bystander effect that impedes the development of Th2 T cells and allergic responses to harmless environmental antigens such as foods and pollens. Therefore the reduced microbial exposure that infants now experience is associated with reduced constraints on the development of Th2 T cells. The hygiene hypothesis also fits well with the notion (Adkins, 2000; Prescott et al., 1998; Rowe et al., 2001; Siegrist, 2001), not yet firmly established as fact (Delespesse et al., 1998; Hassan and Reen, 2000; Lewis and Wilson, 2001; Marchant et al., 1999), that T cell responses of the human fetus and young infant are Th2-biased and

gradually switch to a more balanced pattern over the first year or two of life in nonallergic children.

Although these mechanisms were consistent with observed increases in allergic diseases, they ran counter to two other observations. First, the incidence of autoimmune diseases, particularly type 1 diabetes and MS, appears to have increased in the same or overlapping populations. These diseases, however, are characterized primarily by Th1 T cell responses. Second, although worms or helminthic parasites induce robust Th2 and IgE responses, children in the developing world with large worm burdens have a lower incidence of asthma or allergic diseases (van den Biggelaar et al., 2000). Moreover, in certain mouse models intestinal worms can protect from allergic diseases (Wang et al., 2001), and conversely Th1 promoters can exacerbate allergic disease, depending on the context in which they are administered (Bryan et al., 2000; Hansen et al., 1999).

To address these apparent inconsistencies, modifications of the hygiene hypothesis posit that microbial exposure primarily acts not by deviating the immune response from Th2 to Th1, but by inducing the production of immunoregulatory cytokines (including IL-10 and TGF-β) and T cells that dampen the immune response broadly, including both Th1 and Th2 responses (Rook et al., 2000; Wills-Karp et al., 2001). Many microbes, including worms or helminthic parasites, bacteria, and viruses, induce IL-10 and/or TGF-β production (Letterio and Roberts, 1998; Moore et al., 2001; Rook et al., 2000; Wills-Karp et al., 2001). For example, increased IL-10 production in response to chronic parasitic infection with *Schistosoma haematobium* has been correlated with reduced evidence of allergic sensitization (van den Biggelaar et al., 2000). IL-10 and TGF-β can impede antigen-specific T cell responses directly, by impairing antigen presenting cell function, or by the induction of anergic or regulatory T cells. When stimulated via the T-cell receptor, regulatory T cells suppress the responses of other T cells in a nonspecific manner by contact-dependent mechanisms and by production of IL-10 or TGF-β. Mice that lack these regulatory cytokines or regulatory T cells develop inflammatory bowel disease or inflammatory or autoimmune disease in other tissues (Ermann and Fathman, 2001; Maloy and Powrie, 2001; Roncarolo and Levings, 2000; Rook et al., 2000; Shevach, 2000; Singh, 2000; Wills-Karp et al., 2001; Zhang et al., 2001).

Various findings suggest that that the human neonate can produce regulatory cytokines and T cells, supporting the notion that the neonate's immune system has the requisite immunoregulatory potential if the proper environmental signals are provided. Regulatory T cells are present and inducible in the blood of neonates (Roncarolo and Levings, 2000). Although the conditions required for their induction may differ somewhat from those in adults, it is not known at present if these differences are reproducible or biologically important. In addition, peripheral blood mononuclear cells and monocytes from the blood of human neonates can produce IL-10 and TGF-β in response to microbes or their components (reviewed in Lewis and Wilson, 2001). Although the magnitude of the

response may be reduced compared with that in adults, the production of pro-inflammatory cytokines is also reduced in neonates, suggesting no imbalance in the production of pro- and anti-inflammatory cytokines.

Thus the extent, nature, and timing of contact with microbes are proposed to play an important role in establishing a proper balance in the immune response in early childhood and in maintaining this balance thereafter. A balanced immune response fosters the development of protective immune responses against pathogenic microbes, while preventing both a deleterious Th1 response to self antigens or harmless commensal microbes and a Th2-mediated allergic response to harmless environmental antigens. The type of microbial exposure that is important in establishing this balance is not currently known. Proposed candidates include various gut microbial commensals, chronic infections with intestinal worms or helminthic parasites or *Mycobacterium tuberculosis*, frequent exposure to environmental mycobacteria or other soil organisms, and the timing, number, and nature of acute infections. Factors such as breast feeding, number of siblings and birth order, day care attendance, contact with animals, antibiotic use, and the timing and nature of immunizations have been proposed to affect risk for autoimmune (or allergic) diseases through their effects on the extent and nature of microbial contact (Rook, 2001; Rook and Stanford, 1998; Singh, 2000; Strachan, 2000; Wills-Karp et al., 2001). Whether the sum of all microbial exposure, some specific combination of exposures, or one particular type of exposure is the important factor, or whether these are surrogates for an as yet undefined factor that is important, is uncertain.

Possible impact of vaccines on autoimmunity. On a numerical basis, vaccine-preventable infections represent a minute fraction of the overall infectious and microbial exposure in childhood. For immunization to have an impact on autoimmunity under the hygiene hypothesis, it would be necessary for one or more vaccine-preventable diseases to be particularly important for conditioning immunoregulatory immune responses. The gastrointestinal tract is proposed to play a particularly critical role in this process, so it would follow that immunizations that affect infection or colonization of the gut would be good candidates, but none of the childhood vaccines currently in use do so. (The rotavirus vaccine, which did affect the gut, was in use for too short a time to influence rates of autoimmunity.)

Data from animal models suggest that no one infection is likely to be key, but, rather, a global reduction in microbial contact could be a factor. For example, prior exposure to or infection with a variety of microbes can prevent type 1 diabetes in non-obese diabetic (NOD) mice, as can certain vaccines (reviewed in Bach, 2001; Bach and Chatenoud, 2001; Hiltunen et al., 1999; Singh, 2000). The role of infection is complex in the EAE model. The potentially protective effect of prior mycobacterial or *B. pertussis* exposure (Bach, 2001; Ben-Nun et al., 1993, 1997; Hempel et al., 1985; Mostaricka-Stojkovic et al., 1988) may be related directly to their use as adjuvants at the time of subsequent immunization

with myelin proteins; thus the effect is not generalizable to autoimmune disease developing through more natural mechanisms, as in humans with MS. Nonetheless, if prior infection with one or both of these agents is assumed to be particularly important in establishing protection from autoimmune disease, the immunization schedule in the United States would have had no effect; use of BCG vaccine has never been recommended and, by analogy to the studies of EAE, administration of whole-cell *B. pertussis* vaccine—even as given in alum along with DT (Hempel et al., 1985)—should have been protective. It is possible that the acellular pertussis vaccines might lack the key components needed to provide protection against human autoimmune diseases, but even if this is so, the apparent increase in autoimmune disease began much earlier than the use of the acellular vaccine.

If immunoregulatory cytokines and regulatory T cells play an essential role in impeding the untoward inflammatory responses to normal microbial flora that result in autoimmunity and allergy, and their generation or function depends on microbial contact, it follows that the necessary microbial cues must be established early in postnatal life, in parallel with the development of effector T and B cell responses. Furthermore, such cues must either be persistent or sufficiently frequent to maintain these protective immunoregulatory mechanisms. Because these mechanisms have presumably been operative in all human populations for millennia and only recently perturbed, the associated microbial exposure must be both universally present and long established. None of the diseases prevented by the current U.S. immunization program meets those conditions, nor does tuberculosis or measles, the two candidates proposed from studies of heterologous vaccine-induced protection in Africa (Kristensen et al., 2000). Although tuberculosis may induce persistent infection, fulfilling one requirement, it has not been endemic worldwide until the relatively recent past, nor has measles (Cherry, 1998; Daniel et al., 1994). The more likely candidates are commensal bacteria and ubiquitous environmental microbes, the richness and diversity of which are reduced in hygienic urban environments, or the cumulative exposure to these nonpathogenic microbes and to various invasive infections rather than any specific infection.

The hygiene hypothesis is a model originally proposed based on epidemiological data. The biological mechanisms by which this model could explain an increase in incidence of autoimmune (or allergic) disease are substantial, and the biological evidence in support of the model is moderate to strong. However, the potential contribution of vaccine-preventable diseases as part of this model is minimal. **In the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that this mechanism is only theoretical.**

In theory, molecular mimicry, bystander activation, and impaired immunoregulatory mechanisms might act in an additive or synergistic manner to affect the risk of autoimmunity. **Considering molecular mimicry, bystander activation, and impaired immunoregulation collectively rather than individually, the committee concludes that there is weak evidence for these mechanisms as means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity.**

Multiple Immunizations and Allergy

Allergic responses are directed against environmental antigens rather than self-antigens as in autoimmunity. In allergic disease, harmless environmental agents evoke Th2 responses and IgE antibody, which otherwise mediate useful protective responses to infections with worms or helminthic parasites. Allergic responses, such as anaphylaxis, are known to occur following vaccination and are reactions either to the vaccine antigens themselves or to other vaccine components. However, the major concern addressed here is whether there are biologically plausible mechanisms by which multiple immunizations might increase the risk of allergic responses to environmental antigens other than those contained in the vaccines—that is, *heterologous* allergic responses.

By analogy to the theoretical frameworks in which the potential effects on autoimmunity were considered, multiple immunizations might influence heterologous allergic responses through a bystander mechanism that modifies the magnitude or quality of the immune response to environmental antigens, or they might prevent infectious diseases that do so.

Bystander Effects

The elimination of smallpox vaccine in 1972 and the substitution of DTaP (containing acellular pertussis vaccine) for DTwP (containing formalin-inactivated *B. pertussis* whole cells) in the 1990s removed two vaccine-based sources of microbial signals favoring Th1 and opposing Th2 responses (Ausiello et al., 1997; Rowe et al., 2001; Ryan et al., 1998). In theory, the replacement of the oral polio vaccine with an injected vaccine given in alum, along with the addition of other vaccines given in alum and administered as early as birth, favors the development of Th2 responses relative to Th1 responses. In mouse neonates (which have a developmentally less mature immune system than that of the human neonate), such a Th2 bias has clearly been shown in response to antigens in alum compared with antigens administered with microbial adjuvants (Adkins, 2000; Barrios et al., 1996; Siegrist, 2001). Alum also induces IL-4 production

from human mononuclear cells (Ulanova et al., 2001). However, except for evidence supporting a more Th2-directed immune response to components of DTaP than to DTwP (both of which are administered in alum), direct evidence is lacking that alum-containing vaccines deviate the immune response of human infants to environmental antigens toward Th2 responses. (For more details regarding this point, see the discussion of Th1 versus Th2 responses related to bystander effects of immunization and autoimmunity.) If such a deviation were to occur, whether it would be sufficient to result in clinically manifest allergy to these antigens would depend on other factors that are as yet incompletely elucidated.

Nonetheless, the biological mechanisms by which immunizations that contain microbial stimuli favor Th1 responses and immunizations containing alum favor Th2 responses are well established. Although the impact of immunization on heterologous allergic responses is unknown, on balance the current routine childhood immunization schedule in the United States is less likely to favor Th1 responses to heterologous antigens and more likely to favor Th2 responses.

The committee concludes that there is weak evidence for bystander activation as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.

Prevention of Protective Infections: The Hygiene Hypothesis.

The hygiene hypothesis is discussed in detail in the above autoimmunity section on "Heterologous Effects and the Hygiene Hypothesis". In the context of allergic diseases, either a shift of the Th1–Th2 balance, a loss of immunoregulatory mechanisms that block untoward immune responses to environmental antigens, or both, could result in an increase in allergy. All but the first of these mechanisms are compatible with a parallel increase in allergic and autoimmune diseases. The same reasoning applied to the potential role of vaccine-preventable diseases in reducing risk of autoimmunity can be applied to the question of allergy, with one modification. If a specific type of infection or microbial exposure impaired heterologous Th2 responses, even if it did not play an important role in the generation of immunoregulatory cytokines or regulatory T cells, a vaccine that prevented the disease but was not an effective surrogate for the infection could contribute to the increased incidence of allergy. It does not appear that this occurs. Tuberculosis and measles infection have been proposed as agents that impair heterologous Th2 responses, although, unlike tuberculosis which is a strong Th1-inducing microbe, measles virus is unlikely to have such an effect (Wills-Karp et al., 2001) and neither disease meets the requirement of having been a long-time, ubiquitous infection of all human populations. Although the evidence is conflicting, it has also been proposed that the vaccines against these two diseases are effective surrogates for the infections in the prevention of allergy.

The hygiene hypothesis is a theoretical model, originally proposed on the basis of epidemiological data. The biological mechanisms by which this model could explain an increase in incidence of allergic diseases are substantial, and the model is considered to be moderately to strongly plausible. However, the potential contribution of vaccine-preventable diseases as part of this theory is minimal. **In the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy, the committee concludes that this mechanism is only theoretical.**

The committee concludes that there is weak evidence for the existence of any biological mechanisms, collectively or individually, by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.

Multiple Immunizations and Heterologous Infections

Simultaneous or sequential infection or immunization with multiple vaccines or antigens can, through various mechanisms, influence the magnitude and/or quality of the immune response to individual antigens, either impeding or enhancing the immune response to one or the other, thereby affecting immune-mediated resolution of an infection and/or the development of protective immunity. There are several potential mechanisms by which this can occur, which vary with the nature of the antigen/agent and with the component of the immune response being evaluated or most important for providing protection. These include immune interference, T cell cross-reactivity, carrier-induced epitope suppression, and competition for antigen presentation (peptide competition for binding to MHC molecules or competition between T cells for the same antigen presenting cells). These mechanisms have been discussed in earlier reports from this committee (IOM, 2001a), and some have also been referred to in the preceding sections of this report. There is experimental animal evidence for each of these mechanisms in certain contexts. For the latter two mechanisms, there is also evidence from human studies that are relevant to the possible effects of multiple immunizations on risk for heterologous infections, which is briefly reviewed here.

Carrier-Induced Epitope Suppression

This process was first described in model systems, but has become clinically important in the context of conjugate vaccines. In such systems, the carrier is a protein antigen, to which is conjugated (covalently linked to create a single molecule) a non-protein antigen. In clinical practice, conjugation of a bacterial non-protein antigen to a protein carrier has been used to convert a

T cell-independent antigen (e.g., the type b capsular polysaccharide of *Haemophilus influenzae* or pneumococcal capsular polysaccharides) into a T cell-dependent antigen. Such conjugate vaccines are immunogenic in infants, inducing high-affinity IgG antibody and long-term immunological memory, whereas none of these features occurs when the polysaccharide alone is used as a vaccine. The basis for this is that the polysaccharide-protein conjugate will bind to and partially activate B cells that are specific for the polysaccharide, which internalize the conjugate, then process and present peptides from the protein component to $CD4^+$ (helper) T cells specific for these peptides. This leads to activation of the T cells, that in turn help the B cells to produce high-affinity antibodies to the linked polysaccharide and mature into long-term memory B cells. In competition with these polysaccharide-specific B cells, are other B cells specific for the protein component of the conjugate. These B cells also present peptides to $CD4^+$ T cells and in turn receive second signals allowing them to produce antibodies to the protein component of the conjugate vaccine. If the numbers of $CD4^+$ T cells specific for the protein are limiting, then B cells specific for the polysaccharide component and B cells specific for the protein component of the conjugate are in competition with each other for limited numbers of $CD4^+$ T cells capable of providing help (Insel, 1995). A variant of this can occur if multiple different carbohydrate antigens are conjugated to the same protein. In this case, the B cells specific for different carbohydrates may compete with each other for limited numbers of $CD4^+$ T cells. The latter situation may account in part for reduced responses seen when multivalent pneumococcal-tetanus toxoid conjugate vaccine was given along with *H. influenzae* type b-tetanus toxoid conjugate vaccine (Dagan et al., 1998).

Competition for Antigen Presentation

This describes a situation in which T cells responding to one antigen or infection compete with other T cells that are responding during the same time frame to other antigens or another infection, and one of the responses has a head start—it precedes the other by a few days or weeks. This gives the response to the earlier challenge a competitive advantage, such that it dominates and impedes the response to the delayed antigenic challenge or infection. Such competition is most readily observed in the context of strong CD8 T cell responses to viral infections (Chen, HD, 2001; Selin et al., 1998, 1999) or artificially manipulated immune responses (Kedl, 2000) in experimental animals. Bystander effects, including viral immune interference (see IOM, 2001a for more details) rather than competition for antigen presentation may affect responses to heterologous viral infections. An example of a heterologous effect in humans is the recent findings related to the timing of administration of MMR vaccine and varicella vaccine. If MMR and varicella vaccine are given at the same time or an interval of 30 or more days elapses between the administration of MMR and varicella vaccines, MMR and

varicella vaccine efficacy is not compromised. However, if varicella vaccine is given after but within 30 days of MMR the relative risk for later development of breakthrough varicella, defined as cases of varicella that occur following exposure to wild-type virus >42 days after varicella vaccine administration, is 2.5 (1.3–4.9). The risk for breakthrough varicella is not increased when varicella vaccine is given within 30 days after DTP, Hib, OPV, IPV, or hepatitis B vaccines. These findings parallel those in earlier reports that had shown a reduction in responsiveness to smallpox vaccine following measles vaccine (MMWR, 2001c).

The committee concludes that there is strong evidence for the existence of biological mechanisms by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk for heterologous infections.

SIGNIFICANCE ASSESSMENT

The charge to the Immunization Safety Review committee includes consideration of the public health response to the immunization safety concerns it examines. Most previous IOM immunization-safety studies by contrast, were limited to conclusions from causality assessments and to recommendations for future research. The public health response to an immunization safety concern potentially encompasses a broad range of activities, including policy reviews, new research directions, and changes in communication to the public and health care providers about issues of immunization safety. In formulating the breadth and direction of the recommended public health response, the committee considers not only its conclusions regarding causality and biological mechanisms, but also the significance of the immunization safety issues for society—the context in which policy decisions must be made.

Public concerns about immunization safety must be examined carefully because most vaccines are given to healthy children not only for their direct protection but also to help protect others in the population. In fact, to achieve this broader level of protection, certain vaccines are mandatory in all 50 states for school and day-care entry. Exemptions on medical grounds (contraindications) are allowed, although they are considered too limited by some (Fisher, 2001a). Exemptions are also allowed on religious grounds in 48 states and on philosophic grounds in 15 states (Evans, 1999). Such exemptions are rare, however, and it is argued that these public health mandates, because they are imposed on healthy children, place a special responsibility on the government for rigorous attention to safety issues, even for rare adverse outcomes.

In the present case, the committee considers the possibility that the exposure of infants to multiple immunizations might increase risks of immune dysfunction. This issue has gained attention because of indications that autoimmune and allergic diseases are increasingly common in children and because of the likelihood that yet more vaccines will be added to the recommended schedule of childhood immunizations. As part of the committee's assessment of the

significance of this issue, the disease burden (e.g., seriousness, treatment, complications) associated with autoimmune and allergic diseases, especially type 1 diabetes and asthma, is reviewed here. Also discussed are indications of public concern about the safety of multiple immunizations and ideas that have been put forward about alternative approaches to the formulation of immunization policy.

Disease Burden

Autoimmune Disorders: Type 1 Diabetes

As noted, diseases of autoimmunity affect 3 to 5 percent of the U.S. population (Jacobson et al., 1997), which translates into as many as 14 million people in 2001. From 500,000 to 1,000,000 people in the United States are thought to have type 1 diabetes, based on estimates that this form of the disease accounts for 5 to 10 percent of the roughly 10 million diagnosed diabetes cases (NIH, 1999). No national surveillance system exists to provide data on the incidence of type 1 diabetes. Rates from local diabetes registries and research projects suggest that about 30,000 new cases develop each year in the United States (LaPorte et al., 1995). Internationally, various registries indicate an average incidence increase of 3% per year (Onkamo et al., 1999). The disease can develop at any age, but incidence rates are higher in children and young adults. Moreover, among children under age 16, the incidence of type 1 diabetes is higher than that of other chronic illnesses, including all forms of cancer combined (Libman et al., 1993).

In type 1 diabetes, the destruction of insulin-producing beta cells in the pancreas prevents proper metabolism of glucose. If not treated, the disease is fatal. Administration of insulin one or more times each day helps compensate for the loss of the beta cells, but the dosage must be calibrated to account for food intake and exercise levels. Children and adults with type 1 diabetes must monitor their blood sugar levels regularly. If blood sugar is not maintained at appropriate levels, there is risk of acute complications, particularly coma. Ketoacidotic coma occurs if insulin administration is inadequate, resulting in hyperglycemia and ketone production. Hypoglycemic coma results if insulin administration is excessive for the blood glucose level.

Type 1 diabetes is associated with many serious long-term complications (Harris, 1995). Mortality rates are elevated at all ages, especially for women and girls, and life expectancy may be reduced by as much as 15 years. Acute coma is the greatest mortality risk during the first years with the disease, replaced over time by renal disease. Among persons who have had Type 1 diabetes for 30 years or more, cardiovascular disease accounts for most deaths. Several chronic complications are also common, and they are more likely to occur if blood sugar levels are poorly controlled. One such complication, diabetic retinopathy, is a leading cause of blindness in the United States. People with diabetes are also at risk of kidney damage that can progress to end-stage renal disease. Neuropathies

are common, and along with peripheral vascular disease, can result in damage to lower extremities (e.g., ulcers, infections) that necessitates amputations. Infection rates are higher, as are periodontal disease rates. Women with type 1 diabetes who become pregnant may see a worsening of any existing eye or kidney damage, and they are at increased risk of spontaneous abortion, preterm delivery, and birth defects.

The financial cost of type 1 diabetes is high. People with this disease are more likely to experience work disability, and they make greater than average use of health care services. A 1988 paper estimated treatment cost for a patient through age 40 at $40,000 (LaPorte et al., 1995). Health expenses and office visits for diabetics exceed those of nondiabetics.[7] For example, the estimated annual cost of physician visits for a diabetic was nearly twice that for a nondiabetic ($1,045 versus $554). Costs of prescriptions and medical supplies are over five times as expensive for diabetics as for nondiabetics ($1,056 versus $201). Increased costs in overall health expenses also affect diabetics far more than nondiabetics ($11,157 versus $2,604 annually) (Javitt and Chiang, 1995).

Allergic Disorders: Asthma

Allergic disorders—including asthma, rhinitis, and dermatitis—are the sixth most common chronic disease in the United States. Together, they result in $18 billion in health care costs annually (AAAAI, 2000). For this report the committee focused on asthma.

A serious allergic disease, asthma was estimated to have affected 14.6 million adults in 2000 (CDC, 2001b) and about 4 million children in 1998 (CDC, 2001a). The prevalence rates of self-reported asthma appear to have increased overall by 74 percent between 1980 and 1994 (Mannino et al., 1998). For children age 0 to 4 years, rates increased by 159 percent during this period (from 22.0 per 1,000 to 57.4 per 1,000). Increases in asthma prevalence were seen in all race, sex, age, and regional groups. The reasons for the increasing prevalence are unclear, although changes in environmental or behavioral factors are considered likely (IOM, 2000).

Symptoms of asthma include shortness of breath, coughing, wheezing, and chest tightness. Some people experience these symptoms only occasionally, but in the most severe cases, symptoms are continuous. Even when the general level of disease is mild or moderate, individual episodes can be severe and may require hospital or emergency department care. Without proper treatment, severe episodes can be life-threatening. Management of the disease includes limiting exposure to environmental triggers (e.g., allergens, tobacco smoke, exercise, viral infections) and appropriate use of medications in response to the underlying level of symptoms and any acute changes. Daily use of medications may be

[7] Most estimates of treatment cost in the medical literature are for both type 1 and 2 diabetes.

necessary. In addition to disease-related complications, children with asthma are more susceptible to comorbid upper and lower respiratory conditions (Weiss and Sullivan, 2001).

The societal impact of asthma is reflected in over 10 million missed school days and 100 million days of restricted activity (AAAAI, 2000). In 1998, asthma was also responsible for almost 13.9 million office visits, 2.0 million emergency department visits, and 423,000 hospitalizations (CDC, 2001a). In 1998, asthma-related costs were estimated at $12.7 billion, attributable to medications and healthcare (Weiss and Sullivan, 2001). Disease severity affects the cost of treatment. Malone and colleagues (2000) found that fewer than 20 percent of asthma patients accounted for more than 80 percent of treatment costs. This high-cost minority was composed of individuals who reported their health as poor or fair, and used four or more different asthma medications.

Attitudes Toward Multiple Immunizations and Vaccine Safety

As this report reflects, there are concerns that the growing number of immunizations routinely given to young children could be a contributing factor to increases in rates of some allergic and autoimmune conditions. The extent of this concern among parents with young children is suggested by a national telephone survey conducted in spring 1999 (Gellin et al., 2000). Among these parents of children under age 6 or expectant parents, 87 percent of the respondents rated immunization as extremely important. But 25 percent agreed with the statement that they were concerned that the immune system could be weakened by too many immunizations, and 23 percent agreed with the statement that children receive more immunizations than are good for them.

Gellin and colleagues (2000) note that levels of concern about immunization safety might now be even higher because of events following the survey. In July 1999, the American Academy of Pediatrics and the U.S. Public Health Service called for the removal of thimerosal, a mercury-based preservative, from vaccines (CDC, 1999a); and in October 1999, the rotavirus vaccine was withdrawn from the childhood immunization schedule because of its association with increased reports of intussusception.[8] Most recently, the threat of bioterrorism has led to discussion of vaccines against smallpox and anthrax, focusing attention on the benefits as well as the risks of using those vaccines.

Without direct evidence, however, it is hard to know what effect such events have on beliefs and perceptions regarding vaccine safety, including any concerns regarding administration of multiple vaccines. Moreover, interpretations of an event can vary. For example, some may view the withdrawal of rotavirus vaccine

[8] Based on reports of intussusception to VAERS, the CDC recommended in July 1999 that r o-tavirus vaccination be postponed, and in October 1999, the ACIP recommended rotavirus vaccine not be given to infants (CDC, 1999b).

as an indication of inadequate pre-licensing testing. Others, however, may view the withdrawal as an indication of the successful use of VAERS as a warning system and appropriate responsiveness of immunization policymakers.

A fundamental concern for immunization policymakers, discussed in previous reports from this committee (IOM, 2001a,b), is that apprehensions about the safety of vaccines will lead to lower rates of vaccination and increases in serious morbidity and mortality from vaccine-preventable disease, as experienced recently in the United Kingdom (Communicable Disease Report, 2001). Gellin and colleagues (2000) called for periodic assessments of parental attitudes toward vaccines and immunization policy so that clinicians, researchers, and policymakers will have a better understanding of concerns about immunization and can develop more effective responses. But a better understanding of how such concerns affect decisions about immunization will also be needed.

Considering Alternative Approaches to Immunization Policy

The increasing number of vaccines in the childhood immunization schedule—and the anticipated addition of still more vaccines—is raising questions not only about the safety of multiple immunizations but also about the adequacy of the current approach to immunization policy-making, which emphasizes national recommendations and state mandates for universal immunization. For example, the public may perceive new vaccines as less compelling if an assessment of these vaccines are based on their cost-benefit, not their public health benefit. Immunization policies must, implicitly or explicitly, make tradeoffs among a variety of factors, including disease risks, the efficacy and safety of vaccines, the financial costs of disease and vaccines, and the differing perspectives of individuals and society.

A recent paper by Feudtner and Marcuse (2001) argued for greater attention to ethical considerations in developing immunization policies and explores some of the complexities that should be addressed in evaluating policy alternatives. The authors propose a policy framework that explicitly incorporates ethical considerations along with the epidemiological and economic considerations that dominate current decisionmaking. Such a framework should guide both the articulation of policy objectives and the evaluation of policy options to achieve those objectives. In particular, they emphasize the importance of considering matters of personal liberty and equity in the distribution of the benefits and burdens of immunization. For instance, there may be benefits to individuals who have philosophical reasons to refuse immunization. However, there also may be an increased burden on those individuals should they be affected by a vaccine-preventable illness, and the burden would extend to the caretakers of those individuals and to society at large.

Feudtner and Marcuse (2001) also proposed consideration of a broader range of policy options to accommodate a greater degree of autonomy in immunization decisions. The current emphasis on universal immunization recommendations and state mandates may not be appropriate or necessary. The experience of the 15 states that allow philosophic exemptions to required immunization illustrates that the availability of exemptions does not appear to be directly related to levels of immunization coverage. In 2000, although some states that allow philosophic exemptions had some of the lowest immunization rates, other states offering exemptions had some of the highest rates (Marcuse, 2001). An alternative approach might allow for a range of priorities (e.g., mandatory, recommended, or elective), based on an evaluation of the immunization objectives and tradeoffs associated with specific vaccines.

Feudtner and Marcuse (2001) acknowledged the challenges of reaching consensus regarding immunization policies with their broader approach to these issues, but they argued that more explicit attention to a wider range of conflicting views and values is needed to maintain public trust in immunization and other public health programs.

Conclusions

The committee's assessment of the significance of concerns about possible immune system dysfunctions as a result of multiple immunizations took several factors into account: the burden of the possible adverse outcomes of autoimmune diseases such as type 1 diabetes and allergic diseases such as asthma; indications of the extent of the concern about multiple immunizations; and views regarding the framework for immunization policy-making.

Although parents appear to value immunization, a substantial minority believes that multiple immunizations could be harmful. Autoimmune and allergic diseases are common in the United States, after all, and the incidence of these conditions appears to be increasing. As represented by type 1 diabetes and asthma, these conditions are life-threatening if not adequately treated and are associated with substantial health care costs. Given also the prevalence of allergic diseases, specifically asthma, a relatively small increase in risk may lead to a significant public health impact.

A better understanding of parents' perceptions of risk and decision-making may be necessary to prevent decreases in immunization rates and increases in vaccine-preventable disease. Current approaches to immunization policy-making emphasize epidemiological and economic considerations, but may benefit from greater attention to ethical issues, including personal liberty and equity in allocation of the benefits and burdens of immunization. With new vaccines in development and discussions of the wider use of existing vaccines, more flexible approaches to immunization policies—especially regarding priorities—may be needed. Thus, **the committee concludes that concern about multiple**

immunizations has been, and could continue to be, of societal significance in terms of parental worries, potential health burdens, and future challenges for immunization policy-making.

RECOMMENDATIONS FOR PUBLIC HEALTH RESPONSE

With government and professional recommendations calling for young children to receive increasing numbers of immunizations, it is important to respond to concerns about possible increases in risk of allergic or autoimmune diseases. Although the committee's review favors rejection of a causal association between multiple immunizations and type 1 diabetes or risk of infection, and the review is inconclusive for asthma, the biological evidence does provide weak support for increased risk of allergy and for autoimmunity and strong support for increased risk of infection (see Table 6 for a summary). The committee was not able to address more than one autoimmune disease and one specific allergic disease in this report. The generalizability of the epidemiological evidence and the causality assessments to every possible type of exposure to multiple immunizations and every type of immune dysfunction is not clear. In addition, the burden of autoimmune and allergic diseases is great. Investigating whether associations indeed exist poses difficult scientific challenges, and relevant epidemiological evidence remains limited. Several important scientific and policy issues, therefore, deserve further public health attention.

Policy Review

The nature of the childhood immunization schedule is likely to change in response to such factors as the development of new vaccines and utilization of novel delivery systems. Changing perceptions of disease risks—derived from antibiotic resistance, threats of bioterrorism, or (re)emerging infectious diseases—could also lead to wider use of existing vaccines not currently included in the immunization schedule. As the array of available vaccines and disease targets expands, the current emphasis on universal recommendations and state mandates for vaccine use should be reassessed (Feudtner and Marcuse, 2001). **The committee recommends that state and federal vaccine policymakers consider a broader and more explicit strategy for developing recommendations for the use of vaccines.**

Such a strategy should include consideration of a range of perspectives (e.g., those of individuals, families, organizations, society) regarding the benefits, risks, and ethical implications of vaccine use and immunization policies. Priorities can be expected to differ among those diverse perspectives, and policymakers must consider how to achieve an equitable balance (Feudtner and Marcuse, 2001).

As part of that exercise, the committee also encourages state and federal immunization policymakers to include a discussion of state mandates for vaccine use. The committee is encouraged by an activity, tentatively called the "Workgroup on Public Health Options for Implementing Vaccine Recommendations," currently underway by the National Vaccine Advisory Committee (NVAC) of the National Vaccine Program Office (NVPO). The exact nature of that activity—its scope, timetable, and authority to initiate action—are not clear, but it appears to be an important first step toward this dialogue. The committee hopes that this important activity remains a priority for NVPO and NVAC, even as other timely vaccine-related issues influence the agenda. Such issues require long-term planning and evaluation; a reactive response to the next schedule addition will be much less effective than a proactive assessment and strategy development across the board.

As part of this overall effort, the committee encourages an exploration of the merits of accommodating requests for alternative vaccine dosing schedules and the development of appropriate clinical guidance for any such alternatives. A more flexible schedule might allow for a reduction in the number of vaccines administered at one time. Such a change would respond to some concerns about multiple immunizations; but it could also have disadvantages, such as requiring more health care visits, that might contribute to lower rates of immunization coverage in the population and consequent increases in morbidity and mortality. In addition, such a change would require extensive communication with healthcare providers and health plans in order that appropriate immunizations occur and are compensated as much as they are for the "traditional" schedule. A more flexible schedule might also permit innovative epidemiological research that currently is difficult because of the homogenous immunization schedules now extant in the United States. If more flexible schedules do gain acceptance, policymakers must ensure that those options are equally available to children who receive immunizations in public clinics and those who are served by private providers.

By issuing the recommendation listed above, the committee does not intend to signal concern about health consequences of the multiple immunizations in the recommended childhood immunization schedule. In fact, **the committee does not recommend a policy review—by the CDC's Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics' Committee on Infectious Diseases, and the American Academy of Family Physicians—of the current recommended childhood immunization schedule on the basis of concerns about immune system dysfunction.**

Similarly, the committee does not recommend a policy review by the Food and Drug Administration's Vaccines and Related Biologic Products Advisory Committee of any currently licensed vaccines on the basis of concerns about immune system dysfunction.

The committee's review of evidence regarding multiple immunizations and immune system dysfunction provides no basis for recommending

reconsideration at this time of the current childhood immunization schedule or of any specific vaccine.

Research

The committee concluded that the findings available from epidemiological sources and consideration of possible biological mechanisms—which were deemed weak—do not at this time warrant specialized studies of possible associations between multiple immunizations and immune system dysfunction. Instead, the committee encourages epidemiological studies conducted within the framework of ongoing research and surveillance programs on allergy, autoimmune disease, and vaccine safety; it also encourages additional basic research on the immune system and on allergy and autoimmune diseases.

Epidemiological Studies

The committee emphasizes the need for continuing surveillance of vaccine recipients and possible adverse events. Changes in the immunization schedule may present opportunities to study whether or not the incidence of adverse health outcomes also changes. However, one of the challenges in addressing concerns about multiple immunizations is identification of appropriate and adequately sized study populations; allergy or autoimmune diseases have complex risk factors and potentially long intervals between vaccine exposure and diagnosis.

Several vaccine-related data resources already exist, including the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), and state and local immunization registries. **The committee recommends exploring the feasibility of using existing vaccine surveillance systems, alone or in combination, to study safety questions related to asthma and other important allergic disorders, as well as to study type 1 diabetes and other important autoimmune diseases.**

In addition, surveillance of autoimmune diseases and allergic disorders should be strengthened. Despite the routine diagnosis of asthma, finding a widely accepted definition for the disease has been problematic (Samet 1987, Toelle et al., 1997). The absence of a universally accepted definition of asthma makes it difficult to determine a consistent operational definition for epidemiological studies (IOM, 2000).

Disease registries and long-term research programs that identify individuals with these diseases, or with known genetic risk factors, could be an efficient means of finding subjects for either retrospective or prospective studies of possible vaccine-related risks. **The committee recommends exploring the use of such cohorts for research on possible vaccine-related disease risks. Furthermore, the committee recommends that disease registries and research programs for autoimmune and allergic disorders routinely collect**

immunization histories as part of their study protocols. The committee is encouraged to see that the Diabetes Autoimmunity Study in the Young (DAISY), which includes cohorts drawn from the general population and from siblings and offspring of persons with IDDM, is already including immunizations as a routinely monitored variable.

Basic and Clinical Science

Research on the developing human immune system, especially in relation to vaccines, is limited. Studies of animal models are essential to advancing knowledge of the immune system, but those studies have limits because of important differences between humans and animals. Thus, **the committee recommends continued research on the development of the human infant immune system.** A better understanding of the development of the human immune system is needed as a basis for improved understanding of infants' response to vaccines and other environmental exposures. In addition, the committee encourages collaborative activities, such as NIAID/NICHD workshops and initiatives, that help the research community synthesize the results of individual research efforts. The inclusion of vaccinologists and vaccine safety researchers in these efforts is encouraged.

Genetic factors are known to be an important source of variability in the responses of the human immune system and in the risks of allergic or autoimmune disease. But understanding of the complex interactions among genetic variables, as well as of the interactions between those variables and environmental exposures (including vaccines and wild-type viral and bacterial agents), remains incomplete. **The committee endorses current research efforts aimed at identifying genetic variability in human immune system development and immune system responsiveness as a way to gain a better understanding of genetic susceptibility to vaccine-based adverse events.**

For some autoimmune and allergic disorders, surrogate biological markers of disease or disease risk have been identified. In particular, in individuals at risk for type I diabetes, the development of multiple autoantibodies to GAD65 (glutamic acid decarboxylase), IA-2 (protein tyrosine phosphatase-like molecule), and insulin correlate strongly with later development of overt type I diabetes (Notkins and Lernmark, 2001). However, there are to date no other surrogate markers that have sufficient predictive power to be useful in monitoring risk for other autoimmune diseases in children receiving routine immunizations (Leslie et al., 2001). For allergic disorders, the clinical history of allergic diseases should be collected in follow-up evaluations, and the feasibility of specific tests for atopy considered. Studies of the normal development of the immune system in conjunction with surrogate markers of autoimmune and allergic disease and a cohort analysis of autoimmune and allergic disease could be carried out not only in the United States but in infants in a less developed country. Such a compari-

son might more clearly define how an earlier and more intense exposure to microbes might influence the maturation process and alter the proposed impact of immunizations on allergy and autoimmune disease. In theory, collecting data on known markers in the course of vaccine research and testing would present an opportunity to study the prevalence of such markers before and after immunization. Similarly, it might also be possible to study whether the prior presence of a marker was associated with differences in the response to a vaccine. **The committee recommends exploring the feasibility of collecting data on surrogate markers for type I diabetes and clinical history of allergic diseases in the vaccine testing and licensing process.** Such data might also be useful in vaccine-related studies in high-risk cohorts, such as those in the DAISY study. **The committee recommends exploring surrogates for type I diabetes and clinical history of allergic diseases in existing cohort studies of variations in the immunization schedule.**

Communication

Along with the increasingly complex immunization schedule has come a dramatic increase in the complexity of vaccine safety issues, and it appears that some people have redefined their conceptions of the related risks and benefits. The focus seems to have shifted from whether children will get a disease if they are not vaccinated to whether children will experience temporary or potentially longer-term adverse events if they *are* vaccinated (McPhilips and Marcuse, 2001).

The committee is not convinced, however, that available reports on such attitudes provide an adequate scientific basis for understanding either these changes in perception or the groups that are experiencing them. Reports from population-based telephone surveys, for example, typically provide information about what people think, but such surveys rarely can probe adequately about why respondents think the way they do. More information is needed in order to develop effective risk-benefit communication strategies on immunization and vaccine safety.

A deeper understanding of why and how people make decisions as they do is needed, but relying on impressions, assumptions, or any single research method (e.g., survey, focus group, mental modeling, decision analysis) will be too limited. Therefore, **the committee recommends that an appropriate panel of multidisciplinary experts be convened by the Department of Health and Human Services. It would develop a comprehensive research strategy for knowledge leading to the optimal design and evaluation of vaccine risk-benefit communication approaches.** By communication approaches, the committee is not referring to communication tools, such as vaccine information statements, lists of frequently asked questions (FAQs), or websites. Instead, the committee intends that this panel consider a larger definition of risk-benefit communication goals and strategies. In addition, this multidisciplinary panel

may wish to explore the assessment and characterization of these risks. Finally, it must be emphasized that the Immunization Safety Review Committee is not the panel being recommended. A new panel with specialized expertise related to communication issues is necessary.

SUMMARY

A substantial minority of parents (23–25%) participating in a recent survey agreed with the statement that getting too many vaccines is not good for a baby and can weaken the immune system (Gellin, 2000). But a review of the possible biological mechanisms for any adverse effects of multiple immunization on immune function suggests that the infant immune system is inherently capable of handling the numbers of antigens presented during routine immunization.

A review of the clinical and epidemiological literature favors rejection of a causal relationship between multiple immunizations and risk of infection and type 1 diabetes. The evidence was inadequate to accept or reject a causal relationship. Meanwhile, the biological evidence that immunization might lead to infection, autoimmune disease, or allergy is more than only theoretical. This literature base is somewhat limited, however.

Therefore, the committee recommends limited but continued public health attention to this issue in terms of capitalizing on current research efforts. No recommendations for policy review is made, but the committee does recommend an analysis of new frameworks for immunization policy, particularly as the number of licensed vaccines increases.

TABLE 6 Biological Mechanisms for the Possible Role of Immunizations in Increasing the Risk of Immune Dysfunction

Adverse Health Outcome	Mechanism	Committee Conclusion About the Weight of the Biological Evidence
Autoimmune disease	Molecular mimicry	Theoretical only
	Bystander effect	Weak
	Loss of protection induced by homologous infection	Theoretical only
	Via the hygiene hypothesis	Theoretical only
	Collective mechanistic possibilities	Weak
Allergic disease	Bystander effect	Weak
	Via the hygiene hypothesis	Theoretical only
	Collective mechanistic possibilities	Weak
Heterologous Infections	Carrier-induced epitope suppression	Strong
	Competition for antigen presentation	

BOX 1 Committee Conclusions and Recommendations

SCIENTIFIC ASSESSMENT

Causality Conclusions

The committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of heterologous infections.

The committee concludes that the epidemiological and clinical evidence favors rejection of a causal relationship between multiple immunizations and an increased risk of type 1 diabetes.

The committee concludes that the epidemiological and clinical evidence is inadequate to accept or reject a causal relationship between multiple immunizations and an increased risk of allergic disease, particularly asthma.

Biological Mechanisms Conclusions

Autoimmune Disease

In the absence of experimental or human evidence regarding molecular mimicry or mercury-induced modification of any vaccine component to create an antigenic epitope capable of cross-reaction with self epitopes as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that these mechanisms are only theoretical.

The committee concludes that there is weak evidence for bystander activation, alone or in concert with molecular mimicry, as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity.

In the absence of experimental or human evidence regarding loss of protection against a homologous infection as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that this mechanism is only theoretical.

In the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity, the committee concludes that this mechanism is only theoretical.

Considering molecular mimicry, bystander activation, and impaired immunoregulation collectively rather than individually, the committee concludes that there is weak evidence for these mechanisms as means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of autoimmunity.

Allergic Disease

The committee concludes that there is weak evidence for bystander activation as a mechanism by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.

In the absence of experimental or human evidence regarding mechanisms related to the hygiene hypothesis as a means by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy, the committee concludes that this mechanism is only theoretical.

The committee concludes that there is weak evidence for the existence of any biological mechanisms, collectively or individually, by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk of allergy.

Heterologous Infection

The committee concludes that there is strong evidence for the existence of biological mechanisms by which multiple immunizations under the U.S. infant immunization schedule could possibly influence an individual's risk for heterologous infections.

SIGNIFICANCE ASSESSMENT

Conclusions

The committee concludes that concern about multiple immunizations has been, and could continue to be, of societal significance in terms of parental worries, potential health burdens, and future challenges for immunization policy-making.

PUBLIC HEALTH RESPONSE RECOMMENDATIONS

Policy Review

The committee recommends that state and federal vaccine policymakers consider a broader and more explicit strategy for developing recommendations for the use of vaccines.

The committee does not recommend a policy review—by the CDC's Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics' Committee on Infectious Diseases, and the American Academy of Family Physicians—of the current recommended childhood immunization schedule on the basis of concerns about immune system dysfunction.

The committee does not recommend a policy review by the Food and Drug Administration's Vaccines and Related Biologic Products Advisory

Committee of any currently licensed vaccines on the basis of concerns about immune system dysfunction.

Research

Epidemiological Research

The committee recommends exploring the feasibility of using existing vaccine surveillance systems, alone or in combination, to study safety questions related to asthma and other important allergic disorders, as well as to study type 1 diabetes and other important autoimmune diseases.

The committee recommends exploring the use of cohorts for research on possible vaccine-related disease risks. Furthermore, the committee recommends that disease registries and research programs for autoimmune and allergic disorders routinely collect immunization histories as part of their study protocol.

Basic Science and Clinical Research

The committee recommends continued research on the development of the human infant immune system.

The committee endorses current research efforts aimed at identifying genetic variability in human immune system development and immune system responsiveness as a way to gain a better understanding of genetic susceptibility to vaccine-based adverse events.

The committee recommends exploring the feasibility of collecting data on surrogate markers for type I diabetes and clinical history of allergic diseases in the vaccine testing and licensing process.

The committee recommends exploring surrogates for type I diabetes and clinical history of allergic diseases in existing cohort studies of variations in the immunization schedule.

Communication

The committee recommends that an appropriate panel of multidisciplinary experts be convened by the Department of Health and Human Services. It would develop a comprehensive research strategy for knowledge leading to the optimal design and evaluation of vaccine risk-benefit communication approaches.

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Appendix A

Chronology of Important Events Regarding Vaccine Safety

Year	Vaccine Licensure	Legislation and/or Policy Statements	IOM Reports on Vaccine Safety
1955	Inactivated poliomyelitis vaccine (IPV) available		
1963	Oral poliomyelitis vaccine (OPV) available, replaces IPV		
	Measles vaccine available		
1967	Mumps vaccine available		
1969	Rubella vaccine available		
1971	Measles-Mumps-Rubella (MMR) vaccine available		
1977		Mumps vaccination recommended	*Evaluation of Poliomyelitis Vaccines*
1979	Current formulation of Rubella vaccine available, replaces earlier versions		
1982	Plasma-derived hepatitis B vaccine available		

Continued

Year	Vaccine Licensure	Legislation and/or Policy Statements	IOM Reports on Vaccine Safety
1985	Hib vaccine licensed for children >15 months		
1986		Congress passes Public Law 99-660, the National Childhood Vaccine Injury Act (introduced in 1984) calls for: est. of NVPO est. of NVAC est. of VICP est. of ACCV IOM review of 1) pertussis and rubella, 2) routine child vaccines	
1988			*Evaluation of Poliomyelitis Vaccine Policy Options*
1990	2 Hib conjugate vaccines licensed for use beginning at 2 months		
1991	Acellular pertussis component licensed for the 4th and 5th doses of the 5-part DTP series in ACEL-IMUNE	Hepatitis B recommended by ACIP for addition to childhood immunization schedule ACIP recommends Hib be added to childhood immunization schedule	*Adverse Effects of Pertussis and Rubella Vaccines*
1992	Acellular pertussis component licensed for the 4th and 5th doses of the 5-part DTP series in Tripedia	Hepatitis B vaccine: Added universal vaccination for all infants, high-risk adolescents (e.g., IV drug users, persons with multiple sex partners)	
1993	Combined DTP and Hib vaccine (Tetramune) licensed		
1994			*Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* *DPT and Chronic Nervous System Dysfunction: A New Analysis*

Year	Vaccine Licensure	Legislation and/or Policy Statements	IOM Reports on Vaccine Safety
1995	Varicella virus vaccine available (Varivax)		
1996	DTaP vaccine (Tripedia and ACEL-IMUNE licensed for complete 5-dose series	ACIP recommends using IPV for the first 2 polio vaccinations, followed by OPV for remaining doses. Intended to be a transitional schedule for 3–5 years until an all -IPV series is available ACIP recommends children 12months – 12 years receive Varicella vaccin	*Options for Poliomyelitis Vaccinations in the United States: Workshop Summary*
1997	Additional DTaP vaccine (Infanrix) licensed for first 4 doses of 5-part series	ACIP recommends DTaP in place of DTP	*Vaccine Safety Forum: Summary of Two Workshops* *Risk Communication and Vaccination: Workshop Summary*
1998	Additional DTaP vaccine (Certiva) licensed for first 4 doses of 5-part series	ACIP updates MMR recommendation, encouraging use of the combined MMR vaccine	
1999		ACIP updates varicella vaccine recommendation, requiring immunity for child care and school entry ACIP recommends an all-IPV schedule begin January 2000 to prevent cases of vaccine-associated paralytic polio AAP and PHS recommend removal of thimerosal from vaccines Also recommended postponement of hepatitis B vaccine from birth to 2–6 months for infants of hepatitis B surface antigen-negative mothers	
	Additional supply of thimerosal-free hepatitis B vaccine made available	MMWR notifies readers of the availability of a thimerosal-free hepatitis B vaccine, enabling the resumption of the birth dose	

Continued

Year	Vaccine Licensure	Legislation and/or Policy Statements	IOM Reports on Vaccine Safety
2000	Pneumococcal vaccine for infants and young children licensed (Prevnar)	ACIP recommends pneumococcal vaccination for all children 2–23 months, and at-risk children 24–59 months (e.g., immunocompromised)	
2001		October: ACIP drafts statement expressing a preference for use of thimerosal-free DtaP, Hib, and Hep B vaccines by March 2002	*Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism* *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders*

Appendix B

Committee Conclusions and Recommendations from Previous Reports

MEASLES-MUMPS-RUBELLA VACCINE AND AUTISM

Conclusions

The committee concludes that the evidence favors rejection of a causal relationship at the population level between measles-mumps-rubella (MMR) vaccine and autistic spectrum disorders (ASD). However, this conclusion does not exclude the possibility that MMR vaccine could contribute to ASD in a small number of children.

The committee concludes that further research on the possible occurrence of ASD in a small number of children subsequent to MMR vaccination is warranted, and it has identified targeted research opportunities that could lead to firmer understanding of the relationship.

Recommendations

Public Health Response

The committee recommends that the relationship between the MMR vaccine and autistic spectrum disorders receive continued attention.

Policy Review

The committee does not recommend a policy review at this time of the licensure of MMR vaccine or of the current schedule and recommendations for administration of MMR vaccine.

Research Regarding MMR and ASD

The committee recommends the use of accepted and consistent case definitions and assessment protocols for ASD in order to enhance the precision and comparability of results from surveillance, epidemiological, and biologic investigations.

The committee recommends the exploration of whether exposure to MMR vaccine is a risk factor for autistic spectrum disorder in a small number of children.

The committee recommends the development of targeted investigations of whether or not measles vaccine-strain virus is present in the intestines of some children with ASD.

The committee encourages all who submit reports to VAERS of any diagnosis of ASD thought to be related to MMR vaccine to provide as much detail and as much documentation as possible.

The committee recommends studying the possible effects of different MMR immunization exposures.

The committee recommends conducting further clinical and epidemiological studies of sufficient rigor to identify risk factors and biological markers of ASD in order to better understand genetic or environmental causes.

Communications

The committee recommends that government agencies and professional organizations, CDC and the Food and Drug Administration (FDA) in particular, review some of the most prominent forms of communication regarding the hypothesized relationship between MMR vaccine and ASD, including information they provide via the Internet and the ease with which Internet information can be accessed.

THIMEROSAL-CONTAINING VACCINES AND NEURODEVELOPMENTAL DISORDERS

Conclusions

The committee concludes that although the hypothesis that exposure to thimerosal-containing vaccines could be associated with neurodevelopmental disorders is not established and rests on indirect and incomplete information, primarily from analogies with methylmercury and levels of maximum mercury exposure from vaccines given in children, the hypothesis is biologically plausible.

The committee also concludes that the evidence is inadequate to accept or reject a causal relationship between thimerosal exposures from childhood vaccines and the neurodevelopmental disorders of autism, ADHD, and speech or language delay.

Public Health Response Recommendations

Policy Review and Analysis

The committee recommends the use of the thimerosal-free DTaP, Hib, and hepatitis B vaccines in the United States, despite the fact that there might be remaining supplies of thimerosal-containing vaccine available.

The committee recommends that full consideration be given by appropriate professional societies and government agencies to removing thimerosal from vaccines administered to infants, children, or pregnant women in the United States.

The committee recommends that appropriate professional societies and government agencies review their policies about the non-vaccine biological and pharmaceutical products that contain thimerosal and are used by infants, children, and pregnant women in the United States.

The committee recommends that policy analyses be conducted that will inform these discussions in the future.

The committee recommends a review and assessment of how public health policy decisions are made under uncertainty.

The committee recommends a review of the strategies used to communicate rapid changes in vaccine policy, and it recommends research on how to improve those strategies.

Public Health and Biomedical Research

The committee recommends a diverse public health and biomedical research portfolio.

Epidemiological Research

The committee recommends case-control studies examining the potential link between neurodevelopmental disorders and thimerosal-containing vaccines.

The committee recommends further analysis of neurodevelopmental disorders in cohorts of children who did not receive thimerosal-containing doses as part of a clinical trial of DTaP vaccine.

The committee recommends conducting epidemiological studies that compare the incidence and prevalence of neurodevelopmental disorders before and after the removal of thimerosal from vaccines.

The committee recommends an increased effort to identify the primary sources and levels of prenatal and postnatal background exposure to thimerosal (e.g., Rho (D) Immune Globulin) and other forms of mercury (e.g., maternal consumption of fish) in infants, children, and pregnant women.

Clinical Research

The committee recommends research on how children, including those diagnosed with neurodevelopmental disorders, metabolize and excrete metals—particularly mercury.

The committee recommends continued research on theoretical modeling of ethylmercury exposures, including the incremental burden of thimerosal with background mercury exposure from other sources.

The committee recommends careful, rigorous, and scientific investigations of chelation when used in children with neurodevelopmental disorders, especially autism.

Basic Science Research

The committee recommends research to identify a safe, effective, and inexpensive alternative to thimerosal for countries that decide they need to switch from using thimerosal as a preservative.

The committee recommends research in appropriate animal models on the neurodevelopmental effects of ethylmercury.

Appendix C

Immunization Safety Review Committee

Multiple Immunizations in Newborns and Infants and Immune System Dysfunction

Public Meeting
Monday, November 12, 2001

Aljoya Conference Center
Seattle, Washington

AGENDA

8:00–8:15 a.m. **Welcome and Introductions**
Marie McCormick, M.D., Sc.D.
Chair, Immunization Safety Review Committee

Additional Comments
Christopher Wilson, M.D.
Member, Immunization Safety Review Committee

8:15–9:00 a.m. **Immunological Competition and the Infant Immune Response to Vaccines**
Richard Insel, M.D.
University of Rochester School of Medicine

9:00–9:20 a.m. **T Cell Immunity in Infants and Immune System Overload Hypothesis**
Tobias Kollman, M.D.
University of Washington

9:20–10:00 a.m. **Hygiene Hypothesis**
Graham Rook, M.D.
Royal Free and University College Medical School, London

10:00–10:30 a.m. **Discussion**

10:30–10:45 a.m. **Break**

10:45–11:30 a.m. **Immunizations and Autoimmunity: Mechanisms, Plausibility, and Genetic Susceptibility**
Gerald Nepom, M.D., Ph.D.
University of Washington

11:30a.m.–
12:15 p.m. **Diabetes: Incidence and Possible Triggers**
George Eisenbarth, M.D., Ph.D.
University of Colorado Health Sciences Center

12:15–12:45 p.m. **Discussion**

12:45–1:45 p.m. **Lunch**

1:45–2:30 p.m. **Genetic Screening and Diabetes: A New Prospective Study**
Marian Rewers, M.D., Ph.D.
University of Colorado Health Sciences Center

2:30–3:15 p.m. **Autoimmunity and the Central Nervous System**
Olaf Stuve, M.D.
University of California at San Francisco

3:15–3:45 p.m. **Research Strategies**
Ronald Kennedy, Ph.D.
Texas Tech University Health Sciences Center

3:45–4:00 p.m. **Break**

4:00–4:45 p.m. **Immunization Hesitancy**
Edgar Marcuse, M.D., M.P.H.
University of Washington

4:45–5:15 p.m. **Discussion**

5:15–5:30 p.m. **Public Comment**

5:30 p.m. **Adjourn**

Appendix D

Methods of Identifying the Literature for the Causality Assessment

To evaluate the hypothesis on multiple immunizations and immune system dysfunction, the committee collected information from several sources. At an open scientific meeting in November 2001, academic researchers gave presentations on specific scientific issues germane to the topic. All information presented to the committee at that meeting can be viewed on the project website (www.iom.edu/imsafety). An extensive review was performed of the published, peer-reviewed scientific and medical literature pertinent to the hypothesis.

Search Strategy for the Causality Assessment

To inform the committee's causality assessments, the following searches were performed. As epidemiological studies carry the most weight in a causality assessment, all searches were limited to human subjects.

Diabetes A search for relevant articles was conducted on PubMed using the MeSH term "diabetes mellitus, insulin dependent" with the terms "vaccin*" or "immunization*" in the MeSH field. The search was further limited to articles in English.

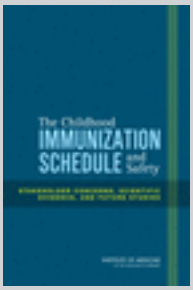
Asthma A search was conducted on PubMed. The terms "vaccines" OR "immunizations" were combined with the term "hypersensitivity" in the MeSH field. This search was then combined with NOT "cancer" OR "occupational diseases,"also in the MeSH field. The search was further narrowed by combining the results with "epidemiologic methods" in the MeSH field, and limiting it to studies in English. A total of 363 articles were found.

Heterologous Infection To examine the heterologous effects of vaccines, several searches were conducted on PubMed. In the first, the terms "vaccines/adverse effects" were combined with "viruses/etiology" in the MeSH field. The search was further limited to studies in which "vaccines/adverse effects" had to appear as a MeSH major topic—a MeSH term that is one of the main topics discussed in the article.

A second search for articles pertaining to heterologous effects of vaccines combined "pneumococcal OR polio OR diphtheria OR tetanus vaccine" with "invasive bacterial disease." A similar search combined "vaccine/adverse ef-

fects" with "bacterial infections/epidemiology," limited to MeSH terms. The final two searches combined "vaccines/adverse effects" with "morbidity" OR "mortality" in the MeSH field. The search was further limited to articles in which "vaccines/adverse effects" was a MeSH major topic.

EXHIBIT D



The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies

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NOTICE: The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

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"Knowing is not enough; we must apply.
Willing is not enough; we must do."
—Goethe

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COMMITTEE ON THE ASSESSMENT OF STUDIES OF HEALTH OUTCOMES RELATED TO THE RECOMMENDED CHILDHOOD IMMUNIZATION SCHEDULE

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*Until August 2012.

Reviewers

This report has been reviewed in draft form by persons chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Ann Bostrom, University of Washington
Doug Campos-Outcalt, University of Arizona, Phoenix
Louis Z. Cooper, Columbia University
Rebecca Fleischauer, Steege Thomson Communications
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Arthur Reingold, University of California, Berkeley

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions

or recommendations nor did they see the final draft of the report before its release. The review of this report was overseen by **Bradford H. Gray,** the *Milbank Quarterly*, the Urban Institute, and **Donald M. Steinwachs,** Johns Hopkins University. Appointed by the National Research Council and the Institute of Medicine, they were responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

Acknowledgments

The committee thanks colleagues both within and outside the National Academies who provided expertise and time to inform the committee and enhanced the quality of the report. Numerous individuals and organizations shared their knowledge and expertise with the committee during information-gathering sessions held on February 9, March 8, and May 29, 2012. These sessions were intended to assist the committee in collecting information on the safety and study of current and past vaccine schedules in the United States and abroad to inform the committee's understanding and vision in completing its task. These individuals are listed in Appendix E.

Of particular note, Martin Kulldorff provided a commissioned paper on study designs that could be considered to assess the safety of the immunization schedule (see Appendix D). Both draft and revised versions of the paper were posted on the study's website to receive public comments to inform the committee's work. In total, the committee reviewed more than 900 public comments. The commissioned paper and public submissions were critical to ensuring fruitful discussions among the members of the committee.

Committee members Alfred Berg and Elena Fuentes-Afflick graciously hosted committee meetings near their respective institutions. The committee thanks the numerous staff members of the Institute of Medicine (IOM), the National Research Council, and the National Academies Press who contributed to the development, production, and dissemination of the report, including study staff Karen Helsing, Suzanne Landi, Chelsea Frakes, Rose Marie Martinez, and Hope Hare. In addition, the study received valuable contributions from Christine Stencel (Office of News and Public

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Contents

APPENDIXES

Abstract

The charge to the Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule was to (1) review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule and (2) identify potential research approaches, methodologies, and study designs that could inform this question, considering strengths, weaknesses, as well as the ethical and financial feasibility of each approach. As reviewed by prior Institute of Medicine studies, a substantial literature exists on adverse effects of individual vaccines, but few studies have focused on elements of or the recommended childhood immunization schedule as a whole. The lack of conclusive evidence linking adverse events to multiple immunizations or other "schedule" exposures suggests that the recommended schedule is safe. There are concerns from some stakeholders that merit exploration through research if epidemiological signals are detected and an indication of biological plausibility is available. However, the committee concludes that it is not ethical to implement any study requiring that some children receive fewer vaccines than recommended as part of the childhood immunization schedule because this would needlessly endanger children's lives. The committee concludes that data from existing surveillance systems, such as the Vaccine Safety Datalink, could be used and offer the best means for ongoing research efforts regarding the safety of the schedule. In recognition of this, future federal research approaches should

- collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the

goal to improve communication with health care professionals, and between health care professionals and the public regarding safety;
- standardize definitions of key elements of the schedule, and relevant health outcomes;
- establish research priorities on the basis of epidemiological evidence, biological plausibility, and feasibility; and
- continue to fund and support the Vaccine Safety Datalink project to study the safety of the recommended immunization schedule.

Summary

BACKGROUND

Vaccines are among the most effective and safe public health interventions available to prevent serious disease and death. As the incidence of vaccine-preventable diseases has declined because of the widespread use of immunizations, potential adverse effects of the vaccines themselves have taken on greater saliency among stakeholders. The U.S. Advisory Committee on Immunization Practices (ACIP) has created a schedule of vaccines that should be administered at various intervals. ACIP recommends immunization with vaccines that protect young children (age 6 years and under) against 14 pathogens (see Appendix A) and strives to protect children at the youngest age necessary to shield them from diseases when they are the most vulnerable. The childhood immunization schedule (defined in this report as the immunization schedule covering children from birth through age 6 years) immunizes children in a manner consistent with demonstrated efficacy, safety, and feasibility but also permits some degree of flexibility to accommodate individual preferences and logistics.

With the current schedule, children may receive up to 24 immunizations by age 2 years and up to 5 injections in a single visit. Although the number of vaccines has increased over the years to protect against a greater number of diseases, because of technological advances children now receive fewer antigens, which are the components of vaccines that stimulate the immune system.

In the United States, manufacturers extensively test new vaccine products and then the federal government undertakes a formal process of review

and approval before vaccines are made publicly available. Each new vaccine considered for inclusion in the immunization schedule is tested within the context of the existing schedule and reviewed by clinical researchers, who analyze the balance of demonstrated benefits and risks. Thus, each new vaccine is approved on the basis of a detailed evaluation of both the vaccine itself and the immunization schedule. Every year, the Centers for Disease Control and Prevention (CDC) issues guidance on the vaccines to be administered and immunization schedules for children, adolescents, and adults, based on recommendations from ACIP.

To recommend new vaccines, ACIP uses a process in which it reviews a comprehensive set of data associated with the vaccine, including illnesses and deaths associated with the disease and specific high-risk groups; the results of clinical trials, including indicators of safety, efficacy, and effectiveness; cost-effectiveness; information on vaccine use provided by the manufacturer in the product's labeling or package insert; and the feasibility of incorporation of the vaccine into the existing immunization schedule.

Ongoing surveillance systems are the primary source of data on vaccine safety postmarketing. CDC maintains three major postmarketing surveillance systems: the Vaccine Adverse Event Reporting System, which is jointly managed with the Food and Drug Administration (FDA); the Vaccine Safety Datalink (VSD); and the Clinical Immunization Safety Assessment Network. In addition to the surveillance systems managed by CDC, FDA has established the Sentinel Initiative, a supplementary mechanism for monitoring vaccine safety.

Immunization coverage among children entering kindergarten currently exceeds 90 percent for most recommended vaccines. However, concerns about vaccine safety have contributed to increases in the delay or refusal of immunization, which have, in turn, contributed to a reemergence of vaccine-preventable illnesses. For example, measles and pertussis (whooping cough) outbreaks have occurred in areas where higher proportions of children are unimmunized.

Vaccines—like all drugs or medical interventions—are neither 100 percent risk-free nor 100 percent effective. Additionally, population-wide prevention of vaccine-preventable diseases relies on community immunity, also commonly referred to as herd immunity, which is the shared protective effect conferred on unimmunized individuals when a sufficiently large proportion of the population is immunized against infectious diseases. This phenomenon is achieved when too few people who are vulnerable to development of a disease remain in the population to maintain the chain of disease transmission. Community immunity is waning, however, in places with increasing numbers of unimmunized, incompletely immunized individuals and/or individuals with waning immunity.

Even though children are required to be immunized to enter school

and child care, medical exemptions are allowed in all states, and almost all states allow immunization exemptions for people who have religious beliefs against them. Furthermore, 20 states permit exemptions for those who object to immunizations because of personal, moral, or other beliefs.

THE COMMITTEE

The National Vaccine Program Office (NVPO) of the U.S. Department of Health and Human Services (HHS) asked the Institute of Medicine (IOM) to convene a committee of experts in pediatrics, neurology, medical ethics, immunology, statistics, epidemiology, and public health to identify feasible study designs to explore the safety of the U.S. childhood immunization schedule. A 14-member committee was assembled to address the statement of task. The committee's charge is independent of the charges for previous IOM vaccine studies, and committee members were selected to avoid any real or perceived biases or conflicts. Strict criteria for membership prevented members from having financial ties to vaccine manufacturers or their parent companies, previous service on federal vaccine advisory committees, or having delivered expert testimony or written publications on vaccine safety. The committee's charge is detailed in Box S-1.

COMMITTEE PROCESS

To complete its charge, the committee held three information-gathering meetings in two locations. Before the first meeting and throughout the committee's deliberations, the committee gathered information on public

BOX S-1
Statement of Task

The Institute of Medicine will convene an expert committee to

1. Review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule.
2. Identify potential research approaches, methodologies, and study designs that could inform this question, including an assessment of the potential strengths and limitations of each approach, methodology and design, as well as the financial and ethical feasibility of doing them.
3. Issue a report summarizing their findings.

perspectives and reviewed the scientific literature on the safety of the recommended childhood immunization schedule. At the public forums, the committee heard presentations by pediatricians, representatives of federal and state agencies and public health agencies in other countries, vaccine safety researchers, advocacy groups, vaccine manufacturers, and methodological experts. The committee invited comments (both written and oral) from the general public and representatives from numerous organizations with an interest in vaccine safety.

The committee held five deliberative meetings over 6 months. To address its charge, the committee requested from consultant Martin Kulldorff a commissioned paper on study designs that could be used to assess the safety of the immunization schedule (see Appendix D). The paper was intended to provide methodological input to the committee but the paper does not necessarily reflect the committee's views. To solicit stakeholders' feedback, the commissioned paper was posted on the committee's website.

STAKEHOLDER CONCERNS

A review of the scientific literature, as well as a detailed review of the oral and written public comments, revealed that among the various stakeholder groups,[1] parents, health care providers, and public health officials share the sentiment that there is insufficient communication between providers and parents about the schedule's safety. Even though the vast majority of parents adhere to the ACIP-recommended immunization schedule, some parents are concerned that the schedule may present unnecessary risks because of the timing and number of vaccinations.

Some parents request variations in the immunization schedule, such as a delay of one or more immunizations or the administration of fewer vaccinations at each visit. Some parents also refuse immunizations entirely on the basis of the premise that their children's risks from vaccine-preventable diseases are less than the risks of adverse events associated with immunizations. Such decisions may reflect, in part, the significant and sustained decline in vaccine-preventable diseases that immunization policy has achieved in the past several decades and against which the risk of even extremely rare adverse events may be seen as not worth taking. Some parents are concerned about their child's risk of complications after immunization on the basis of a family history or the child's medical condition and thereby

[1]Stakeholder groups include researchers; advocacy groups; federal agencies and advisory committees; the general public (including parents); the health care system and providers; international organizations; media; nongovernmental organizations; philanthropic organizations; state, local, and tribal government agencies; industries, such as travel and vaccine manufacturing industries; vaccine distributors; and investors in vaccine manufacturers.

decide to delay or omit immunizations. Other parents express a general lack of confidence in U.S. government decisions about the safety and benefits of the childhood immunization schedule.

The committee understands that these parental concerns are an expression of concern and a way to care for their children's health and well-being. However, the committee also recognizes that a delay or refusal to immunize their children has already contributed to outbreaks of disease across the United States that pose a risk to the health of many people, particularly those with compromised immune systems.

The committee's review of the literature also focused on factors that affect public trust in vaccination campaigns and information on vaccines. Improved communication between public health authorities and parents will require improvements to the clarity of information as well as the building of trust and the use of a systematic approach to elicit public concerns. Further research into questions that parents seek to answer by use of the scientific methods of social, behavioral, and decision science is indicated.

HEALTH OUTCOMES

The committee searched for, assembled, and summarized evidence on the association between the immunization schedule and specific health conditions that was already published in the peer-reviewed literature. The health outcomes that the committee chose to review were selected on the basis of an examination of the peer-reviewed literature, previous IOM vaccine safety studies, and public presentations at open meetings of this committee. The number of studies that addressed aspects of the immunization schedule varied; for some outcomes, several studies had examined the cumulative effects of vaccines and adjuvants or preservatives, whereas very few studies could be found for other outcomes.

The committee's literature searches and review were intended to identify health outcomes associated with some aspect of the childhood immunization schedule. Allergy and asthma, autoimmunity, autism, other neurodevelopmental disorders (e.g., learning disabilities, tics, behavioral disorders, and intellectual disabilities), seizures, and epilepsy were included as search terms. Furthermore, the committee reviewed papers on immunization and premature infants.

In summary, few studies have comprehensively assessed the association between the entire immunization schedule or variations in the overall schedule and categories of health outcomes, and no study has directly examined health outcomes and stakeholder concerns in precisely the way that the committee was charged to address in its statement of task. No studies have compared the differences in health outcomes that some stakeholders questioned between entirely unimmunized populations of children and fully

immunized children. Experts who addressed the committee pointed not to a body of evidence that had been overlooked but rather to the fact that existing research has not been designed to test the entire immunization schedule.

The committee believes that although the available evidence is reassuring, studies designed to examine the long-term effects of the cumulative number of vaccines or other aspects of the immunization schedule have not been conducted. Nevertheless, in its literature review, the committee found useful designs for studies to measure exposures and outcomes and identified strategies for expanding or adapting conventional study designs to clearly address whether any adverse health outcomes are associated with the overall immunization schedule.

METHODOLOGICAL APPROACHES

Moving from an analysis of stakeholder concerns and the limited scientific evidence about the association between the immunization schedule and adverse events to recommendation of specific research methods and study designs to address that association is an ambitious task in light of the complexity and changing nature of the recommended immunization schedule. Variables such as the number of doses, the age of administration, and the amount of time between doses permit the examination of a large number of potential research questions. Among the many questions about the current immunization schedule that could be posed, the committee parsed the phrase "this question" in Part 2 of the statement of task (Box S-1) into four broad research questions of interest to stakeholders. These are identified in Box S-2.

The committee broadly considered several general research strategies that might be used to address these questions: randomized controlled trials (RCTs), prospective and retrospective observational studies, animal models, and secondary analyses of existing data.

Randomized Controlled Trials

When it is possible to randomize study participants, the RCT is widely acknowledged to be the preferred study design for determining cause and effect. RCTs are currently used as part of the FDA approval process to evaluate the safety and effectiveness of individual vaccines in the context of the recommended immunization schedule. Although this is the strongest type of study design, the committee concluded that costs, the large number of participants that would be required, ethical concerns, and other factors make it an inappropriate design for addressing the research questions at hand.

RCTs require participants to be randomly assigned to a study group.

BOX S-2
Leading Research Questions of Interest to Select Stakeholders

1. How do child health outcomes compare between those who receive no vaccinations and those who receive the full currently recommended immunization schedule?
2. How do child health outcomes compare between (a) those who receive the full currently recommended immunization schedule and (b) those who omit specific vaccines?
3. For children who receive the currently recommended immunization schedule, do short- or long-term health outcomes differ for those who receive fewer immunizations per visit (e.g., when immunizations are spread out over multiple occasions), or for those who receive their immunizations at later ages but still within the recommended ranges?
4. Do potentially susceptible subpopulations—for example, children from families with a history of allergies or autoimmune diseases—who may experience adverse health consequences in association with immunization with the currently recommended immunization schedule exist?

However, the random placement of children into a study group in which they would receive less than the full immunization schedule or no vaccines would not be ethical because they would be exposed to a greater risk for the development of diseases and community immunity would be compromised. Furthermore, parents who reject vaccination likely would not allow their children to be randomized to the group that receives full immunization. Additionally, health care professionals serving participants placed in the group to receive fewer or no vaccines would have to go against professional medical guidelines that call on them to encourage patients to follow the recommended schedule.

Even the use of a dispersed immunization schedule that is still within the accepted ACIP time frame for vaccinations as a trial arm would require an increased number of clinic visits, often in rapid succession over a period of a few weeks, which could prove difficult and costly for both the clinics and participating families and may be unacceptable to insurers if its improved effectiveness—measured as a decreased rate of adverse outcomes—was negligible. Although the use of a different schedule that still conforms to the ACIP vaccination time frame is unobjectionable ethically, the committee cannot endorse this method as a feasible option.

The conduct of an RCT would require thousands of participants to be of sufficient size to answer questions about the outcomes of different immunization schedules, and the study would have to span at least 6 to 10 years, meaning that it would likely cost the nation tens of millions of dollars. The risks to participants' health, the cost and time involved, and the ethical challenges all make the conduct of an RCT unsuitable for addressing the research questions, at least until further work with secondary data has been conducted.

New Prospective Observational Studies

Observational studies are another form of clinical research that can provide useful insights and information that may be used to answer research questions. The committee reviewed opportunities to study groups that choose not to vaccinate using a prospective cohort study design. However, such a study would not conclusively reveal differences in health outcomes between unimmunized and fully immunized children for two main reasons. First, to be informative, cohort studies require sufficiently large numbers of participants in each study group and the sample populations often suggested for use in a comparison of vaccinated and unvaccinated children (such as some religious groups) are too small to adequately power a comparative analysis, particularly in the case of rare adverse health outcomes. Because meaningful comparisons require thousands of participants in each study group and less than 1 percent of the U.S. population refuses all immunizations, the detection of enough unvaccinated children would be prohibitively time-consuming and difficult.

Second, such a study would also need to account for the many confounding variables that separate some populations from the average U.S. child, including lifestyle factors and genetic variables. To be useful, a comparison would require children matched by age; sex; geographic location; rural, urban, or suburban setting; socioeconomic group; and race/ethnicity.

The committee acknowledges that large-scale, long-term studies of infants through adulthood would be informative for evaluating health outcomes associated with immunization. A new research initiative, the National Children's Study, is a multicenter, congressionally funded effort that meets these criteria. Although such studies would be the optimal design for evaluating long-term health outcomes associated with the childhood immunization schedule, they would require considerable time and funding, and the committee did not find adequate epidemiological evidence to recommend investment in this type of research at this time.

Secondary Analyses of Existing Data

The most feasible approach to studying the safety of the childhood immunization schedule is through analyses of data obtained by VSD. VSD is a collaborative effort between CDC and 9 managed care organizations that maintain a large database of linked data for monitoring immunization safety and studying potential rare and serious adverse events. VSD member sites include data for more than 9 million children and adults receiving vaccinations on a variety of immunization schedules. However, children who are vaccinated on alternative schedules (including those who are not vaccinated) may differ in meaningful ways. Although this confounding can be minimized through matching and controlling for variations, differences in nonrandomly constructed cohorts cannot be fully accounted for by the use of these data.

The committee discussed several potential modifications that could be introduced into this system that would enable new analyses of the key research questions (Box S-2), including collection of additional data on the participants. The committee found that secondary analyses within VSD would advance knowledge of the safety of the immunization schedule and identified enhancements to improve the data in VSD.

Animal Models

The committee also reviewed the potential for animal studies to be used to study the childhood immunization schedule. Given the committee's recognition of the complexity of the immunization schedule, the importance of family history, the role of individual immunologic factors, and the complex interaction of the immunization schedule with the health care system, the committee determined that it was more appropriate to focus future research efforts on human research.

Population Impacts of Alternative Schedules

The committee agreed that evaluations of the recommended immunization schedule need to be attentive to effects at the population level as well as the individual level. Attempts to quantify the relative safety of contrasting immunization schedules need to take into account at least two separate health outcomes: adverse events after the administration of specific vaccines and the overall immunization schedule, and the respective impacts of alternative schedules on the circulation of vaccine-preventable diseases and the consequent adverse outcomes associated with infection.

The intimate association between immunization and age-specific disease incidence needs to be addressed. Specifically, any changes in the immu-

nization schedule that lead to an increase in exposure to preventable disease will increase the spread of the pathogens responsible for these diseases. The population-level impacts of such an outcome would be a simultaneous rise in the incidence of infectious diseases and a reduction in the age at which these illnesses are contracted. Thus, not only is the risk of exposure to preventable diseases increased, but the severity of infection, which is age dependent, is also likely to increase.

CONCLUSIONS ABOUT STAKEHOLDER CONCERNS

The committee identified concerns among some parents about the number, frequency, and timing of immunizations in the overall immunization schedule. These concerns were not expressed by clinicians, public health personnel, or policy makers in the committee's review. Among the last three groups, the childhood immunization schedule is considered one of the most effective and safest public health interventions available to prevent serious disease and death. Furthermore, the committee's review of the literature did not find high quality evidence supporting safety concerns about the immunization schedule.

In its role to ensure vaccine safety, the federal government has emphasized the engagement of stakeholders in multiple activities. However, an effective national vaccine program will require a more complete and systematic collection of information about stakeholder concerns about vaccine safety, the severity of vaccine-preventable diseases, individual- and population-level immunization rates, the efficacy of immunization, and the delivery and supply of vaccines recommended in the childhood immunization schedule.

To more effectively implement immunization programs, a robust communication and engagement strategy that includes careful study of safety concerns is needed. Currently, the designs used in most studies of immunizations do not permit a detailed analysis of the impact of parental concerns on the decision to immunize their children. Most concerns about safety are expressed by parents, but multiple stakeholders should be included in NVPO efforts. For example, even health care providers with much knowledge about individual vaccines may have less information about the effects of administering multiple vaccines at a single visit or the timing of the immunizations.

Recommendation 4-1: The committee recommends that the National Vaccine Program Office systematically collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the goal to improve communication with

health care professionals, and between health care professionals and the public regarding the safety of the schedule.

CONCLUSIONS ABOUT SCIENTIFIC FINDINGS

The committee encountered two major issues in its review of the findings in the scientific literature. First, the concept of the immunization "schedule" is not well developed. Most vaccine-related research focuses on the outcomes of single immunizations or combinations of vaccines administered at a single visit. Although each new vaccine is evaluated in the context of the overall immunization schedule that existed at the time of review of that vaccine, elements of the schedule are not evaluated once it is adjusted to accommodate a new vaccine. Thus, key elements of the entire schedule—the number, frequency, timing, order, and age at administration of vaccines—have not been systematically examined in research studies.

The second major issue that the committee encountered was uncertainty over whether the scientific literature has addressed all health outcomes and safety concerns. The committee could not tell whether its list was complete or whether a more comprehensive system of surveillance might have been able to identify other outcomes of potential significance to vaccine safety. In addition, the conditions of concern to some stakeholders, such as immunologic, neurologic, and developmental problems, are illnesses and conditions for which etiologies, in general, are not well understood.

Finally, the committee found that evidence assessing outcomes in subpopulations of children who may be potentially susceptible to adverse reactions to vaccines (such as children with a family history of autoimmune disease or allergies or children born prematurely) was limited and is characterized by uncertainty about the definition of populations of interest and definitions of exposures and outcomes.

In summary, to consider whether and how to study the safety and health outcomes of the entire childhood immunization schedule, the field needs valid and accepted metrics of the entire schedule (the "exposure") and clearer definitions of health outcomes linked to stakeholder concerns (the "outcomes") in rigorous research that will ensure validity and generalizability.

Recommendation 5-1: To improve the utility of studies of the entire childhood immunization schedule, the committee recommends that the National Vaccine Program Office develop a framework that clarifies and standardizes definitions of

- **key elements of the schedule,**
- **relevant health outcomes, and**
- **populations that are potentially susceptible to adverse events.**

CONCLUSIONS ABOUT RESEARCH METHODS

Vaccine safety is critically important, but a determination of safety is ultimately a value judgment. For example, some might believe that a serious adverse event that occurs once in 1 million doses is "safe enough" relative to the benefit of preventing a serious disease, whereas others may consider that risk unacceptably high. The committee did not set a specific numerical target or goal for what should be considered "safe enough." Instead, based on the literature, the committee made a judgment that failed to link adverse effects to schedule exposures or multiple immunizations, concluding that there is no evidence that the schedule is not safe.

The committee identified four broad research questions of interest to stakeholders (Box S-2) and discussed general research approaches that could be used to address these questions. Setting of priorities for research will be challenging. The committee proposes a process for setting research priorities that incorporates epidemiological and other evidence (formal systematic reviews), biological plausibility, feasibility, and stakeholder concerns. Before HHS agencies, such as CDC, FDA, the National Institutes of Health, and NVPO, initiate further research on the entire immunization schedule, a thorough review of the biological plausibility of the association of a particular outcome with an aspect of the immunization schedule should be conducted.

Recommendation 6-1: The committee recommends that the Department of Health and Human Services incorporate study of the safety of the overall childhood immunization schedule into its processes for setting priorities for research, recognizing stakeholder concerns, and establishing the priorities on the basis of epidemiological evidence, biological plausibility, and feasibility.

The decision to initiate further studies should depend on the evaluation of three considerations that the committee identified through its review of stakeholder concerns and scientific findings:

1. epidemiological evidence of potential adverse health outcomes associated with elements of the immunization schedule (such as postmarketing signals or indications of an elevated risk from observational studies);
2. biological plausibility supporting hypotheses linking specific aspects of the immunization schedule with particular adverse health outcomes; and
3. expressed stakeholder concerns about the immunization schedule's safety, which should initiate efforts to explore the previous two considerations.

The committee acknowledges the evidence that reduced immunization coverage is associated with increases in the incidence of vaccine-preventable disease and found inconsistent and anecdotal evidence to imply that the recommended immunization schedule is not safe. Moreover, existing adverse event detection systems provide confidence that the existing childhood immunization schedule is safe, and the committee recognizes that the federal government invests considerable resources to ensure vaccine safety. However, some stakeholders have suggested that further research is warranted, such as a comparison of vaccinated children with unvaccinated children or children immunized on alternative schedules.

It is possible to make this comparison through analyses of patient information contained in large databases such as VSD, but it would be unethical and infeasible to conduct an RCT, as summarized above and detailed in Chapter 6. Because an RCT would increase the risk of preventable diseases in individuals and in the community and entail significant amounts of time, money, and other resources, the committee concludes that new RCTs of the childhood immunization schedule are not justified at this time.

Recommendation 6-2: The Department of Health and Human Services should refrain from initiating randomized controlled trials of the childhood immunization schedule that compare safety outcomes in fully vaccinated children with those in unvaccinated children or those vaccinated by use of an alternative schedule.

The committee concludes that secondary analyses of existing data are more promising approaches to examination of the research questions identified by the committee in future studies of the childhood immunization schedule. VSD is a useful collaborative project for conducting both postmarketing surveillance and longer-term targeted research. The ability to augment the routinely collected administrative data in VSD with parent interviews and reviews of medical records for selected study populations is an important strength.

VSD is currently the best available system for studying the safety of the immunization schedule in the United States. VSD should strive to improve its generalizability to the U.S. population by enhancing the quality of its demographic information or by expanding its scope to include more diversity in its study populations. Secondary analyses with data from other existing databases could also be feasible, ethical, and cost-effective in investigating several of the research questions that the committee identified.

The committee recognizes that the currently funded managed care organizations' commitment to VSD studies needs to remain high to continue and build on existing efforts. The committee concludes that VSD is a valuable component of the federal research infrastructure and will be the best-suited source of data for studying the childhood immunization schedule. VSD's

utility will be expanded with the addition of more detailed demographic data and family medical histories.

Recommendation 6-3: The committee recommends that the Department of Health and Human Services (HHS) and its partners continue to fund and support the Vaccine Safety Datalink project to study the safety of the recommended immunization schedule. Furthermore, HHS should consider expanding the collaboration with new health plan members and enhancing the data to improve its utility and generalizability.

CONCLUDING OBSERVATIONS

The committee's efforts to identify priorities for recommended research studies did not reveal an evidence base suggesting that the childhood immunization schedule is linked to autoimmune diseases, asthma, hypersensitivity, seizures, child developmental disorders, learning disorders or developmental disorders, or attention deficit or disruptive behavior disorders. Although stakeholder concerns should be one of the elements used to drive searches for scientific evidence, these concerns alone, absent epidemiological or biological evidence, do not warrant the initiation of high-cost research studies. The committee concludes that the use of existing data from database systems to conduct observational studies offers the best means for ongoing research efforts about the immunization schedule's safety.

The committee found no significant evidence to imply that the recommended immunization schedule is not safe. Furthermore, existing surveillance and response systems have identified known adverse events associated with vaccination. The federal research infrastructure is a strong system. A key component is the VSD project, which with ongoing support will be able to feasibly address the committee's research questions identified in Box S-2. Although the committee concluded that protecting children from vaccine-preventable diseases is of higher importance than testing alternative immunization schedules without epidemiological or biological evidence indicating a safety problem, VSD should continue to examine the health outcomes of people who choose alternative schedules.

Looking to the future, the committee supports the work of the federal research infrastructure to ensure that stakeholders are involved in all stages of the development, implementation, evaluation, and dissemination of the immunization schedule. As electronic medical records become more commonly used, they may provide an opportunity to capture complete immunization data linked with hospital discharge records, which will be useful to future studies. Newer initiatives such as the National Children's Study

and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program also hold promise in providing further study opportunities.

The childhood immunization schedule may become more complex over time as scientific advances are made and new vaccines are developed and incorporated into the schedule. Feasible research approaches to study potential adverse health outcomes will emerge only with sustained and substantial federal commitment to research on vaccine safety.

1

Introduction

Vaccines have significantly contributed to worldwide reductions in morbidity and mortality by reducing the incidence of serious infectious diseases (IOM, 2012). Today, people all over the world experience the benefits of immunizations, beginning in infancy. Most adults in the United States have not witnessed firsthand the devastating illnesses against which vaccines offer protection, for example, polio, diphtheria, and *Haemophilus influenzae* meningitis. However, as the incidence of vaccine-preventable disease has declined, many do not appreciate the potential of these diseases to reemerge, and the potential adverse effects of the vaccines themselves take on greater saliency among certain stakeholders. Indeed, vaccine safety concerns exist among a diverse range of individuals, institutions, and formal and informal networks worldwide.

Healthy individuals are immunized with immunogenic materials that induce immunity to serious pathogens. A "schedule" is a tool that is used to ensure that the recommended immunizations are provided to shield both children and adults from disease when they are the most vulnerable. In the United States, schedules recommended by the U.S. Advisory Committee on Immunization Practices (ACIP) (schedules for children from birth to age 6 years, children and adolescents ages 7 through 18 years, and adults) are based on the immunogenicity of vaccines and the burden and timing of disease (CDC, 2011a). Each schedule is designed and updated yearly on the basis of new evidence (see Appendix A). This report focuses on the vaccines that protect young children under age 6 years against 14 different pathogens because that time period is when multiple inoculations are given (see Appendix A).

Children may receive as many as 24 injections by 2 years of age and up to 5 injections in a single visit (see Appendix A). Immunization schedules vary around the world, however, with the variability being due in part to the different patterns of disease that exist globally (Lopalco et al., 2009; WHO, 2012). Additionally, levels of antigens and immunization timing and number differ. Some countries also have differing approaches to postmarketing surveillance systems, as will be described in Chapter 3.

Although the number of vaccinations recommended is greater than ever before, the vaccines used in the current immunization schedule actually have fewer antigens (inactivated or dead viruses and bacteria, altered bacterial toxins, or altered bacterial toxins that cause disease and infection) because of developments in vaccine technology (Offit et al., 2002). For example, the vaccines to prevent whooping cough used before 1991 contained 3,000 different potentially antigenic proteins (IOM, 2002). From 1980 to 2000, the immunization schedule's total number of antigens decreased by approximately 96 percent (from 3,041 to 123-126) (Offit et al., 2002).

Ever since vaccines were introduced in the 18th century, questions and concerns about their safety have been voiced. However, the protection against feared, deadly diseases that vaccines offer encourages the majority of health care professionals and laypeople to support immunization (Stern and Markel, 2005). Although research on the adverse effects of individual vaccines is robust and a required part of the approval process by ACIP, questions about the safety of the entire recommended immunization schedule for children persist. Moreover, how safety is interpreted varies according to the severity of an adverse event and the benefit of the vaccine. For example, some might believe that one serious adverse event that occurs once in 1 million doses is "safe enough" compared with the benefit of prevention of serious disease, whereas others may consider that risk unacceptably high.

As the number of recommended vaccines has increased in recent years, some parents and advocacy groups have expressed the concern that the immunization schedule is too crowded and complex because of the increasing number of vaccines administered during the first 2 years of a child's life (Offit et al., 2002). In addition to the complexity of vaccine delivery, some people have raised questions about the potential for adverse health outcomes as a consequence of the simultaneous or sequential administration of childhood vaccines (Gregson and Edelman, 2003). Even though the current childhood immunization schedule offers flexibility for administration of recommended vaccines (see Appendix A), some parents elect not to follow the recommended schedule (Dempsey et al., 2011).

Analysis of current U.S. data shows that the vaccination rate among children entering kindergarten exceeds 90 percent for most recommended vaccines (CDC, 2012b). However, increases in the prevalence of delay or refusal of recommended vaccines have contributed to the emergence of

vaccine-preventable illnesses across the country. For example, measles and pertussis outbreaks have occurred in recent years in geographic areas with higher concentrations of unimmunized children (Felkin et al., 2000). States with easy procedures for granting exemptions were associated with a 90 percent higher incidence of pertussis in 2004 (Omer et al., 2006). Some vaccine-preventable diseases can be fatal and have caused morbidity and mortality in infants and people with compromised immune systems. The impacts on disease prevention that vaccines have had in the United States are illustrated in Table 1-1.

Vaccinations—like all medical procedures—are neither 100 percent free of risk nor 100 percent effective. Vaccines, in rare cases, can cause illness. Most children who experience an adverse reaction to immunization have a preexisting susceptibility. Some predispositions may be detectable prior to vaccination; others, at least with current technology and practice, are not (IOM, 2012, p. 82). The U.S. Department of Health and Human Services (HHS), through its agencies responsible for vaccine safety, supports such research and surveillance, including studies addressing concerns and fears over the current childhood immunization schedule. The system in the United States designed to ensure vaccine safety is detailed in Chapter 3. While immunization may be one of the greatest achievements in public health, the complex interactions among populations, health care systems,

TABLE 1-1 Comparison of Pre-Vaccine Annual Incidence and Current Morbidity for Vaccine-Preventable Diseases

Disease	20th Century Annual Morbidity (No. of Cases)[a]	No. of Cases Reported in 2011[b]	Percent Decrease
Congenital rubella syndrome	152	0	100
Diphtheria	21,053	0	100
Haemophilus influenzae (<5 years of age)	20,000[c]	14[d]	>99
Measles	530,217	220	>99
Mumps	162,344	404	>99
Pertussis	200,752	18,719	89
Polio (paralytic)	16,316	0	100
Rubella	47,745	4	>99
Smallpox	29,005	0	100
Tetanus	580	36	98

[a] SOURCE: Roush et al., 2007.
[b] SOURCE: CDC, 2012a.
[c] Estimated.
[d] *Haemophilus influenzae* type b among children <5 years of age.

families, children, and so forth that are affected by the immunization schedule cannot be ignored.

STUDY BACKGROUND

On June 2, 2009, the National Vaccine Advisory Committee (NVAC) reviewed the nation's vaccine safety system and endorsed the recommendation of the NVAC Safety Working Group for an external expert committee, such as a committee convened by the Institute of Medicine (IOM), "with broad expertise in research methodologies, study design, and the ethical conduct of research to consider the strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine-delayed and vaccinated children and report back to the NVAC" (CDC, 2011b, p. 72).

The recommendation by the NVAC Safety Working Group was based on a series of meetings and discussions on the U.S. childhood immunization schedule in which individuals raised concerns that the schedule could potentially harm children because of immunological or neurodevelopmental adverse effects. Furthermore, in the minds of some parents, concerns about potential harms outweigh the well-documented benefits of immunization for the prevention of morbidity and mortality, with the result being that their children are less than fully immunized (NVAC, 2009).

After years of debate, some people continue to advocate for a study to compare health outcomes among vaccinated and unvaccinated children. The NVAC report stated that "the strongest study design, a randomized clinical trial that includes a study arm receiving no vaccine or vaccine not given in accord with the current recommended schedule, is not ethical, would not pass Institutional Review Board (IRB) review, and cannot be done" (NVAC, 2009, p. 38). (Chapter 6 discusses some of the ethical considerations in detail.) Furthermore, it may be impossible to draw unbiased results from an observational study of this issue because of potential differences in baseline health and social characteristics of populations and subgroups.

COMMITTEE ON THE ASSESSMENT OF STUDIES OF HEALTH OUTCOMES RELATED TO THE RECOMMENDED CHILDHOOD IMMUNIZATION SCHEDULE

The National Vaccine Program Office of HHS asked the IOM to convene a diverse committee of experts in pediatrics, neurology, medical ethics, immunology, statistics, epidemiology, and public health to identify study designs feasible to address questions about the safety of the United States' childhood immunization schedule. A 14-member committee was selected to

BOX 1-1
Statement of Task

The Institute of Medicine will convene an expert committee to

1. Review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule.
2. Identify potential research approaches, methodologies, and study designs that could inform this question, including an assessment of the potential strengths and limitations of each approach, methodology and design, as well as the financial and ethical feasibility of doing them.
3. Issue a report summarizing their findings.

complete a study addressing the statement of task (see Box 1-1). The committee's charge was independent of the charges for previous IOM studies of vaccines, and committee members were carefully selected to avoid real or perceived biases or conflicts of interest. Strict criteria for membership prevented any members from having financial ties to vaccine manufacturers or their parent companies, previous service on federal vaccine advisory committees, or delivered expert testimony or written publications on issues of vaccine safety.

Biographical sketches of the members of committee can be found in Appendix F. The committee's charge is detailed in Box 1-1.

COMMITTEE PROCESS

To complete its charge, the committee held three information-gathering meetings in two different locations. Before the first meeting and throughout the committee's deliberations, the committee gathered information on public perspectives and reviewed the scientific literature on the safety of the recommended childhood immunization schedule. At the public forums held in February, March, and May 2012, the committee heard presentations from clinicians, representatives of U.S. federal and state agencies and public health agencies in other countries, vaccine safety researchers, advocacy groups, vaccine manufacturers, and methodological experts. During the public forums, the committee invited comments (both written and oral) from the general public and representatives from numerous organizations with an interest in vaccine safety. Additionally, the committee received and

reviewed written correspondence from the public throughout the duration of the study.

The committee held 5 deliberative meetings over 6 months between February and August 2012. To fully address its charge, the committee identified a consultant who prepared a commissioned paper on study designs that could be used to assess the safety of the immunization schedule (see Appendix D). The paper, written by Martin Kulldorff, was intended to provide methodological input to the committee, but the paper does not necessarily reflect the committee's views or deliberations. To solicit stakeholders' interest and feedback, a draft version of the commissioned paper was posted on the committee's website on May 14, 2012, and comments on the paper were invited from the public. The comment period extended to May 31, 2012, and approximately 230 individuals provided written feedback. After a review of these comments and committee discussion, the committee requested revisions from the consultant. The commissioned paper was finalized on July 3, 2012, and again posted online for comment. The committee reviewed an additional 700 comments.

PREVIOUS IOM VACCINE STUDIES

Since the late 1970s, the IOM has conducted 60 studies on vaccination (see Appendix G). Each IOM study has relied on scientific evidence as the basis for its findings, conclusions, and recommendations. Committee members reviewed the summaries of 18 IOM studies that focused on vaccine safety. Reexaminations of safety are often prompted by new scientific findings and rising concerns usually in relationship to an individual vaccine and a possible adverse health outcome. However, the study of the present IOM committee is unique in that its focus is on the complete childhood immunization schedule.

This report follows a series of eight reports on vaccine safety that appeared between 2001 and 2004. The eighth report in this series examined the evidence about a possible link between autism and vaccines. That examination of the evidence found no association. A striking element described in each of these IOM reports is society's sustained interest in vaccines (Fineberg, 2011).

The 2012 IOM committee report *Adverse Effects of Vaccines: Evidence and Causality* examined 158 pairs of vaccines and putative adverse effects and was the IOM's most recent study of vaccine safety (IOM, 2012). No evidence to support a link between a vaccine and adverse events was found for the majority of adverse events, but this was often due to the rarity of the adverse event and the lack of evidence in general to support or reject a causal link. However, the committee concluded that very few health problems are caused by or are clearly associated with vaccines.

ORGANIZATION OF THE REPORT

This report is organized into seven chapters and seven appendixes. Chapter 2 provides background on how vaccines are developed and recommended for U.S. children. Chapter 3 details existing surveillance and data systems for evaluating vaccine safety. Chapter 4 reports on the committee's review of stakeholder concerns. Chapter 5 describes the methods used to perform and the results of a literature review on the scientific findings of studies of selected health outcomes and the recommended immunization schedule. Chapter 6 presents several methodological approaches for future studies. Chapter 7 summarizes the committee's findings, conclusions, and recommendations. The appendixes include ACIP's 2012 recommended immunization schedule for children (Appendix A), a glossary (Appendix B), a list of acronyms used in this report (Appendix C), the commissioned paper by Martin Kulldorff (Appendix D), agendas from public meetings held by the committee (Appendix E), biographical sketches of the committee members (Appendix F), and a chronological list of the IOM's vaccine publications (Appendix G).

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2

Determination of the Immunization Schedule

The immunization schedule recommended by the U.S. Advisory Committee on Immunization Practices (ACIP) is determined through consideration of numerous factors and the cooperation of numerous federal agencies in an extensive federal research infrastructure that includes the National Institutes of Health, the Food and Drug Administration (FDA), and the Centers for Disease Control and Prevention (CDC). This chapter provides an overview of some of these factors and the processes in place to help ensure that the immunization schedule benefits the recipients.

IMMUNE SYSTEM RESPONSES

The biology of the immune system response to pathogens and foreign substances is complex and was reviewed in a 2012 Institute of Medicine report. A broad overview of how vaccines work to protect the human body against disease is first presented as a prelude to consideration of the safety of the aggregate of vaccines that are part of the immunization schedule from the perspective of immune system responses.

The fundamental goal of vaccination is to prepare the immune system to defend the host against disease by intentionally exposing the body to all or part of an infectious agent in an effort to confer long-term protective immunity against future infection and to protect the most vulnerable individuals against disease.

Immunity protects the body against infectious diseases mainly through the production of specialized protein molecules, known as "antibodies" or "immunoglobulins," once the immune system has been stimulated by the

presence of foreign substances, called "antigens," from, for example, pathogens or vaccines (CDC, 2012d; Siegrist, 2008). In addition to immunoglobulins, other parts of the immune system also contribute to protection, including lymphocytes (specialized white blood cells), antigen-presenting cells (which recognize the foreign elements of the vaccine or the virus or bacterium that is the cause of an infectious disease and which help initiate the steps involved in protection), the spleen, and the skin itself, which serves as a protective barrier against bacteria and viruses.

For a vaccine to be efficacious and reduce the incidence of vaccine-preventable diseases, it must elicit the production of high-quality antibodies against the pathogen responsible for disease. Certain vaccines are able to generate an immunologic memory similar to that generated by natural infection, which often confers lifelong protection, whereas other vaccines may require boosters over time to maintain immunity.

The immune response is largely dependent upon the properties of the antigen used to develop the vaccine and on the route of administration. Live attenuated vaccines contain viruses or bacteria that are weakened versions of the naturally occurring infectious agent, whereas inactivated vaccines contain either antigens that are grown in laboratory culture media and inactivated by the use of heat or chemicals, altered bacterial toxins (toxoids) that when administered do not result in natural disease, or antigens that are produced artificially to mimic the surface properties of the pathogen.

Vaccines containing live, attenuated antigens confer a stronger immune response because the antigen is more similar to that encountered during natural infection; however, in rare cases, the virus may replicate uncontrollably in immunocompromised individuals and lead to a severe or fatal reaction. In an inactivated vaccine, the virus or bacterium is not alive and is not able to cause an infectious disease through unintended replication.

The type of vaccine is one factor that determines where the vaccine appears in the recommended immunization schedule. For example, the measles, mumps, rubella (MMR) vaccine is a live attenuated vaccine that for most recipients confers immunity after just one dose. Children following the recommended immunization schedule receive one dose of MMR at between 12 and 15 months of age and a second dose after age 4 years to ensure immunity. An inactivated vaccine such as diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine adsorbed, which contains diphtheria and tetanus toxoids combined with a subunit of the bacterium that causes pertussis, does not confer full immunity until after the second or third dose and requires later booster doses to remain immunologically effective, as the antibody titers that maintain immunity diminish with time.

Adjuvants can provide improved immunity by delaying the absorption of the antigens or by arousing or boosting the immune system response (IOM, 2012; Melvold, 2009). The immunoglobulin M (IgM) isotype is the

primary immunoglobulin generated after immunization, quickly followed by the IgG isotype. To demonstrate the immunogenicity of a vaccine, serum antivaccine (or antigenic marker) IgG antibodies are measured. For example, in studies of immunization with pandemic swine influenza A virus (H1N1) vaccines, detection of antibodies demonstrating inhibition of hemagglutination at a serum titer of 1:40 or greater provides evidence of seroprotection to the individual (Liang et al., 2010). These antibodies reduce infection by blocking the interaction between the influenza virus antigen, hemagglutinin, and cell surface receptors that it will use to enter the cell (Reddy et al., 2011). For the group of subjects studied, after a single immunization of 7.5 μg of a nonadjuvant split-virion formulation of the H1N1 vaccine in children ages 3 to <12 years, the increase in the hemagglutination titer over the baseline titer by 3 weeks postimmunization was robust (from a baseline mean titer of 6 to a postimmunization titer of 178) (Liang et al., 2010). When the titers are presented as geometric means to account for the distribution of responses, the baseline geometric mean titer was 5.3 and the postimmunization geometric mean titer was 178, a 32-fold response achieved by 3 weeks postimmunization. In adolescents (individuals ages 12 to <18 years), the geometric mean titers increased even more over the first 3 weeks postimmunization, from a baseline of 7 to 578, an 82-fold change (Liang et al., 2010).

The response to vaccination can be blunted in individuals who lack critical components of the immune system. For example, the responses to influenza immunization can be nonexistent or poor in patients who have received rituximab, which is an antibody to CD20, a membrane surface marker on B cells, present from early to full maturation of B cells and plasma cells, which secrete immunoglobulins (Bedognetti et al., 2011). Rituximab is useful therapeutically for the treatment of multiple conditions, including forms of lymphoma and collagen vascular diseases. However, the number of B ($CD19^+$) cells can be reduced for 6 months or longer after discontinuation of rituximab in patients who are in remission from lymphoma. Treatment with rituximab was found to greatly reduce the number of memory B cells characterized as $CD27^+$ and was associated with a poor or absent response to influenza immunization (Bedognetti et al., 2011). Although the patients had detectable $CD4^+$ and $CD8^+$ lymphocytes, they did not have $CD19^+$ B cells and did have reduced numbers of $CD27^+$ memory B cells, a condition which was associated with failure to mount a protective response after immunization (Bedognetti et al., 2011).

Another factor used to determine where a vaccine appears in the immunization schedule is vulnerability to the vaccine-preventable disease by age. This determination requires some knowledge of the pattern of disease in the community, which may differ by region of the world. As the immunity afforded by maternal antibodies at birth wanes, infants become

more susceptible to pathogens, many of which may lead to serious or fatal infections. Therefore, to be effective, a vaccine should be administered early enough to protect the infant or child against preventable diseases.

The age range for which a childhood vaccine is developed and recommended as part of the immunization schedule takes into account the age at which the immune system can tolerate vaccine components, potential interference with the immune response from maternal antibodies, and the age at which a child is most at risk for disease transmission and mortality. ACIP recommends vaccines "for members of the youngest age group at risk for experiencing the disease for which efficacy and safety have been demonstrated," and its recommendations are based on the best evidence available (CDC, 2011a, p. 4).

IMMUNIZATION AT THE POPULATION LEVEL

For immunizations to adequately protect individuals and the individuals in the communities in which they live against outbreaks of vaccine-preventable diseases, a high proportion of vaccinated individuals needs to be maintained in the general population. The success of vaccination to preserve low levels of disease incidence depends on the population level of "community immunity," also commonly known as herd immunity, which refers to the immunity of a group that is afforded when a high proportion of individuals are not susceptible to infection. Community immunity is maintained by vaccination against communicable diseases, and this concept is expertly discussed in other sources (Fine, 1993; Fine et al., 2011).

It is possible to quantify the fraction of the population that needs to be protected to prevent disease spread on the basis of the epidemiological traits of the pathogen in question (such as its transmissibility and duration of infectivity). The calculation requires an understanding of the so-called basic reproduction ratio, or R_0, which quantifies the maximum transmission potential of an infectious disease. It is strictly defined as the number of secondary cases generated by a typical primary case in a fully susceptible population. If R_0 is >1, then the pathogen is predicted to transmit to more than one other person and successfully invade the population. For the major childhood infectious diseases, such as measles, mumps, rubella, chickenpox, and polio, a variety of methods have been devised to estimate R_0 from longitudinal incidence reports, outbreak data, and age-stratified serology (Anderson and May, 1982, 1992; Becker, 1989; Keeling and Rohani, 2008).

The quantity R_0 has been used to guide vaccination policy with recognition that it is defined when the entire population is susceptible to the pathogen. That is, the number of susceptible individuals (S) is equal to the population size (N). To determine the size to which the pool of susceptible individuals needs to be reduced (via immunization) to control the infection,

researchers consider the following expression: $R_0 \times S/N$. This quantity takes into account both the fundamental transmission potential of the pathogen (quantified by the use of R_0) and the fraction of the population that is susceptible (S/N). The aim of vaccination is therefore to ensure that $R_0 \times S/N$ remains less than 1; that is, less than one transmission will result from an infection. To achieve this goal, immunization needs to reduce the proportion of the population unprotected (S/N) to less than $1/R_0$, which implies that the fraction of the population that needs to be immunized is $1 - 1/R_0$ (Fine et al., 2011). This principle is illustrated in Figure 2-1.

The relationship between the estimated R_0 and the targeted vaccination coverage is illustrated in Figure 2-2. This calculation has been of practical use in guiding the setting of immunization targets, albeit with the recognition that for any infectious disease, R_0 is likely to change in different settings and is determined by population density, contact patterns, and access to health care (Anderson and May, 1982). The gray regions translate ranges of the estimated R_0 into vaccination targets. For instance, on the basis of

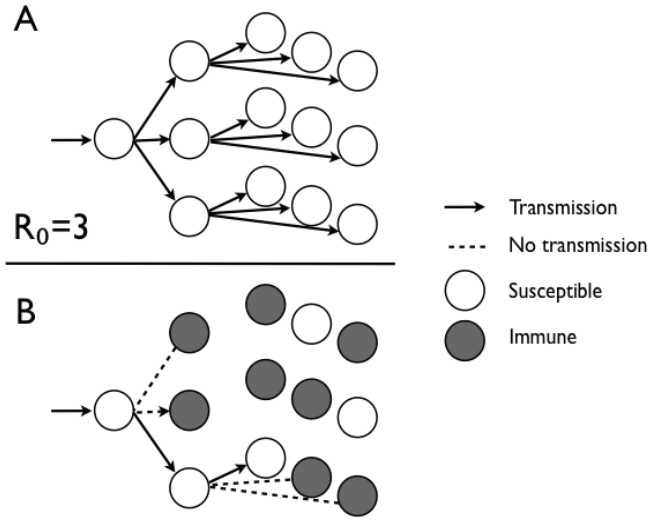

FIGURE 2-1 Different transmission outcomes with immunization when R_0 is equal to 3. (A) With the entire population susceptible, successive generations lead to one, three, and, eventually, nine transmissions. (B) When $1 - 1/R_0$ is equal to 2/3 of the population protected by immunization, each infected individual will infect only one other individual.
SOURCE: Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule.

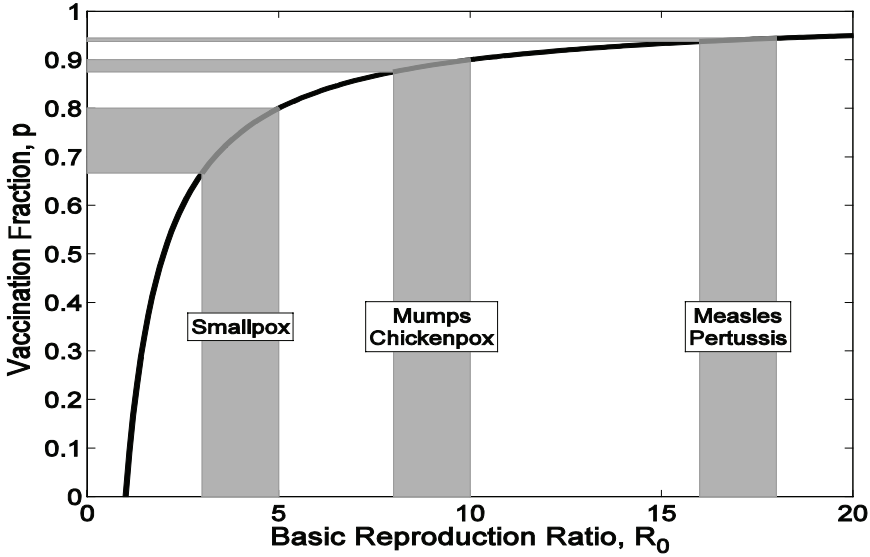

FIGURE 2-2 Relationship between the estimated R_0 and the immunization target (solid black line). The gray regions translate ranges of the estimated R_0 into the vaccination target.
SOURCE: Adapted and reprinted by the Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule.

historical records, the estimated R_0 values for mumps and chickenpox in North America prevaccination were 8 to 10, leading to a vaccination target threshold of 87.5 to 90 percent of the population. Similarly, for measles and pertussis in England and Wales before the introduction of immunization, R_0 values ranged from 16 to 18 (Anderson and May, 1992), leading to a vaccination target of between 93.75 and 94.4 percent of the population.

IMMUNIZATION POLICY

Vaccines are held to the highest possible standard of safety, in part because they are provided to healthy individuals with the purpose of preventing illness (Chen et al., 2005). In the United States, before a vaccine is introduced into the population as part of the recommended childhood immunization schedule, it must undergo careful analysis and evaluation, principally by FDA and ACIP. The review examines the immunologic properties of the vaccine and its probable effect on population health.

Each new vaccine is tested within the context of the existing immunization schedule, for example, by identification of the biologically optimal

time during childhood when the immunization should be received and then testing of the new vaccine by incorporation of the vaccine into the existing schedule within that time frame. Selection of a particular moment within that biologically appropriate time frame is done mainly on the basis of considerations of safety and effectiveness (i.e., it should not be administered too early, when a child cannot generate an effective immune response, yet it should be administered soon enough to protect the child against the disease) (Siegrist, 2008).

Logistics and feasibility also need to be considered; for example, a vaccine could be scheduled for administration at times when a child is already likely to be visiting a provider for a normal periodic health care visit based on conventional guidelines (CDC, 2011a). Thus, approval of each new vaccine is premised on evaluation of the vaccine itself and of the entire schedule within which it is situated.

Although this process results in an evaluation of whether the observed benefits outweigh the observed risks for the new vaccine and, by extension, for the schedule, it does not include studies specifically designed to test variations in the schedule in an effort to identify the optimal schedule. Chapter 5 reviews researchers' efforts in testing variations in immunization schedules. An overview of the licensure and recommended practice review is discussed below.

VACCINE DEVELOPMENT AND APPROVAL SPECIFICS

Role of FDA

Since 1902, the U.S. government has exercised increasingly strict control over the development, manufacture, and sale of vaccines (Baylor and Midthun, 2004). At present, all vaccines marketed in the United States must be licensed by FDA. The licensing requirement provides the means by which FDA exercises authority over the testing and approval of new vaccines, as well as the manufacture, labeling, and continued safety and effectiveness of approved vaccines (Baylor and Midthun, 2004; FDA, 2010).

The clinical development of a vaccine in the United States begins when a sponsor submits the required Investigational New Drug (IND) application to FDA. The IND application includes information on the vaccine's safety and immunogenicity in animal trials, its manufacturing details, and the proposed protocol of clinical trials for testing in humans.

When the FDA accepts an IND application, manufacturers proceed with premarketing Phase I, II, and III clinical trials (Baylor and Midthun, 2004). Phase I and II clinical trials enroll fewer than 1,000 participants and are designed to draw conclusions about the vaccine's components, dosing effectiveness and the need for booster doses, and route of administration

and to evaluate common reactions. The results of these trials may influence the choice of the candidate vaccine to be used in subsequent studies, such as additional Phase I or II trials or after Phase III trials. Phase III trials are large-scale trials conducted to provide a more thorough assessment of safety. Sample sizes for Phase III trials are determined to evaluate a vaccine's efficacy, and therefore such trials have larger sample sizes (up to 100,000 participants in some rare cases) than do Phase I or II trials for vaccines or other premarketing trials for therapeutic drugs. Because Phase III trials are primarily powered for determination of efficacy (Hudgens et al., 2004), conclusions about vaccine safety derived from these trials are limited and may best extrapolate to common adverse events (Chen and Orenstein, 1996; Chen et al., 2005).

Throughout this process, FDA has the authority to request additional information about the clinical trials or to interrupt the clinical trials if concerns about safety or effectiveness emerge. If the clinical trials demonstrate that a vaccine is safe and effective, the licensing procedures begin with the submission of a Biologics License Application and a review of the immunization benefits and risk demonstrated by the clinical evidence. If FDA's Center for Biologics Evaluation and Research is convinced that the vaccine's benefits significantly outweigh potential risks for use in the general population, the vaccine is licensed and will undergo further evaluation of product safety through activities such as periodic facility inspections, as well as postmarketing clinical safety evaluation (FDA, 2010). Manufacturers may be asked to undergo Phase IV studies, which include a larger population and are used to assess less common adverse events or the length of time for which the vaccine induces immunity (Baylor and Midthun, 2004). Following vaccine licensure, manufacturers are required by 21 CFR 600.80 to report to the FDA serious or unexpected adverse events within 15 days of the event occurring, and to report other adverse events quarterly for the first 3 years after the vaccine is licensed, and then once per year thereafter (Baylor and Midthun, 2004; Farizo, 2012; FDA, 2010). Postmarketing surveillance efforts that are coordinated as part of the federal research infrastructure are discussed in detail in Chapter 3.

Role of ACIP

In the United States, immunization policy is developed and implemented through collaborations among federal partners, state and local governments, professional medical associations, and other relevant organizations. These organizations are represented on ACIP, which is the federal advisory committee that provides expert external advice and guidance on the use of FDA-licensed vaccines and related agents in the U.S. population

to the director of CDC and the secretary of the U.S. Department of Health and Human Services.

Each year CDC issues recommendations on the use of vaccines and immunization schedules for children, adolescents, and adults (Kroger et al., 2011; NVAC, 2011). A number of liaison organizations, such as the American Academy of Pediatrics (AAP), the American College of Physicians, and the American Academy of Family Physicians (AAFP), issue recommendations on the immunization schedule that are harmonized to the greatest extent possible with the annual recommendations from CDC (NVAC, 2011; Smith, 2010; Smith et al., 2009). A representative from ACIP serves as a liaison on the National Vaccine Advisory Committee, which is the federal advisory committee responsible for advising the National Vaccine Program Office (NVPO) on priorities of vaccine supply and enhancing vaccine safety and efficacy (HHS, 2012).

In the process of making recommendations for new vaccines, ACIP first reviews a wide range of data associated with the vaccine, including the rates of morbidity and mortality from the disease that the vaccine protects against in the general U.S. population and specific high-risk groups; cost-effectiveness; the results of clinical trials, including indicators of safety, efficacy, and effectiveness; information on vaccine use provided by the manufacturer in the product's labeling or package insert; and the feasibility of incorporating the vaccine into the existing immunization program. Expert opinions from voting members and other experts may also be incorporated into the deliberations (NVAC, 2011; Smith, 2010; Smith et al., 2009).

As of October 2010, ACIP has adopted an evidence-based framework, Grading of Recommendations Assessment, Development, and Evaluation (GRADE), which it uses when making new recommendations or substantial revisions of vaccination recommendations. The GRADE framework is a method for ACIP to systematically assess the type or quality of evidence about the health outcomes after immunization with a vaccine. The evidence that ACIP reviews is grouped into four categories that reflect the reviewers' level of confidence in the estimated effect of vaccination on health outcomes on the basis of the strength of the design of the study used to provide the evidence considered. The GRADE categories are as follows (CDC, 2012b):

1. randomized controlled trials or overwhelming evidence from observational studies;
2. randomized controlled trials with important limitations or exceptionally strong evidence from observational studies;
3. observational studies or randomized controlled trials with notable limitations; and

4. clinical experience and observations, observational studies with important limitations, or randomized controlled trials with several major limitations.

Recommendations from ACIP are also categorized into Category A or B recommendations, although the distinction does not reflect the quality of the evidence reviewed. Category A recommends vaccination for all people in a particular age group or for a group at increased risk for vaccine-preventable diseases. Category B recommendations do not apply to all members of a group; rather, they are intended to provide guidance to a clinician when determining if vaccination is appropriate for an individual. After review, if CDC accepts the recommendations of ACIP, they are published in *Morbidity and Mortality Weekly Reports* (MMWR) (Smith, 2010; Smith et al., 2009).

PAST AND PRESENT IMMUNIZATION SCHEDULES

The current schedule of recommended immunizations for infants and children from birth through age 6 years comprises vaccines that prevent 14 infectious diseases, a remarkable achievement compared with the schedule in 1948, when immunizations against only diphtheria, tetanus, pertussis, and smallpox were available and recommended for administration for protection. In 1955, the polio vaccine was licensed and added to the recommended immunizations to eliminate yearly outbreaks. Over the next 40 years, vaccines were added to the recommended schedule as they were licensed, including MMR, the hepatitis B vaccine, and the *Haemophilus influenzae* type b vaccine (Hib). Smallpox vaccine was removed from the U.S. recommended schedule in 1972, as the disease had been eliminated as a result of great public health efforts.

It became increasingly evident that as the schedule became more complex, providers would benefit from annual updates with detailed information about new vaccines, who should receive each vaccine, the age(s) at the time of receipt, the dose, and the use of combination vaccines in their practices. In 1995, CDC, AAP, and AAFP created a harmonized immunization schedule. Since then, the ACIP-recommended schedule has been adopted by the CDC and both professional associations, along with others (CDC, 2012c). Today, combination vaccines deliver immunizations against up to five separate diseases in a single injection, including DTaP-Hib-inactivated poliovirus vaccine (IPV) and DTaP-hepatitis B (recombinant) virus vaccine-IPV.

Immunization rates for children in the United States are generally high, with some variation occurring depending on geography and the specific vaccine. The majority of children are fully immunized with the recommended

component of vaccines (not including influenza and hepatitis A virus vaccines) by age 3 years. According to the National Immunization Survey (NIS), less than 1 percent of U.S. children aged 19 to 35 months receive no vaccinations at all (CDC, 2011c). However, not every vaccine on the schedule has equal coverage in this population. In the NIS study population for children born between January 2008 and May 2010, vaccines with higher coverage included the poliovirus vaccine (93.9 percent), MMR (91.6 percent), the hepatitis B vaccine (91.1 percent), and the varicella vaccine (90.8 percent). In contrast, the rotavirus vaccine was received by only 67.3 percent of children, and just 80.7 percent of children received the full series of the Hib vaccine, which is an increase from previous years during which a shortage of the vaccine was experienced (CDC, 2012a). A review of data from the 2003 NIS revealed that more than one in three children were undervaccinated (missing age-appropriate doses from the recommended immunization schedule) during the first 24 months of life and that only 18 percent of U.S. children received all vaccinations at the recommended times or acceptably early (Luman et al., 2005). Immunizations are recommended to protect children when they are most vulnerable to vaccine-preventable diseases, and delays in timely immunization leave children susceptible to disease.

For some children, vaccination on the recommended schedule may be contraindicated, either permanently or temporarily, and the CDC offers guidelines on conditions that may require that vaccination with certain vaccines be postponed or avoided altogether (CDC, 2011b).

Most health care providers encourage adherence with the recommended immunization schedule for children; however, a compelling motivator to see that children receive their full immunizations is their requirement to attend school. Since the early 1980s, all 50 states have made policy decisions to require immunizations for school entry. These immunization requirements were originally enacted to prevent and control frequent outbreaks of vaccine-preventable diseases. Furthermore, during outbreaks, officials have removed unvaccinated children from school, which has proved to be a successful control measure (Omer et al., 2006).

Because school-based immunization requirements are determined on a state-by-state basis, differences in age requirements, processes for adding new vaccines, and exemptions to immunizations exist across the country. Exemptions may be medical in nature, such as exemptions for delayed or skipped immunization if the child has a condition that contraindicates immunization with the vaccine, as referenced above.

Currently, every state law covering immunization requirements has a provision that allows medical exemptions. Parents may also request an exemption on religious grounds, and such exemptions are permitted in 48 states. Exemptions because of personal beliefs, which include religious,

philosophical, or other nonmedical beliefs, are granted in 20 states, including Colorado and Washington, two states that saw localized outbreaks of pertussis in 2012 (Omer et al., 2006).

Although rates of medical exemptions are relatively constant nationwide, rates of nonmedical exemptions vary considerably (CDC, 2010, 2011d). For example, from 2006 to 2007, the average nonmedical exemption rate in the state of Washington was 6 percent, although some counties had exemption rates as high as 27 percent (Omer et al., 2006).

Adverse Effects of Vaccines

Parents may be what is referred to as vaccine-hesitant (refusing, delaying, or feeling unsure about some immunizations) because vaccines, like other drugs and biologicals, can in some cases be associated with adverse events (Opel et al., 2011). Vaccines that are commonly associated with serious adverse events are never licensed. Likewise, if a serious or frequent adverse event is discovered during postmarketing surveillance, the vaccine is taken off the schedule (e.g., the first rotavirus vaccine).

Most adverse events are mild or self-limited, for example, fever after measles vaccine or a sore, swollen injection site after the tetanus booster. Many events may occur in the days and weeks following vaccination, however, typically few are a result of vaccination, and most are coincidental. Ongoing research continues to examine such adverse events (IOM, 2012).

In the 1980s, the United States experienced an increase in civil lawsuits filed against vaccine manufacturers for injury compensation, which led to hesitancy on the part of the manufacturers to produce enough vaccines to keep the supply stable at a reasonable price. To streamline the legal process and maintain the vaccine supply, the U.S. Congress enacted the National Childhood Vaccine Injury Act in 1986 to establish a no-fault system for compensating individuals for vaccine-related injuries, the National Vaccine Injury Compensation Program (VICP). Individuals or parents of children who experience a vaccine-related injury must first file their petition with VICP before pursuing a civil case. As a no-fault system, the possible negligence of the manufacturer or physician is not considered in determination of compensation, which is funded by an excise tax on vaccines.

VICP covers all vaccines routinely administered to children as part of the recommended childhood immunization schedule and all injuries listed in its injury table. A claimant who seeks compensation for an adverse event that has not been established and placed in this table has the option of providing evidence to establish causation (Cook and Evans, 2011). The National Childhood Vaccine Injury Act also established the Vaccine Adverse Event Reporting System to track adverse events and created NVPO

to coordinate immunization-related activities among federal agencies (Cook and Evans, 2011).

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3

Existing Data Sources and Systems

While the Advisory Committee on Immunization Practices (ACIP) is tasked with making recommendations on vaccine usage, the National Vaccine Advisory Committee (NVAC) directs research priorities on vaccine development, efficacy, and safety. Included in the membership of NVAC are a number of ex officio representatives from federal agencies engaged in vaccine safety monitoring. Several systems that are part of the federal research infrastructure provide postmarketing data on vaccines that are used for immunization safety surveillance, to determine immunization coverage, and to assess the effects of vaccines on vaccine-preventable diseases. In turn, vaccine safety research is often conducted using data obtained from ongoing surveillance. This chapter reviews these systems and discusses how data from these systems are used to help assess the safety of cumulative immunizations, the timing of immunizations, and other aspects of the immunization schedule.

IMMUNIZATION SAFETY SURVEILLANCE

A number of systems for ongoing monitoring and study of the safety of vaccines recommended for use are in place in the United States (and other nations as well), where the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and vaccine manufacturers have systems in place for postmarketing surveillance and research.

CDC and FDA manage a number of postmarketing activities, including surveillance of vaccine-preventable diseases, monitoring of adverse events following immunization, tracking of vaccine coverage and issuance

of guidance on vaccine shortages. Although vaccine safety is rigorously assessed during prelicensing clinical trials, this postmarketing monitoring is important because the sample sizes in prelicensing clinical trials may not have been adequate to detect rare adverse events, the prelicensing study population may not have been monitored for long-term adverse events, and populations may not have been heterogeneous (Baggs et al., 2011; Chen et al., 2000). Consequently, postmarketing evaluation of vaccine safety is needed to assess rare, delayed, or unusual reactions and in general provides a fuller understanding of the safety of vaccines recommended in the immunization schedule (Chen et al., 1997).

Ongoing surveillance systems serve as the primary resource for information and research on postmarketing vaccine safety. The CDC Immunization Safety Office (ISO) maintains three major postmarketing surveillance systems: the Vaccine Adverse Event Reporting System (VAERS; jointly managed with FDA), the Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment (CISA) Network. Most CDC immunization activities are located in the National Center for Immunization and Respiratory Diseases. Since 2005, the ISO was moved to the National Center for Emerging and Zoonotic Infectious Diseases as its mission is clearly distinct from other immunization programs within the agency. This organizational change ensures the separation at CDC between vaccine promotion and safety. In addition to the surveillance systems managed by CDC, FDA has established a supplementary mechanism for monitoring vaccine safety called the Sentinel Initiative.

Vaccine Adverse Event Reporting System

VAERS is a passive reporting surveillance system that is jointly managed by CDC and FDA and serves as a warning system for potential adverse events and side effects from a recommended vaccine that may not have been detectable in clinical trials (NVAC, 2011). Anyone, including parents and providers, may submit voluntary, spontaneous reports of adverse events observed after administration of licensed vaccines. Reports received by VAERS are analyzed and recorded for possible follow-up (CDC and FDA, 2012).

Although VAERS is useful for the early detection of signals of adverse events, the data obtained from the system have limitations. The reports received may not be fully documented, or the adverse event attributed to the vaccine may, in actuality, be a case not caused by the vaccine on the basis of background rates of clinical events. In addition, data on the number of doses of vaccine administered or number of vaccinated people do not exist and are thus not available for use as the denominator, so researchers cannot calculate what proportion of individuals were affected by an adverse event for comparison with the background rate of the event in the general

population. Because no denominator data are available, VAERS cannot be used to evaluate causality. The VAERS data are useful, however, for the development of adverse event signals and the formation of related hypotheses that can be further tested and validated by more robust methods.

Vaccine Safety Datalink

One system better suited to the testing of hypotheses about vaccine safety is VSD. The VSD project was formed in the 1990s as a collaborative effort between CDC and a group of managed care organizations (MCOs) to maintain a large linked database for monitoring immunization safety and studying potential rare and serious adverse events. The number of VSD member sites has increased over the years and now includes nine MCOs that enroll approximately 9.5 million children and adults, or about 3 percent of the U.S. population. VSD sites are located at geographically diverse locations in California, Colorado, Georgia, Hawaii, Massachusetts, Michigan, Minnesota, Oregon, and Washington (Frank DeStefano, CDC, personal communication, October 18, 2012). Because the data in the database are generated as a by-product of the routine administration of health care and the system does not rely on voluntary adverse event reporting (as VAERS does), the problems of underreporting and recall bias are reduced.

VSD is a useful system that includes demographic data and information on the medical services that have been provided to those enrolled in the health plans, such as age and gender; vaccinations; hospitalizations; outpatient clinic, emergency department, and urgent care visits; mortality data; and additional birth information (e.g., birth weight) (Baggs et al., 2011). Automated pharmacy and laboratory data as well as information on diagnostic procedures (e.g., radiography and electroencephalography) that the patient has undergone are also included (Chen et al., 2000). Data on adverse events, including deaths (from probabilistic matching of death files), are routinely collected (Chen et al., 1997). Covariates used to control for potential confounders include birth certificates and variables from the decennial census at the zip code level, in addition to demographic data from the health plans.

Each site collects data on vaccinations (the type, date, and concurrent vaccinations), medical outcomes (diagnoses and procedures associated with outpatient, inpatient, and urgent care visits), and birth and census data. To ensure compliance of federal regulations and to protect confidentiality, each person within the VSD is assigned a unique random VSD study identification number which is not linked to their MCO member identification number. These VSD study identification numbers can be used to link data on demographics and medical services (Baggs et al., 2011).

Since 2001, VSD has used a distributed data model whereby each MCO

assembles and maintains its computerized files on a secure server at the site. This distributed data model has permitted the creation of dynamic data files that permit the ongoing capture of near real-time event-based MCO administrative data. These include data on vaccinations, hospitalizations, emergency department and clinical care visits, and certain demographic characteristics. While most files are updated weekly with new data from each MCO, some files are updated less frequently (Baggs et al., 2011). This organization of the data enables near real-time postmarketing surveillance to be conducted and enhances the timeliness of certain studies.

Surveillance and Research

The VSD has been used to conduct rigorous epidemiological studies on a wide range of immunization safety topics. Strategic priorities for research and surveillance are developed and updated regularly. The following priorities were reported in 2011 (Baggs et al., 2011):

- Evaluate the safety of newly licensed vaccines.
- Evaluate the safety of new immunization recommendations for existing vaccines.
- Evaluate clinical disorders after immunization.
- Assess vaccine safety in particular populations at high risk.
- Develop and evaluate methodologies for vaccine safety assessment.

The enhancements in data transfer and updating permit near real-time postmarketing surveillance. Adverse events identified in the VSD system are analyzed by use of an active surveillance system called Rapid Cycle Analysis. Every week, the Rapid Cycle Analysis team determines the rates of adverse events associated with newly licensed or recommended vaccines in the study population. This information allows VSD researchers to compare the rates of adverse events in similar groups of people to determine if an event is related to the vaccine. If an increased risk is detected, VSD project scientists implement a formal, population-based epidemiological study to test the hypothesis of a causal relationship.

VSD data are also used in conjunction with data from VAERS to determine, for example, whether the number of adverse events reported to VAERS exceeds the background occurrence of the events shown in VSD.

VSD has been used to conduct rigorous studies on a wide range of topics on vaccine safety, as well as studies on immunization coverage, disease incidence, research methodologies, cost-effectiveness, and medical informatics (Baggs et al., 2011; DeStefano, 2001). For example, VSD has been used to study immunization safety concerns, such as the risk of seizures following receipt of the whole-cell pertussis vaccine or the measles, mumps,

rubella (MMR) vaccine, and to evaluate the safety of thimerosal-containing vaccines (Barlow et al., 2001; CDC, 2011b; Verstraeten et al., 2003).

Importantly, in selected studies, the automatically collected administrative data in VSD have been supplemented with information from other sources to test selected hypotheses on vaccine safety. For example, in a study examining the hepatitis B vaccine and the risk of autoimmune thyroid disease, cases were initially identified through VSD and then validated through a review of the medical records. Telephone interviews were then conducted with the parents to confirm the child's hepatitis B vaccination status (Yu et al., 2007).

As another example, in a study of early thimerosal exposure and neuropsychological outcomes, mercury exposure was determined from VSD medical and personal immunization records and interviews with parents. The study also used the results of standardized tests that assessed 42 neuropsychological outcomes (Thompson et al., 2007).

Studying the Safety of the Immunization Schedule

Some characteristics of VSD lend themselves to the study of the safety of the immunization schedule. The fact that MCOs have different vaccination policies (after the first year of life)—along with deviations in the immunization schedule due to variations in clinical practice, vaccine shortages, problems with access, or intentional denial of vaccine coverage—yields differences in vaccine exposure in this large cohort (Chen et al., 1997). These differences have been leveraged to examine the safety of aspects of the immunization schedule (Chen et al., 1997; see Appendix D). Because relatively few children are completely unvaccinated, study designs do not rely on comparison groups of children but instead use case-only methods such as self-controlled case-series designs (Baggs et al., 2011; see Appendix D).

Limitations of VSD

The MCOs that make up VSD are largely private plans; thus, the population, although large, is not demographically representative of the children in the United States. Safety outcomes or other medical consequences may not vary on the basis of income or insurance status; but other information collected by VSD—such as the completeness of the immunization schedule, immunization delays, or the amount of time that an individual receives immunizations off of the immunization schedule—may be related to such socioeconomic factors (Luman et al., 2005).

Furthermore, because beneficiaries move between plans because of choice, a job change, or other factors, the ability to monitor children for an extended period may be limited. Although the average time spent in

the VSD is not known, more than half of the children born in 2001 and included in the system at that time are still in the system (Frank DeStefano, personal communication). Although studies have used the VSD to select the cohort and have augmented VSD data with data from other sources, the committee was not aware of any studies that have monitored a VSD cohort outside the health plan structure over time. This sort of longer-term follow-up may be important to the study of the safety of the immunization schedule, and if such follow-up is undertaken, ethical and confidentiality issues will need to be explored.

Sentinel Initiative

The Sentinel Initiative program, established by FDA, is designed to build and implement a national electronic system to monitor the safety of FDA-approved drugs and other medical products. The pilot project for this initiative, the Mini-Sentinel, is currently collecting data from 17 collaborating institutions with databases containing health care data collected from 2000 to 2011 from 126 million participants and data on more than 345 million person-years of observation time (Mini-Sentinel Coordinating Center, 2011).

The Mini-Sentinel is an active surveillance system that uses a distributed database design, which means that the data remain in their existing secure environments at collaborating institutions rather than being centralized into one database. When it is fully implemented, the Sentinel Initiative will complement the existing passive surveillance system, VAERS, in capturing reports of adverse events after immunization and will enable FDA to use existing electronic health care data to perform near real-time analyses (NVAC, 2011).

FDA's Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program similarly captures claims data from the Mini-Sentinel sites to establish a large cohort with which to analyze vaccine exposure and adverse events with a high degree of statistical power. This active surveillance system, which is updated quarterly, has the capacity to link claims data from collaborating health insurers to immunization registries. To date, the program has been used to conduct various epidemiological analyses, such as an investigation of postmarketing adverse events after administration of the 2009 pandemic H1N1 influenza vaccine which evaluated vaccine safety data for over 38 million individuals (Nguyen et al., 2012; see Appendix D). Although PRISM's database is larger than that of the VSD, PRISM is newer and less able to rapidly conduct medical record review to confirm suspected outcomes of interest initially identified in claims data. Though neither Mini-Sentinel nor any of the other existing surveillance systems described above have yet been used to evaluate health outcomes associated with the entire

recommended childhood immunization schedule, there is great potential in these large database initiatives to monitor rare adverse events potentially associated with the childhood immunization schedule.

Clinical Immunization Safety Assessment Network

CDC also maintains the CISA Network to perform clinical research on biological mechanisms of adverse events, which are often hypothesized on the basis of reports to VAERS. The CISA Network is a network of six U.S. academic medical centers with experts in vaccinology and vaccine safety who collaborate in discussions about adverse events (CDC, 2011c). Although VSD researchers conduct population-based research on vaccine safety, experts in the CISA Network investigate the pathophysiological basis for an adverse event to counsel clinicians on individual variations in reactions to vaccines and to help policy makers determine precaution and contraindication criteria for vaccines. CISA investigators have performed causality assessments on reports received from VAERS, including a recent assessment of serious neurologic adverse events following immunization with the H1N1 influenza vaccine (Williams et al., 2011). The CISA Network has maintained for future study a repository of biological samples obtained from individuals who have experienced unusual adverse events (NVAC, 2011).

National Institutes of Health

The National Institutes of Health (NIH) have an important role in maintaining the safety of vaccines, from basic biological study that leads to new vaccine development through supporting research to address ongoing vaccine safety and efficacy. Two recent initiatives from the NIH are particularly relevant to the study of the recommended childhood immunization schedule. Several NIH institutes, including the National Institute of Allergy and Infectious Diseases (NIAID) and the Eunice Kennedy Shriver National Institute of Child Health and Human Development, have collaborated with the CDC to announce a funding opportunity entitled Research to Advance Vaccine Safety. Researchers from eligible institutions are invited to propose research on topics including but not limited to "evaluation of existing childhood immunization schedules to optimize safe and long-term protective immune memory" (Curlin et al., 2011, p. S13) and "comparison of the immunologic and physiologic effects of different combinations of vaccines and different schedules" (Curlin et al., 2011, p. S14). In addition, research topics can include studies that seek to determine genetic susceptibility to serious adverse events following vaccination and research that attempts

to identify the molecular basis for differential immune responses to vaccination when an underlying health condition is present (Curlin et al., 2011).

Similarly, the Human Immunology Project Consortium (HIPC) program was developed by the NIAID in 2010 to further an understanding of the human immune system and its regulation. HIPC researchers are using innovative technologies to profile human responses and provide new biological evidence to help determine if there is a relationship between short-term adverse events following vaccination and long-term health issues (HIPC, 2012). Although the HIPC offers a promising approach to studying health outcomes of the childhood immunization schedule, researchers will require data on the effects of age, environment, infectious exposures, lifestyle, and many other possibly confounding variables before any conclusions can be drawn (Hackett, 2012). Thus, it is critical to continue epidemiological study of vaccines through systems like VAERS, VSD, and the Sentinel Initiative, as well as study of biological mechanisms through CISA and NIH.

DATABASES USED TO ASSESS COVERAGE

Data from another set of databases are used to assess immunization coverage, including the population-based National Immunization Survey (NIS) telephone survey and the state-level immunization registries.

National Immunization Survey

The surveillance systems described above are tools to monitor vaccine safety. Ensuring that vaccines are safe and present minimal health risks to individuals is an important part of keeping the majority of the population immunized and preserving community immunity. Furthermore, because no vaccine alone is 100 percent effective at preventing disease for any individual, sustaining a low incidence of vaccine-preventable diseases in the United States requires a population-based effort. As such, it is important to have tools to examine populations that may not be adequately immunized and to monitor trends in vaccine coverage. The National Center for Immunization and Respiratory Diseases and the National Center for Health Statistics jointly operate the NIS for this purpose.

The NIS is a large random-digit-dialing telephone survey that collects data on immunization coverage for U.S. children aged 19 to 35 months. The survey sampling methodology provides both national and state-level estimates of coverage. State-level estimates can be used to compare immunization rates among states; the national estimates can be used to compare rates by race/ethnicity or other subpopulation. The survey is conducted in two parts: a telephone interview is conducted with the parents or caregivers in the household, and if the parents or caregivers consent, a subsequent

survey is mailed to the child's immunization provider to verify the parental report of immunizations. Providers are asked to fill out a list of all immunizations, the dates when they were given to the child, and whether the immunizations were given in that or another medical practice. In addition to immunization history, providers are asked about other characteristics of the practice, such as the type of facility, the number of physicians working at the practice, vaccine ordering, and whether the practice reported any of the child's immunizations to the community or state registry (CDC, 2011a).

Using this method, the NIS obtains data for more than 17,000 U.S. children in all 50 states and selected territories and urban areas. The combined surveys produce coverage data for children in the United States by individual vaccine, as well as immunization schedule completion indicators, such as completion of the 4:3:1:3:3:1:4 seven-vaccine series (four or more doses of diphtheria-tetanus-pertussis vaccine, three or more doses of poliovirus vaccine, one or more doses of MMR vaccine, three or more doses of *Haemophilus influenzae* type b, vaccine, three or more doses of hepatitis B vaccine, one or more doses of varicella vaccine, and four doses of seven-valent pneumococcal conjugate vaccine [PCV]). In addition to immunization information, the surveys also obtain information for other variables, such as poverty status; provider facility; race and ethnicity; participation in programs such as Vaccines for Children or the Women, Infants, and Children food program; and a history of breast-feeding.

Scientists often use data from the NIS to track trends in immunization coverage over time and to compare groups of children by demographic characteristics and immunization coverage to formulate hypotheses about what factors may be causing significant differences in immunization coverage (CDC, 2011a).

State Immunization Registries

CDC supports a network of immunization information systems (IISs), formerly called immunization registries, which consist of computerized, population-based databases that confidentially collect and consolidate immunization records from partnering vaccine providers. The 50 states, the District of Columbia, and 5 cities receive CDC grants to maintain their IISs. Providers are able to use the IISs to determine appropriate patient vaccinations, manage their vaccine inventories, and generate reminder and recall messages. The percentage of children whose immunization records are entered into an IIS varies widely by grantee: in 2010, the Connecticut Immunization Registry and Tracking System reported that 75 percent of eligible children in Connecticut participated, whereas Maryland's IIS participation rate was only 42 percent (CDC, 2012a). The IISs count children as participants only if they have received at least two immunizations from

a reporting vaccination provider, and reporting requirements vary between grantees (CDC, 2012c; Hedden et al., 2012).

IISs are primarily useful for tracking vaccine coverage, and those with a high participation rate and comprehensive data are potentially well-suited to evaluate postmarketing vaccine effectiveness (Cortese et al., 2011; Guh and Hadler, 2011). However, as electronic health records become more widely available in the United States, the opportunities for linking immunization history with other health data may increase.

IISs offer some benefits over systems in private health care plans, such as the VSD, for measuring immunization coverage. The systems are established in more than 50 geographic locations and receive data from a larger variety of immunization providers, including providers in private and public health care systems. In 2010, 11,536 public and 36,512 private providers reported participation in the IISs (CDC, 2012c). Nevertheless, children receive immunizations in a number of settings that may not report to an IIS.

The utility of immunization registries is likely to increase, as the provisions of the American Reinvestment and Recovery Act for the meaningful use of interoperable electronic health records require the linkage of a region's IIS to an electronic health record to qualify for incentives (CDC, 2012b).

DATABASES EXAMINING ADVERSE EVENTS AFTER IMMUNIZATION FOR VACCINE-PREVENTABLE DISEASES

A set of national and state databases with data on hospital discharges can be used to monitor events requiring medical attention that occur after immunization with selected vaccines. Data from state-level claims databases and surveys assessing the characteristics of office visits can be used in the same way. If adverse events have a specific diagnosis code, these can be monitored as well.

One such family of health care databases is the Agency for Healthcare Research and Quality–sponsored Healthcare Cost and Utilization Project (HCUP). Through a partnership between industry and government at the state and federal levels, HCUP has the largest collection of longitudinal data on hospital care in the United States, with these data dating back to 1988. All data collected in HCUP are obtained at the encounter level from patients of all payment types (all payers), including uninsured individuals. Some of the HCUP databases most relevant to the examination of immunization outcomes include the following (AHRQ, 2009):

- The Nationwide Inpatient Sample, which collects inpatient data from more than 1,000 hospitals in the United States, is the largest database of its kind in the United States.

- The Kids' Inpatient Database (KID), which also collects hospital inpatient data for children and adolescents ages 20 years and younger, is the only all-payer database with this kind of information.
- The Nationwide Emergency Department Sample captures the records for emergency department encounters from approximately 1,000 community hospitals.

Because the HCUP family of databases includes all discharges at the state level and a large sample at the national level, data from those databases can be used to detect rare events, such as adverse reactions. These data have been used, for example, to examine intussusception rates before and after the introduction of rotavirus vaccination to determine whether increases occurred (Simonsen et al., 2001; Tate et al., 2008; Yen et al., 2011). These analyses generally use data from the universal state-level inpatient databases of several states. Analyses like these require specific diagnosis codes for the adverse events and, in addition, require a causal chain that links the adverse event to vaccines. This is the case for rotavirus and intussusception but is less frequent for adverse events with other vaccines.

In addition, data from these databases can be used to assess the burden of disease for a variety of vaccine-preventable diseases. For example, Ma et al. (2009) used data from KID to assess the burden of hospitalizations for rotavirus infections in children receiving Medicaid compared with that in children not receiving Medicaid. Fischer et al. (2007) used data from these databases to establish the rate of hospitalizations associated with diarrhea and rotavirus infection before the introduction of a new rotavirus vaccine, including baseline rates, trends, and risk factors.

Finally, because they are longitudinal, data from the databases can be used to track the effects of the introduction of a vaccine on the incidence of the disease that it is intended to prevent. For example, these databases have been used to show the reduction in hospitalizations for pneumococcal pneumonia, all-cause pneumonia, and pneumococcal meningitis after introduction of PCV7 for all children and for children with sickle cell disease (Grijalva et al., 2007; McCavit et al., 2012; Simonsen et al., 2011; Tsai et al., 2008). Databases have been used in the same manner to show reductions in the numbers of hospitalizations for acute gastroenteritis after introduction of a rotavirus vaccine (Curns et al., 2010).

A similar database (the National Hospital Discharge Survey, sponsored by the National Center for Health Statistics) has been used, in combination with estimates of vaccine effectiveness, to predict the reduction of the disease burden after introduction of a vaccine against that disease (Curns et al., 2009). Among the limitations of studies like these are that they generally do not rely on laboratory-confirmed disease, and because they are observational, researchers are not able to control the exposures in the

population, and thus may not be able to clearly identify if the disease is a direct result of the vaccine.

State-Level Medicaid Claims and Related Local Databases

Data from state-level Medicaid and health plan databases have been used to assess the disease burden overall and in specific regions or for specific payers (Poehling et al., 2003). Data from these local claims databases have also been used to examine reductions in the incidence of disease after introduction of a vaccine, for example, the reduction in the incidence of otitis media after the introduction of PCV7 (Poehling et al., 2003, 2007). Furthermore, data from these state-level Medicaid or plan-level claims databases have also been used to assess the effectiveness of local immunization campaigns as seen from reductions in the incidence of disease. For example, data from local claims databases in Tennessee were used to assess the effectiveness of school-based influenza campaigns (Grijalva et al., 2010a,b).

National Ambulatory Care Databases

CDC sponsors both the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Care Survey. The National Ambulatory Medical Care Survey is a national survey of visits to nonfederal office-based physicians who are primarily engaged in direct patient care; the National Hospital Ambulatory Care Survey is a national survey of visits to emergency department doctors and the outpatient departments of general and short-stay hospitals. Both surveys collect data on the use and provision of ambulatory medical care services. Physicians also provide information about themselves and their practices. Data from these databases have been used to examine the effect of vaccine introduction on ambulatory care visits of a given type, such as examination of reductions in the rates of visits for otitis media after the introduction of PCV7 mentioned earlier (Grijalva et al., 2006).

IMMUNIZATION DATA SYSTEMS IN OTHER COUNTRIES

A number of other countries have in place data systems that are successfully used to investigate vaccine safety and coverage. Although these systems and those in place in the United States have key differences, starting with differences in the recommended immunization schedules, other countries may be well-equipped to provide data on safety concerns with the immunization schedule identified by the committee. Descriptions of immunization data systems from three countries, including Canada, with populations similar to the population in the United States are presented below.

United Kingdom

Residents of the United Kingdom (England, Northern Ireland, Scotland, and Wales) access health care through the taxpayer-funded National Health Service (NHS), which issues to each resident a unique identifying NHS number. Residents receive immunizations from their general practitioners, who serve as the initial point of access for all primary care provided by the NHS. General practitioners also issue referrals for elective or acute secondary care, although patients can seek care at a hospital emergency room at any time.

Like many other countries, including the United States, the United Kingdom (UK) has a spontaneous reporting system that passively collects data on suspected adverse events after the receipt of vaccines and other drugs. This system is known as the "Yellow Card scheme," so named because yellow cards were historically used for reporting in the British National Formulary. The Yellow Card passive surveillance system was introduced in 1965 and is currently operated by the pharmaceutical licensing authority in the United Kingdom, the Medicines and Healthcare Products Regulatory Agency. Today, UK health care professionals and patients can also report potential adverse events electronically or by phone. In addition, vaccine manufacturers have more recently been required to conduct post-marketing pharmacovigilance for adverse events after immunization or to undertake special studies when appropriate.

The Medicines and Healthcare Products Regulatory Agency also co-sponsors the United Kingdom's Clinical Practice Research Datalink (CPRD) with the NHS National Institute for Health Research. The CPRD was introduced in March 2012 and contains observational data that build on the data collected for its predecessor, the General Practice Research Database (GPRD). The GPRD is a primary care database that contains anonymous records on consultations, secondary care referrals, prescriptions, and vaccinations for about 5 percent of the population of the United Kingdom. The CPRD aims to maximize the linkages that can be made between the data that the GPRD collects and the data from other disease registries or from health care databases maintained in the United Kingdom (CPRD, 2012).

The Health Protection Agency (HPA) is an independent body in the United Kingdom with functions analogous to those of CDC in the United States. Among the HPA's responsibilities are a number of vaccine safety activities, including performing clinical trials, surveillance for vaccine-preventable diseases, and mathematical modeling and economic analyses; maintaining adequate vaccine coverage; and monitoring the safety and efficacy of the vaccines provided by the NHS.

The HPA conducts analytical studies on adverse event signals that arise from the Yellow Card system. HPA researchers also often use the GPRD to

investigate health concerns, but the study population is not large enough to examine the rare adverse events associated with vaccines (Miller, 2012). The Hospital Episode Statistics (HES) database contains records for all hospital admissions in the United Kingdom, along with the individual's NHS number for each admission. Using the NHS number, researchers can contact an individual's general practitioner to obtain immunization records and link those data to any hospital admission from the HES.

England and Wales maintain national child health databases that routinely collect immunization records and can likewise be linked with the HES by use of an NHS number and specified approvals. This method has been used to investigate adverse event signals, such as a suspected increased risk of purpura or convulsions from the meningococcal group C conjugate vaccine and a potential association between MMR and idiopathic thrombocytopenic purpura (Andrews et al., 2007; Miller et al., 2001).

Denmark

Denmark is uniquely positioned to build and maintain large cohorts for the evaluation of vaccine safety thanks to the Danish Civil Registration System (CRS) and the national health care system. The CRS was established in 1968 and registered every living person in Denmark at that time. Every living resident in Denmark, including noncitizens, is issued a unique personal identification number, and the CRS collects data on each individual's gender, date of birth, place of birth, place of residence, citizenship status, and parents and spouses, and the CRS continuously updates vital statistics (Pedersen et al., 2006).

Linking a personal identification number to the data collected by the CRS makes it possible to track demographic trends and vital statistics for Danish residents over time. This identifier is also used to link individuals with data collected by Denmark's many health care registries. The National Board on Health administers registries on the incidence of specific diseases (e.g., the National Diabetes Register and the Danish Cancer Register), and since 1990, Denmark has maintained a registry containing information on all vaccinations administered to children aged 18 years and younger. General practitioners report incidences of vaccination to a state-based administrative registry and are in turn reimbursed by the national health insurance system (Thygesen et al., 2011).

Epidemiological research on vaccine safety is conducted with data from these registries by the Department of Epidemiology Research at the Statens Serum Institut, one of Denmark's largest health research institutions (Statens Serum Institut, 2012). Because each health-related registry records the resident's CRS, it is possible to link the data collected by separate registries. Therefore, much of the formative research on vaccine safety

has been conducted in Denmark with registry linkages. These linkages of data between the childhood vaccination registry and other disease-specific registries provide data that can be used to evaluate hypotheses on vaccine safety for large cohorts of Danish residents (often, more than 500,000). For example, the cohort study design has been used to investigate associations between MMR and autism, childhood vaccinations and type 1 diabetes, and thimerosal-containing vaccines and autism (Hviid et al., 2003, 2004; Madsen et al., 2002).

Canada

Canada's health care system has some similarities with those in countries such as Denmark and the United Kingdom, including the provision of primary care health services without cost sharing. Unlike those countries, Canada's health care system is provincial, rather than federal, meaning that coverage varies across the 13 separate provinces. The determination of an immunization schedule is no exception: each province is given authority to create its own immunization schedule, although evidence of vaccine safety and efficacy is still reviewed by the National Advisory Committee on Immunization. Nevertheless, provinces may have very similar schedules for one vaccine; for example, the only province that does not recommend immunization with MMR at 12 months of age is Prince Edward Island, which recommends the vaccine's first administration 3 months later at age 15 months. For another vaccine, that for hepatitis B, the differences are more striking: the province of Prince Edward Island recommends administration of the first dose in infancy, whereas its provincial neighbor, Nova Scotia, does not recommend administration of the first dose until grade 8 (Macdonald and Bortolussi, 2011).

Canada also has a spontaneous reporting system for suspected adverse events related to vaccines, the Vaccine Associated Adverse Event Reporting System, which was established in 1987. Today, the passive surveillance system is called the Canadian Adverse Events Following Immunization Surveillance System and is maintained by the Public Health Agency of Canada. Health care professionals in Canada can submit reports of suspected adverse events to their local public health authority. Unlike in the United States, however, Canada has no system for the general public to report events without a health professional, who must submit the required form. In the provinces of Manitoba, New Brunswick, Nova Scotia, Ontario, Quebec, and Saskatchewan, reporting of adverse events after immunization is required by law (Public Health Agency of Canada, 2006).

To supplement its passive surveillance system, Canada implemented the Immunization Monitoring Program, Active (IMPACT) in 1991. The IMPACT network is based in 12 pediatric hospitals and is maintained by

the Canadian Paediatric Society. In IMPACT, a nurse monitor and clinical investigator regularly review admission records at network hospitals. Any suspected adverse events are reported to the vaccinee's local public health authorities and the Public Health Agency of Canada (Public Health Agency of Canada, 2006). IMPACT data have been used in studies of suspected adverse events after immunization, including studies of the risk of seizures or encephalopathy after implementation of acellular pertussis-containing vaccines (Scheifele et al., 2003).

International Collaborations

In addition to country-specific data systems, some international collaborations seek to improve assessments of vaccine safety. The Brighton Collaboration is a global research network comprising more than 300 vaccine safety experts from 124 countries, including the United States. The focus of their work is to enhance vaccine safety and it falls into five categories: capacity building, clinical assessments, communication, data linkages, and research standards. Included in their activities is an effort to standardize case definitions of adverse events after immunization (Brighton Collaboration, 2012).

In addition, the Brighton Collaboration operates the Vaccine Adverse Event Surveillance and Communication Network of data linkages in Europe, which is funded by the European Centre for Disease Prevention and Control (VAESCO, 2010). To date, this network of investigative centers has conducted a five-country distributed case-control study to evaluate the risk of Guillain-Barré syndrome after administration of the pandemic influenza (H1N1) vaccine and the incidence of idiopathic thrombocytopenic purpura after immunization with MMR in a combined sample from Denmark and the United Kingdom (Dieleman et al., 2011; Madsen et al., 2002).

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4

Stakeholder Concerns Related to the Safety of the Immunization Schedule

Immunizations represent a unique health intervention because they simultaneously affect the health of individuals and the health of their communities. The success of vaccination programs in reducing the human reservoir of infectious diseases requires the collaboration and participation of a complex system of stakeholders in which each plays a specific role. These stakeholders include but are not limited to the parents of children who receive vaccines, the physicians and other health care professionals who deliver inoculations, and public health professionals who ensure vaccine delivery and safety. The concerns that surround the immunization schedule are equally complex and diverse.

Concerns about vaccines have historically had a significant impact on the immunization system. Decreases in measles, mumps, and rubella (MMR) vaccine coverage in the United Kingdom are largely attributed to parental fears of autism linked to immunization with MMR following publication of the discredited Wakefield paper, which falsely claimed to demonstrate this association and was subsequently retracted years later by *Lancet* (Brown et al., 2012; Madsen and Vestergard, 2004; Taylor et al., 1999). In the 1970s, concerns about adverse effects from the whole-cell pertussis vaccine contributed to a decrease in uptake and halted pertussis vaccination programs in some countries. From this controversy came innovation that created the acellular pertussis vaccine, which has fewer observed adverse effects, as well as policy changes in the United States with the enactment of the National Childhood Vaccine Injury Act (IOM, 1992; Noble et al., 1987).

The committee recognized the challenge and importance of identifying

and understanding the range of stakeholder concerns about the childhood immunization schedule and its safety. To gain a fuller understanding of this system, the committee developed a strategy to gather and analyze stakeholder concerns, which included a review of the existing literature, listening to public testimony, and soliciting comments on a commissioned paper.

IDENTIFICATION OF STAKEHOLDERS

Given the committee's charge, the first step was to identify stakeholders whose concerns focused on the safety of the immunization schedule rather than the safety of individual vaccines or nonsafety issues such as cost or convenience. To begin, the committee consulted the list of stakeholders from the 2008 Institute of Medicine (IOM) report *Initial Guidance for an Update of the National Vaccine Plan: A Letter Report to the National Vaccine Program Office* (IOM, 2008), which is also referenced in the 2010 National Vaccine Plan of the U.S. Department of Health and Human Services. As a second step, the committee categorized the extensive list of stakeholders by their general interest in immunization (Box 4-1).

BOX 4-1
Stakeholders in the U.S. National Vaccine System

- Academic researchers
- Advocacy groups
- Federal government agencies, departments, and federal advisory committees
- General public (including parents)
- Health care system and providers
- International organizations
- Media
- Nongovernmental organizations
- Philanthropic organizations
- State, local, and tribal governments and public health agencies
- Travel industry
- Vaccine distributors
- Vaccine industry
- Vaccine investors

SOURCES: IOM (2008) and adapted from the 2010 National Vaccine Plan (http://www.hhs.gov/nvpo/vacc_plan/2010 percent20Plan/appendix5.pdf).

INFORMATION GATHERING

After identifying key stakeholders, the committee reviewed the most frequently expressed concerns related to the safety of the immunization schedule from three primary sources of information: the current literature, online postings, and public testimony.

The committee reviewed all the information that interest groups, individuals, and researchers provided through the online submissions and in public testimony at the committee meetings and throughout the study period. Even before the first committee meeting, the committee received online testimony as well as many e-mail messages. The committee held three public meetings that included information-gathering sessions and a session during which it heard public testimony. During the three public meetings, the final hour was reserved for stakeholders to share their concerns related to the committee's charge. Throughout the study, the committee also reviewed media coverage and scientific articles related to the safety of the immunization schedule. However, the committee based its review of the safety of the immunization schedule on information reported in the scientific literature.

The literature review focused on the recommended childhood immunization schedule and yielded an extensive body of scientific articles, reports in the popular media, reviews, and summaries. Because the committee's study period was limited (no longer than 12 months), the committee established priorities to identify and review the most common and noteworthy stakeholder concerns about the safety of the childhood immunization schedule.

LITERATURE SEARCH

The committee used the Ovid MEDLINE database to search the scientific literature published within the past 10 years (2002 to 2012). Multiple comprehensive searches were used to identify references that described stakeholder concerns and analyzed health outcomes after immunization according to the recommended childhood immunization schedule. The committee focused on articles published in the past 10 years because the childhood immunization schedule has been modified several times as new vaccines have been approved and incorporated into the schedule. Concerns related to the 2001 recommended childhood immunization schedule are likely to be different from concerns related to 2012's schedule, which recommends additional immunizations for children. Because the committee's task was to assess the safety of the immunization schedule rather than the safety of individual vaccines, the literature searches did not include articles that focused on a single vaccine. The committee's review included peer-reviewed publications such as scientific articles, reviews, commentaries,

and editorials. The committee used medical subject heading searches to identify references, using the terms "immunization" (which includes "immunization schedule"), "vaccines," "attitude to health," and "attitude of health personnel."

The initial literature search yielded 421 articles. To further refine the search, the committee reviewed the titles and abstracts (when available) and removed articles that met any of following three exclusionary criteria. First, from the beginning of the study period, the committee noted that the childhood immunization schedule spans the entire period of childhood (birth to age 18 years). The committee found that the most prominent safety concerns about the immunization schedule are related to vaccinations received during infancy and early childhood. Thus, the committee focused its review on the body of literature that addressed concerns about the short- and long-term effects of the schedule of vaccinations given to young children (birth to age 6 years) and excluded studies that focused on the immunization schedule for older children and adolescents (age >6 years). Second, the committee excluded studies that focused on individual vaccines or combination immunizations rather than the entire childhood immunization schedule. Finally, the committee excluded studies of non-U.S. populations, unless the study focused on the U.S. Advisory Committee on Immunization Practices (ACIP)–recommended immunization schedule for young children.

After the committee applied these criteria, it retained 85 published articles for comprehensive review. Two-thirds of these articles were categorized as studies of parental concerns about either safety ($n = 26$) or communication between providers, public health authorities, and parents ($n = 31$). Several articles that the committee reviewed did not meet the study criteria (largely owing to having an older publication date) but were frequently cited in the literature and added to the committee's knowledge base.

An iterative review of the literature as well as oral and written public comments revealed that among the primary stakeholders (parents, health care providers, public health officials), a subset of parents were the group with the most concerns about the safety of the immunization schedule. The review also revealed that parents, providers, and public health officials all believe that effective communication about these safety concerns remains a challenge.

PARENTAL CONCERNS IN THE SCIENTIFIC LITERATURE

Parental concerns about the safety of vaccines and the immunization schedule have been well publicized but are not well understood by all health care professionals. A number of recent studies have described the challenges associated with research into the safety of the immunization schedule and defined the methods that can be used to elicit and quantify parental con-

cerns (Dempsey et al., 2011; Freed et al., 2010; Gust et al., 2005; Kennedy et al., 2011a; Niederhauser et al., 2001; Salmon et al., 2004).

In 2000, Gellin et al. reported that the two most common concerns that parents expressed about childhood immunizations were that too many vaccines were being administered to infants and children and that childhood vaccines may weaken the immune system (Gellin et al., 2000). The 2002 IOM report *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* determined that no biological or epidemiological evidence for such concerns was available and that infants receive more antigenic exposures from the natural world, including exposures to infections for which no vaccine is provided. The report noted, however, that "the committee concludes that concern about multiple immunizations has been, and could continue to be, of societal significance in terms of parental worries, potential health burdens, and further challenges for immunization policy-making" (IOM, 2002, p. 12)

A recent study of the concerns stated by parents with young children (<7 years) in the 2010 HealthStyles survey revealed a number of vaccine-related attitudes and concerns (Kennedy et al., 2011b). The concerns that 376 respondents reported the most frequently are listed in Table 4-1.

Similar results were found in the 2002 HealthStyles and Consumer-Styles surveys of a nationally representative sample of 697 parents, although the rank order of their concerns was slightly different (Gust et al., 2005). Despite documented parental concerns about vaccines, most parents still have their children receive the recommended immunizations. In fact, the 2010 National Immunization Survey (NIS) reported that less than 1 percent of toddlers had received no vaccines at all (CDC, 2012).

A 2011 article focused on the relationship between parents' attitudes toward childhood immunizations and the decision to delay or decline immunizations (Smith et al., 2011). Using data from the 2009 NIS, the researchers reviewed 11,206 parents' reports of immunization delays and refusals. Approximately 60 percent of parents with children aged 24 to 35 months neither delayed nor refused immunizations; 26 percent only delayed

TABLE 4-1 Vaccine-Related Concerns, 2010

Vaccine-Related Concern	Percentage of Responses
It is painful for children to receive so many shots during one doctor's visit.	38
My child is getting too many vaccines in one doctor's visit.	36
Children get too many vaccines during the first 2 years of life.	34

SOURCE: Kennedy et al., 2011b.

one or more immunizations; 8 percent refused one or more immunizations; and approximately 6 percent both delayed and refused one or more immunizations. Concerns were aggregated into categories such as a lack of trust that vaccines are safe, suspicions that vaccines might produce serious side effects, concerns that too many vaccines can overwhelm a child's immune system, and the general sense that their children are immunized with too many vaccines (Smith et al., 2011).

Safety concerns have led some parents to prefer alternative immunization schedules that may involve delaying specific immunizations or omitting some or all immunizations. A recent review of the literature on the growing trend of following alternative immunization schedules produced a summary of parental concerns, such as concerns about vaccine safety, efficacy, and necessity; distrust of vaccine advocates' motivation; and insufficient information with which to make an informed decision (Dempsey et al., 2011). Health care providers reported that parents' requests for an alternative schedule may be based on a specific immunization schedule or may reflect parental concerns about an individual vaccine rather than the entire schedule.

A recent cross-sectional, Internet-based survey of a representative sample of parents of young children (ages 6 months to 6 years) reported that less than 10 percent of parents indicated that they follow an alternative immunization schedule (Dempsey et al., 2011). The study identified the four vaccines that were the most commonly refused: the H1N1 influenza, seasonal influenza, rotavirus, and varicella vaccines. In general, newer vaccines were more likely to be declined than were established vaccines. Parents who requested a delay for a specific vaccine most commonly (more than 40 percent) requested a delay in receiving MMR and the varicella vaccine.

In 2009, Freed et al. conducted an online survey and reported that the varicella and meningococcal vaccines were the most commonly refused (Freed et al., 2009). An analysis of responses to the NIS in 2003 and 2004 also reported that the varicella vaccine was the one that prompted the most concerns among parents who declined immunizations for their children (Gust et al., 2008).

Although parents have various reasons for declining or delaying immunizations, a 2011 study also reported that a large proportion of parents who requested an alternative immunization schedule understood and acknowledged that undervaccination increases the risk of infection and spread of disease in the community (Dempsey et al., 2011). Despite recent increases in the popularity of alternative immunization schedules, their use remains infrequent (Dempsey et al., 2011; Robison et al., 2012).

Analysis of the data from the 2003-2004 NIS revealed that parents of underimmunized children articulated their concerns about the safety of the immunization schedule in the popular media more forcefully than did

parents of fully immunized children (Gust et al., 2004). Results of a later iteration of the 2009 NIS found that parents of fully immunized children reported concerns about vaccines, but their concerns did not preclude immunization of their children (Kennedy et al., 2011a).

In their public testimony during the committee meetings, parents provided a range of concerns about the immunization schedule; the committee received limited public testimony from parents who endorse the recommended schedule, despite evidence that the majority of U.S. parents support and follow ACIP's recommendations (CDC, 2012).

The 2004 NIS reported that parental concerns about vaccine safety were associated with underimmunization, which is further associated with adverse health outcomes for individuals and their communities, including increases in the prevalence of vaccine-preventable diseases (Gust et al., 2004). Furthermore, the designs used in most studies of immunizations do not permit a detailed analysis of the impact of parental concerns on parents' decision to immunize their children (Kennedy et al., 2011b). And, although many research studies have focused on parental concerns about vaccine safety, they have not adequately explored parental knowledge of the protective benefits of immunizations.

The committee identified a need for further study of parental attitudes and concerns about immunization. Based on the committee's review of the literature and public testimony, the committee strongly endorses research to understand parents' knowledge, beliefs, and concerns about vaccines and vaccine-preventable diseases, which is a key component of the 2010 National Vaccine Plan.

PUBLIC CONCERNS PRESENTED TO THE COMMITTEE

The public testimony presented to the committee highlighted concerns about the quality and strength of existing research on vaccine safety in the United States. Some individuals who provided public testimony focused on the lack of research on vaccine safety for subpopulations that may be potentially susceptible to adverse events. For example, children with family histories of adverse vaccine events, autoimmune diseases, allergies, and neurological diseases were described to be underrepresented in prelicensure and clinical trials of childhood immunizations.

Furthermore, public testimony to the committee described the speculation that children with a family history of autoimmune disease or allergies and premature infants may be additional subpopulations at increased risk for adverse effects from immunizations. The 2012 IOM report *Adverse Effects of Vaccines: Evidence and Causality* supports the fact that individuals with certain characteristics (such as acquired or genetic immunodeficiency)

are more likely to suffer adverse effects from particular immunizations, such as MMR and the varicella vaccine (IOM, 2012).

During each of the three public sessions held in conjunction with committee meetings, the testimony of many individuals and organizational representatives revealed a lack of trust in the quality and thoroughness of vaccine safety research. Several individuals recommended that the committee review the scientific studies that have compared health outcomes among fully vaccinated, partially vaccinated, and unvaccinated children as well as children who have been vaccinated according to alternative schedules.

The comments that were submitted through an online questionnaire in response to the committee's commissioned paper (see Appendix D) echoed many of the concerns and suggestions that were articulated during the three public sessions. The sentiments largely focused on the concern that the recommended immunization schedule bombards children's immune systems with an excessive number of antigens at an early age and may not be as safe as possible.

PATIENT-PROVIDER COMMUNICATION

As indicated by the high rates of vaccination coverage, most American parents believe that vaccinations are an effective way to protect their children from serious infectious diseases (CDC, 2012). Despite this strong support, parents have concerns, questions, and misperceptions about childhood immunizations (Kennedy et al., 2011b). Parents seek information about vaccine safety from a multitude of sources: public health authorities, pediatricians, other child health care professionals, professional organizations' websites, personal blogs, celebrities, and advocacy groups (Freed et al., 2011).

With such a wide range of sources of information about immunizations, the committee recognized the likelihood that parents could receive conflicting information that could exacerbate their concerns and confusion about the safety of vaccines. The committee also noted the many high-quality websites and materials that have recently been produced, including Vaccines.gov and materials produced by the American Academy of Pediatrics (AAP) and available on the AAP website. However, findings from an online survey conducted as part of an ongoing study of 2,521 parents and nonparents demonstrated that although websites from doctors' groups, such as AAP, and government websites were trusted by the greatest proportion of surveyed parents (27 and 7 percent, respectively), a larger proportion did not view or use these resources at all (29 and 38 percent, respectively) (Freed et al., 2011).

Apart from the confusion associated with conflicting sources of information about childhood vaccines (Freed et al., 2011), the committee's

review of the scientific literature and the public testimony identified the lack of parental trust in vaccines and vaccine safety to be an important concern. Overall, a large majority of parents rely on the professional advice they receive from their child's doctor or health care provider, and they report high levels of trust in their doctor's advice (Freed et al., 2011). However, a recent study reported that 26 percent of parents trusted celebrities as a reliable source of information on the safety of vaccines (Freed et al., 2011). Thus, although the relationship between the parent and the child's health care provider is a strong determinant of decision making about childhood vaccines, some parents rely on nonprofessional sources of information to make the same decisions (Gust et al., 2008; Serpell and Green, 2006).

In some cases, pediatricians may dismiss parents from their practice if the parents decline vaccines, delay vaccinations, or base their decisions on unscientific information (Flanagan-Klygis et al., 2005). For example, a 2011 study reported that more than 30 percent of Connecticut pediatricians have dismissed families because of their refusal to immunize their children (Leib et al., 2011). AAP discourages the dismissal of parents on the basis of their refusal to immunize their children (Diekema and the AAP Committee on Bioethics, 2005). Furthermore, AAP believes that providers should maintain a relationship with families that decline immunizations so that children continue to receive appropriate medical care. In addition to the value of that care, the continuing relationship provides an opportunity for the pediatrician to encourage parents to consider immunization of their children in the future (Diekema and the AAP Committee on Bioethics, 2005). The committee also notes that the dismissal of families from pediatric practices could further erode trust in the health care system.

A recent study of 209 pediatricians in Washington State reported that parental requests for alternative immunization schedules are not uncommon (Wightman et al., 2011). Overall, 61 percent of these pediatricians agreed that they were comfortable using different schedules if the parents made this request. The three vaccines that most pediatricians were willing to delay were the hepatitis B vaccine (69 percent), varicella vaccine (53 percent), and inactivated poliovirus vaccine (45 percent) (Wightman et al., 2011).

Based on the literature review and public testimony, the committee noted the importance of providers' knowledge of vaccine safety. Furthermore, the committee found it to be essential that providers use a communication style that elicits parents' concerns and encourages respectful dialogue to address divergent opinions. Even though health care providers may focus on the benefits of childhood immunizations, they may not adequately discuss the anticipated, higher-prevalence side effects or the potential events that are significantly more rare and severe. Therefore, based on the review of the scientific literature and the public input, the committee believes that

all health care providers who immunize children should receive training in communication with the goal of improving provider-parent communication of immunization issues (Gust et al., 2008a).

Apart from the need for training in communication, the committee reviewed several recent studies that identified the need for improved communication about vaccine safety by the scientific community and public media (Gust et al., 2006, 2008b; Levi, 2007). Gust et al. (2006) suggested that enhanced communication training for providers should increase their willingness to engage parents in discussions of vaccine and immunization issues.

Studies are also under way to develop techniques to identify categories of vaccine hesitancy and develop tools to assist providers as they communicate with parents who express concerns about vaccines (Diekema, 2012). The 2002 IOM report *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* recommended that an appropriate panel of multidisciplinary experts be convened to "develop a comprehensive research strategy for knowledge leading to the optimal design and evaluation of vaccine risk-benefit communication approaches" (IOM, 2002, p. 16). Furthermore, the 2010 IOM study described in the report *Priorities for the National Vaccine Plan* emphasized that communication must reflect current research and strategies (IOM, 2010).

Government agencies and professional organizations play a key role in providing parents with information on vaccines and immunizations. However, the public erosion of trust in government and the suboptimal effectiveness of public health campaigns on immunizations in particular highlight the challenges of mounting an effective strategy of communication about the childhood immunization schedule. This challenge is exacerbated by the fact that public decision making as it applies to vaccines is driven not only by scientific and economic evidence but also by political, psychological, and sociocultural factors.

CONCLUSIONS

From the literature review and the comments received online and during the public sessions, the committee determined that although the majority of parents adhere to the ACIP-recommended immunization schedule for their children, many parents remain concerned that their children may face unnecessary risks because of the timing and number of vaccinations.

The decisions that parents make about the risk of disease versus the risk of immunization are attributable, in part, to the significant and sustained declines in most vaccine-preventable diseases that have resulted in the community immunity (also known as herd immunity) that vaccination policy has achieved. Although some parents may not fully understand the

concept of community immunity, at some level, many parents understand that widespread efforts to immunize children protect both vaccinated and unvaccinated children. The protection offered by community immunity may mislead some parents who decline all immunizations and allow them to believe that childhood vaccines are unnecessary, when vaccination in the community has actually shielded their children from serious infectious diseases (Chen et al., 2005). Finally, some parents are concerned about their child's risk of complications of immunization with a vaccine on the basis of family history or the child's medical conditions, and, decide to delay or omit immunizations. Children with certain predispositions are more likely to suffer adverse events from vaccines than are those without that risk factor, such as children with immunodeficiencies who are at increased risk for developing invasive disease from a live virus vaccine (IOM, 2012). The committee recognizes that while the CDC has identified persons who should not be vaccinated because of certain symptoms or conditions, some stakeholders question if that list is complete. Potentially susceptible populations may have an inherited or genetic susceptibility to adverse reactions, and further research in this area is ongoing.

Thus, the committee understands that parental concerns are an expression of concern over and a way to care for their children's health and well-being. However, the committee also recognizes that a growing pattern of delaying or declining all or some vaccines has already contributed to outbreaks of vaccine-preventable diseases and mortality across the United States. These disease outbreaks place children and adults at risk, including children who are only partially immunized or experience waning immunity. Immunized children and adults in the community represent another group of stakeholders, and the committee recognizes the concern about declining community immunity as well.

Research from telephone surveys and other methods reviewed in this chapter typically provide information about what participants think, but such surveys usually cannot probe into why respondents think the way they do. To develop an effective risk-benefit communication strategy, more detailed research is warranted. The committee concludes that parents and health care professionals would benefit from the availability of more comprehensive and detailed information with which to address parental concerns about the safety of the vaccines in the immunization schedule. Such information should clearly address vaccine-preventable diseases, the risks and benefits of immunizations, and the safety of the vaccines in the immunization schedule.

At present, as described in Chapter 5, relatively few studies have directly assessed the immunization schedule. Although health care professionals have a great deal of information about individual vaccines, they have much less information about the effects of immunization with multiple

vaccines at a single visit or the timing of the immunizations. Providers are encouraged to explain to parents how each new vaccine is extensively tested when it is approved for inclusion in the recommended immunization schedule. However, when providers are asked if the entire immunization schedule has been tested to determine if it is the best possible schedule, meaning that it offers the most benefits and the fewest risks, they have very few data on which to base their response. Furthermore, although the 2010 National Vaccine Plan addresses the need to provide health care providers with more timely, accurate, and transparent information about the benefits and risks of vaccines, providers are not singled out in specific strategies offered by the U.S. Department of Health and Human Services.

Although the committee identified several studies that reviewed the outcomes of studies of cumulative immunizations, adjuvants, and preservatives (see Chapter 5), the committee generally found a paucity of information, scientific or otherwise, that addressed the risk of adverse events in association with the complete recommended immunization schedule, even though an extensive literature base about individual vaccines and combination immunizations exists. The committee also acknowledges that the public health community has in place monitoring systems that work very well for the detection of adverse events that occur in the short term after immunization and that could be enhanced for the detection of longer-term outcomes, as discussed in Chapters 3 and 6. The continuation of studies looking at immune phenotyping, such as those of the National Institutes of Health's Human Immunology Project Consortium, is also important in the identification of populations that are potentially susceptible to adverse events (HIPC, 2012).

To achieve the goal of giving health care providers and parents information that addresses the concerns that correlate with delaying or declining childhood immunizations, the committee developed a list of priority areas in which more information or clear communication of existing research is needed. The committee summarizes the priority concerns into the following topics:

1. Immune system overload. As several parents asked, are children given too many vaccines? Do immunizations start when babies are too young? Are immunizations administered too frequently?
2. Immunization schedule. What is the evidence that the ACIP-recommended immunization schedule is better than other schedules? Could the health outcomes among children who are vaccinated according to the recommended schedule be compared with those among unimmunized children? Likewise, could the health outcomes among children vaccinated on the recommended schedule

be compared with those among children vaccinated on alternative schedules?
3. Are subpopulations of children potentially susceptible to adverse reactions to vaccines, such as children with a family history of autoimmune disease or allergies or children born prematurely?

The committee recognizes not only that additional information is needed to address parental concerns but also that other factors will affect parental decision making. For example, in the testimony and online comments, the committee identified skepticism about (1) the quality of vaccine research (prelicensure and postmarketing), (2) the influence of pharmaceutical companies on scientific research, and (3) the influence of the governmental entities that oversee vaccine research. In addition, as stated earlier, clear and effective parent-provider communication is essential to convey accurate information and foster mutual trust.

The committee's review of the determinants of public trust in vaccination campaigns and information on vaccines identified three types of concerns raised by stakeholders:

- knowledge and expertise,
- openness and honesty, and
- concern and care.

Thus, improved communication between public health authorities and parents requires improvements to the clarity of the information and the effectiveness with which the information is conveyed, as well as the building of trust and the use of a systematic approach to elicit public concerns. Further research into the impact of parental perceptions about risk on their decisions about immunizing their children is indicated, and that research should be performed by methods that use decision and social science (Larson et al., 2011).

The committee acknowledges that parents and providers are not the only stakeholders who are concerned about the safety of the immunization schedule. The committee listened to presentations from a range of stakeholders whose concerns focused on providing immunizations to preserve community immunity and to prevent the reemergence of vaccine-preventable diseases, which ultimately requires the cooperation and trust of parents in immunizing their children. These other groups and individuals who also have a vested interest in providing children with a safe and effective immunization schedule include pharmaceutical companies; federal, state, and local governments; health insurers; the many health care providers who oversee administration of vaccines; and many others in the health care system.

The committee also acknowledges that the low rate of many infectious diseases may encourage parents to focus on the risks of immunizations rather than the risk of vaccine-preventable diseases. These low rates of infectious diseases may reinforce parents' reliance on community immunity to protect their child rather than choose immunizations.

The vaccine safety activities of the federal government are prioritizing the engagement of stakeholders in multiple activities, detailed in the 2010 National Vaccine Plan and implementation efforts, as well as the Scientific Agenda of the Centers for Disease Control and Prevention's Immunization Safety Office. However, an effective national vaccine program will require better-quality information on stakeholder concerns about the safety of vaccines, the severity of vaccine-preventable diseases, individual and population-level immunization, vaccine efficacy, and the delivery and supply of vaccines recommended in the childhood immunization schedule. To effectively implement immunization programs, a state-of-the-art communication plan is needed.

Recommendation 4-1: The committee recommends that the National Vaccine Program Office systematically collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the goal to improve communication with health care professionals, and between health care professionals and the public regarding the safety of the schedule.

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5

Review of Scientific Findings

Previous reports from the Institute of Medicine (IOM) have reviewed the evidence regarding individual immunizations and adverse health outcomes. The most recent comprehensive report was *Adverse Effects of Vaccines: Evidence and Causality* (IOM, 2012). Most IOM reviews of vaccine safety have examined the association between adverse events and individual vaccines. One prior IOM review examined the evidence for an association between three adverse outcomes and the overall recommended childhood immunization schedule: increased susceptibility to heterologous infection; autoimmunity, as reflected in type 1 diabetes; and allergy, as reflected in asthma (IOM, 2002). The statement of task for the present IOM committee requests a review of the available data on the relationship between the overall immunization schedule and health effects that might be of concern to stakeholders, including parents, health care providers, and the public health community.

To complete its task, the committee reviewed research on the health outcomes and safety of the immunization schedule. It sought to identify study designs for analysis of health outcomes following immunization and ways to define the health outcomes used in recent studies reviewing aspects of the immunization schedule. Finally, it sought to provide guidance on ways to define exposures and health outcomes in the study designs that the committee may propose.

The committee did not have the time or the resources to conduct formal reviews meeting all criteria for systematic reviews for each question of interest, nor did it find substantial evidence to conduct a quantitative synthesis (IOM, 2011). Therefore, the committee searched for, assembled,

and summarized information on the association between aspects of the immunization schedule and specific health conditions already available in the peer-reviewed literature. The health outcomes that the committee chose to review were selected on the basis of its examination of the peer-reviewed literature, previous IOM vaccine safety studies, and public presentations at open meetings of the committee. The number of studies of aspects of the schedule varied; for some outcomes, several studies examining the cumulative effects of vaccines and adjuvants or preservatives were found; for other outcomes, very few studies were found. The committee's methods and reviews are briefly summarized below.

LITERATURE SEARCH METHODS

The committee members and IOM staff conducted searches of the English-language literature published in the past 10 years (2002 to 2012) for children ages 0 to 18 years using the medical subject headings (MeSH) "immunization" or "vaccines," combined with the following terms for health outcomes of interest:

- "autoimmune diseases" (which captures "diabetes mellitus, type 1"),
- "asthma,"
- "hypersensitivity,"
- "seizures" or "epilepsy" or "febrile seizures,"
- "child developmental disorders, pervasive" (which captures "autistic disorders"),
- "learning disorders" or "communications disorders" or "intellectual disability" or "developmental disorders,"
- "attention deficit and disruptive behavior disorders," and
- "tics" or "Tourette's syndrome."

The literature published in the past 10 years was chosen to fill the gap since the 2002 IOM review and because several changes to the immunization schedule have been made since 2000 (e.g., addition of the pneumococcal and rotavirus vaccines). Studies more than 10 years old would be of outcomes that occurred after use of an immunization schedule with less resemblance to the current one.

All searches were run against the Ovid MEDLINE database (1950 to present). The search excluded reviews, commentaries, editorials, and similar publications. The conventional electronic searches were supplemented with articles identified by committee members and staff and articles that were noted during committee discussions and public presentations at open meetings. Commentaries and reviews were reviewed but not analyzed in the

same detail as were original research papers. The searches initially yielded 748 references. This number was further reduced to 143 by exclusion of articles that reviewed vaccines not included in the current or recent childhood immunization schedule or included vaccines for adolescents, such as the human papillomavirus vaccine, and by elimination of references duplicated in more than one category. The number of articles reviewed was further reduced by limitation of the search to articles describing studies that examined at least one health outcome and at least one of the following elements of the schedule, including

- number of vaccines,
- frequency of administration,
- spacing between doses,
- cumulative doses,
- age of the recipient, and
- order of vaccine administration.

Though the committee did not undertake a formal systematic review, the quality of individual articles was judged by the validity of the study design, the method by which the research was conducted, and the transparency of methods. In the end, 37 articles were chosen, and these, organized by category of health outcome, are briefly summarized below.

A second search was performed by use of the MeSH "immunization schedule" without predefined headings to investigate specific diseases or conditions. This search was conducted to ensure that the committee's review adequately addressed any demonstrated associations between components of the immunization schedule and adverse health outcomes. Again, the search was limited to articles published in the past 10 years and excluded reviews, commentaries, editorials, and similar publications. After application of the exclusionary criteria, 1,235 abstracts were reviewed, and this number was narrowed to 56 that were considered potentially relevant to the committee's charge. The committee concluded that only four of these research papers covered aspects of the childhood immunization schedule and safety. Two were considered not helpful to an evaluation of safety. (One was an economic evaluation of the childhood immunization schedule and did not examine safety; the second had serious limitations and was not considered for this chapter.) Two of the papers provided useful information, so summaries are included under the appropriate outcome section below (one is included under allergy/atopy; the second is included under neurological outcomes).

A third search was done to examine studies of immunization in infants born prematurely. Although prematurity is not a "health outcome," the committee's efforts included collection of data on premature infants because

of concerns about this vulnerable population. The search included the English-language literature published in the past 10 years (2002 to 2012) and used the previously mentioned MeSH terms "vaccines" and "immunization," combined with "infant, premature," and "premature birth." The search was further reduced to include only research on children 0 to 18 years of age and infants from birth to 23 months of age. The initial results yielded 143 abstracts. The committee reviewed the only seven articles that contained relevant data and that met the quality criteria.

LITERATURE SUMMARY

Allergy and Asthma

The Ovid MEDLINE literature search identified 40 references to articles on the relationship between immunizations or vaccines and asthma or hypersensitivity. (Although "atopy" and "allergy" were not search terms, many papers identified by use of the search term "asthma" or "hypersensitivity" included "atopy" or "allergy" as outcomes.) After an initial review, a team of two reviewers determined that 13 papers focused on some aspect of the immunization schedule. The committee's second search provided a 14th paper for review, described below. A number of studies reported in the past 10 years have addressed the association between various aspects of the immunization schedule and asthma, atopy, or allergy. As one author noted (McKeever et al., 2004), it is necessary to have a detailed understanding of the relationship between allergic disease and vaccination, because the effectiveness of the immunization program may be adversely impacted by a perception that vaccination is harmful.

The following summary categorizes papers into groups: (1) studies examining an entire immunization schedule, (2) studies examining pertussis-containing vaccines, and (3) ecological studies (defined in Appendix B) and other studies that do not fit into one of the other two categories. Several papers reported on cohort follow-up studies with asthma, allergy, or atopy as the outcome and cumulative immunizations (the entire schedule for the country and time of the study) as the independent variable.

A longitudinal cohort in Australia was examined for the association between early childhood infection and immunization with the development of allergic diseases, including asthma (Thomson et al., 2010). The cohort included 620 allergy-prone children enrolled in 1989 and monitored from birth to 6 years of age. All data, including immunizations (diphtheria and tetanus toxoids and pertussis vaccine or diphtheria and tetanus toxoids absorbed [DT], oral poliovirus [OPV] vaccine, and measles, mumps, rubella [MMR] vaccine), were collected by telephone interviews. There was no relationship between cumulative immunizations and asthma. Administration

of DT in the first year of life but not the second year of life was associated with asthma and eczema. The study was limited by the self-report nature of the data and the small sample size.

Matheson and colleagues (2010) reported on atopy in the most recent follow-up study of 5,729 adults in the Tasmanian Longitudinal Health Study cohort of 1968 in Australia. This most recent follow-up of 44-year-olds was done by use of a mailed survey and explored the effects of immunization on atopic conditions. Only DTP, polio, and smallpox immunizations were in use in the cohort in 1968. The study is limited by the self-reported nature of the information on atopy. Nevertheless, the long-term follow-up demonstrated no association between immunization and asthma or atopic conditions into middle age.

A small study in France examined the association between vaccines received before age 6 months and asthma, allergic rhinitis, and eczema (Martignon et al., 2005). This was a retrospective cross-sectional study of 718 adolescents. Data on the three vaccines that were received before age 6 months were obtained from the pediatric record: bacillus Calmette-Guérin (BCG), diphtheria-tetanus-poliomyelitis, and pertussis vaccines. Live and inactivated vaccines were administered separately. Vaccinated adolescents were significantly less likely to have asthma, allergic rhinitis, and eczema than those who were not vaccinated. Although no association was found between an increase in cases of asthma, allergy, or eczema and immunization with the vaccines, the sample may have been too small to account for confounders, such as exposure to environmental tobacco smoke.

Benke et al. (2004) studied 4,500 young adults enrolled in a study in Australia in 1992 to determine whether childhood vaccines were associated with atopy and asthma in the cohort. Data on symptoms and vaccinations (including MMR, DTP, OPV, the hepatitis B [HepB] vaccine, and BCG) were collected by a mailed questionnaire. Atopy was measured directly by a skin test. Recall bias due to the collection of data via a mailed questionnaire was a limitation of this study. Overall, this study found no significant association between cumulative vaccinations and asthma.

McKeever et al. (2004) reported on a study of the relationship between vaccination and allergic disease, including asthma and wheezing, in the United Kingdom in individuals born from 1988 to 1999. The study had a retrospective observational cohort design and used the United Kingdom's General Practice Research Database (GPRD). The cohort included 29,238 children ages 0 to 11 years with at least a single visit to a general practitioner in the first 6 months of life. Outcomes examined were asthma, wheeze, and eczema. The analysis controlled for the frequency of physician visits ("consulting frequency"). They examined groups of vaccines and also the total number of vaccines in the recommended immunization schedule. Children diagnosed with allergy before full vaccination was completed

were excluded from part of the analysis. The authors found no relationship between age at the time of the first immunization with DTP or MMR and asthma or eczema and no relationship between the total number of immunizations and allergic diseases. A relationship was explained by ascertainment bias rather than a biological effect for the children with from zero to six office visits, who appeared to have a higher risk of a diagnosis of asthma. The study was limited by the small numbers of unvaccinated children and possible ascertainment bias (number of office visits). No association between vaccinations and allergic disease, including asthma, was found.

Gruber and colleagues (2003) conducted a prospective investigation of atopy among 7,609 infants born in Germany in 1990 and monitored to age 5 years. The objective was to determine prospectively if the number (percentile) of childhood immunizations was associated with atopy in 5-year-olds who had been identified to be a high-risk cohort (at least two family members had atopy and a detectable immunoglobulin E concentration of >0.9 kU/L at birth). Atopy was confirmed by clinical diagnosis. Vaccination history was by parental report. The study analyzed exposure to individual vaccines and the cumulative use of vaccines containing aluminum. Overall, the study reported a negative correlation between atopy and the cumulative number of vaccine doses received, including pertussis vaccine. The principal limitation was the self-reporting of vaccination history. However, the committee believes that this was a well-constructed and well-reported study and may serve as one example of a means by which the U.S. immunization schedule could be studied.

Four Studies of Pertussis Vaccine-Containing Vaccines

Spycher et al. (2009) studied the development of wheezing and asthma among 6,811 children born in the United Kingdom from 1993 to 1997 and monitored to 2003 in a population-based cohort study. Immunization data were obtained from the National Health Service database. Data on the outcomes of wheezing and asthma were collected from repeated questionnaire surveys. The analysis compared children with complete, partial, or no vaccination against pertussis with children who were immunized with the whole-cell pertussis vaccine included in DTP at the time. Limitations included the self-reported nature of the outcomes data by questionnaires and the fact that 96.9 percent of the children were fully immunized: very few children were not vaccinated or incompletely vaccinated. Overall, the authors found no association between vaccination against pertussis and asthma by age 7 years.

A retrospective, longitudinal study in Manitoba, Canada, reported in 2008 (McDonald et al., 2008) examined an association between the timing of immunization with DTP and the development of childhood asthma by

age 7 years. The study used data on asthma risk from health administration records and income data from Canada Census by neighborhood. Manitoba switched from the use of DTP to the use of diphtheria and tetanus toxoids acellular pertussis vaccine adsorbed (DTaP) in 1997; most of the approximately 14,000 children in that study had received DTP and not DTaP. The study reported a decrease in the incidence of asthma for each month of delay in the time of vaccination with the first dose of DTP. A similar but weaker association between the incidence of asthma and each month of delay was also found for the second dose of DTP. The study was limited by potential ascertainment bias: variations in the number of doctor visits; nonrandom reasons for a delay in DTP administration (e.g., because of fever, an infection might promote a T-helper type 1 response [antiviral] over a T-helper type 2 response [proallergy/asthma]); and variations in socioeconomic status. A prospective study of DTaP would be needed to confirm whether these findings can be repeated with DTaP.

A second longitudinal study in the United Kingdom (Maitra et al., 2004) examined the association between pertussis immunization and asthma or atopy by age 7.5 years in a large birth cohort of 13,971 children as part of the Avon Longitudinal Study of Parents and Children. The study used three approaches (symptoms, a doctor's diagnosis, and questionnaires) to identify children with asthma (symptoms reported by the parent or a doctor) via questionnaires. The aspect of the schedule covered in this study was immunization with DTP; the study differentiated between full, partial (diphtheria and tetanus toxoids [DT] but not pertussis vaccine), and no immunization. No association between asthma and pertussis immunization was found in children with a high cumulative prevalence of asthma.

Nilsson et al. (2003) reported on allergic disease in Sweden among 538 children at the age of 7 years after pertussis vaccination during infancy. This analysis was based on a follow-up study of a randomized controlled trial of three vaccines. The objective was to prospectively assess sensitization rates and the development of allergic diseases in a follow-up of children included in a randomized controlled trial of the pertussis vaccine. The group analyzed data from three randomized controlled trials evaluating differences in outcomes by age 7 years after immunization with DT or DT plus pertussis vaccine in a study with four arms: a two-component experimental pertussis vaccine, a five-component pertussis vaccine, a whole-cell pertussis vaccine, or no pertussis vaccine arm. All vaccines had aluminum phosphate as an adjuvant. Rigorous definitions of allergic disease were used, and skin tests of the children were used to demonstrate atopy. Compared with the DT vaccine, none of the three pertussis vaccines was a risk factor for the development of allergy in the first 7 years of life. The two-component pertussis experimental vaccine was associated with increased allergic symptoms after booster vaccination. This vaccine was not subsequently used. No relation-

ship between pertussis vaccines and atopic diseases was detected in children with a history of allergies.

Four Studies That Used Other Methods

One ecological study was done to examine trends in asthma prevalence and the recommended number of childhood immunizations (Enriquez et al., 2007). The group used National Health Interview Survey (NHIS) data on asthma, the timing of immunization, and the number of recommended immunizations by age 2 to determine whether increases in asthma prevalence paralleled trends in the number of immunizations recommended; however, the increase in the incidence of asthma reported in NHIS preceded the increase in the recommended number of vaccines. This information did not support a relationship between the recommended number of childhood immunizations and the increase in the prevalence of asthma and, in fact, provided evidence of no association.

Mullooly et al. (2007) used a case-control study of 6- to 16-year-olds in an allergy clinic with proven new allergic conditions to determine whether the receipt of immunizations or oral antibiotics in the first 2 years of life affected the odds that they would have atopy (measured by skin test). Compared with the control subjects, atopy cases received fewer antigen doses and fewer different antigens, had less exposure to *Haemophilus influenzae* type b conjugate vaccine (Hib), and received fewer doses of the Hib and mumps and rubella vaccines during the first 2 years of life. The study was limited by the fact that data on immunizations and other variables (e.g., family history of atopy, smoking in the home) were collected by retrospective medical record review. Their power to detect associations was also limited by the fact that only 21 percent of eligible allergy patients could be classified as non-atopic, leaving 79 percent as atopic study subjects. Finally, there was limited variation in vaccine exposure, further reducing the power to detect differences. Nevertheless, despite limited statistical power, this study found no association between atopy and vaccine exposure.

Maher et al. (2004) conducted a follow-up of a cohort previously enrolled in a study performed by a U.S.-managed care organization (MCO) as part of the Vaccine Safety Datalink (VSD) project. The analysis examined the association between immunizations and asthma among 1,778 children enrolled from 1991 to 1994. The original study used a matched-pair case-control method. Five vaccines were included: HepB, whole-cell pertussis vaccine, Hib, OPV, and MMR. The analysis was limited by the high rate of vaccine coverage and the small sample size. Childhood immunizations were not associated with asthma by age 5 years, but asthma was related to wheezing episodes in infancy. This study provides useful evidence of no association between vaccinations and asthma.

Bremner et al. (2005) examined the association between allergic rhinitis ("hay fever") and MMR, DTP, and BCG immunization. The study used a case-control design and data from GPRD and the Doctors Independent Network primary care database in the United Kingdom. Children who had been immunized with MMR and DTP did not have greater odds of being diagnosed with hay fever than those who were unvaccinated. Slightly decreased odds of a diagnosis of hay fever in association with delayed DTP administration were detected, however. The researchers suggested that it is possible that an immunization delay in some children is associated with febrile illness. Infectious illness in early childhood could potentially protect against the development of atopy, and the association with delayed immunization with DTP needs further investigation. The small number of children who received BCG had slightly increased odds of having hay fever. The study was limited by the source of the outcomes data, which were based on medical records in which the International Classification of Diseases, revision 9, code for allergic rhinitis was used and medicines commonly prescribed for hay fever were listed. The study has limited value for interpretation of the safety of the U.S. immunization schedule, as the researchers were examining the association between allergic rhinitis and separate vaccines, and neither DTP nor BCG is currently recommended for U.S. children.

In summary, research examining the association between the cumulative number of vaccines received and the timing of vaccination and asthma, atopy, and allergy has been limited; the findings from the research that has been conducted are reassuring, however. No data have demonstrated harm (an increased risk of atopy) from immunizations. Indeed, the opposite may be the case. No evidence is available from studies that have directly examined the current immunization schedule (most studies enrolled children in the 1990s, and most were not conducted in the United States), but no studies suggest harm (e.g., an accelerated or increased likelihood of the development of asthma or atopic diseases). The single study finding an association between age at the time of immunization with the first whole-cell pertussis-containing vaccine and a later diagnosis of asthma (McDonald et al., 2008) has not been extended to examine acellular pertussis vaccine. One publication (Thomson et al., 2010) noted the importance of confounding infectious episodes, especially gastroenteritis, suggesting that childhood infections (a target for future effective vaccines) and not childhood immunizations are associated with asthma.

Autoimmune Diseases

Fifty papers describing studies of a relationship between immunization or vaccines and autoimmune diseases were identified in the initial search.

This list was reduced to six papers after the exclusion criteria described above were used. After further review, four of the papers were believed to focus on some aspect of the immunization schedule and were selected for a more in-depth review.

A study of five U.S. MCOs involving 1.8 million children evaluated the risk of development of immune thrombocytopenic purpura (ITP) after immunization with childhood vaccines other than MMR (O'Leary et al., 2012). The study involved a self-controlled case series and was able to confirm an association between ITP and MMR. It found no increased risk of ITP after immunization with vaccines other than MMR in young children but did find an association between ITP and immunization with HepA; tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed; and varicella vaccine in older children. However, because of the small number of reports of ITP and potential confounders, the researchers concluded that further investigation is needed. A limitation of this study was that ITP is a rare adverse event, and it is difficult to examine the risk of ITP in association with immunization with other vaccines independently when these vaccines are routinely given at the same time as MMR, which has been determined to be one possible cause of rare cases of ITP (IOM, 1994).

Yong et al. (2010) used data from the United Kingdom GPRD to assess the incidence of ITP in the pediatric population in the United Kingdom and to compare the incidence of ITP in children with that in adults in a large population-based study. The researchers examined the evidence of infection and a history of immunization among pediatric patients with ITP, focusing on infections recorded within 8 weeks and immunizations recorded within 6 weeks before the first recorded diagnosis of ITP. A limitation of this study was that the investigators identified cases of infection through computerized records instead of the questionnaires used in other studies, which may have failed to capture a number of mild infections that did not lead to prompt contact with a physician.

Hviid and colleagues (2004) evaluated whether a link exists between childhood vaccinations and the development of type 1 diabetes using data from a cohort of children born between 1990 and 2000. The researchers used Danish data and estimated rates of type 1 diabetes according to vaccination status, including the type and number of doses, among all children and a subgroup of children who had a sibling with type 1 diabetes. Rate ratios were also estimated for the period from 2 to 4 years after vaccination. During the time period of the study, the schedule varied with the introduction of Hib from 1993 to 1995, when it was administered at 5, 6, and 16 months of age, but administration of Hib was then changed to 5, 6, and 15 months of age starting in 1996 and 3, 5, and 12 months of age starting in 1997. The combined diphtheria, tetanus, and inactivated poliovirus vaccine

was given at ages 5, 6, and 15 months until 1996, and a whole-cell pertussis vaccine was given separately at 5 weeks (half-dose), 9 weeks, and 10 months of age. In 1997, the pertussis vaccine was modified to the acellular pertussis vaccine, which was incorporated into the diphtheria, tetanus, and inactivated poliovirus vaccine. The schedule of the combined vaccine was modified to be given at 3, 5, and 12 months of age. Boosters of oral polio vaccine were given at 2, 3, and 4 years of age. The study evaluated 739,694 children for 4,720,517 person years of follow-up. Overall, 681 cases of type 1 diabetes were identified from the Danish National Hospital Register, 26 of whom (4,208 person years) had a sibling with type 1 diabetes. This study found no association between childhood vaccination and the development of type 1 diabetes, even among children who had a sibling with diabetes. A limitation noted by the authors was the use of the Danish National Hospital Register rather than the National Diabetes Registry, which goes back only to 1996, to make sure that they had large enough numbers of children for analysis. A strength of the study is that it was a nationwide cohort with longitudinal, individual-level information on vaccinations and type 1 diabetes incidence, minimizing selection and recall bias.

Verstraeten and colleagues (2008) performed an integrated analysis of studies performed internationally to assess the safety of vaccines containing the AS04 adjuvant according to the incidence of adverse events of potential autoimmune etiology, particularly in adolescents and young adults. The study compared recipients who received vaccines with the AS04 adjuvant and a control group who received nonadjuvanted vaccine (i.e., control), vaccines with aluminum adjuvant, or aluminum hydroxide alone. Overall, the rate of reporting of autoimmune disorders was low, with an event rate of approximately 0.5 percent which did not differ between the groups receiving vaccines with the AS04 adjuvant and the control groups

The distribution of the reports by category did not suggest unusual patterns of autoimmune disorders. The authors concluded that these analyses do not suggest any statistically significant association between the development of autoimmune disorders and immunization with AS04-adjuvanted vaccines. This conclusion reinforces other reports in the literature concluding that no evidence exists for an association between autoimmune disorders and most vaccines. Limitations of the analysis mainly included a lack of validation of each diagnosis, which relied on investigator reports, and variability in the collection of adverse event data between studies (Verstraeten et al., 2008).

In summary, the literature that the committee found to examine the relationship between the overall immunization schedule and autoimmunity was limited. The evidence from a single large Danish study for diabetes is reassuring because it did not detect a relationship between the immunization schedule and autoimmunity. Evidence for ITP confirms prior evidence

of an association with immunization with MMR and is not clear about immunization with other vaccines.

Autism

The initial literature search identified 32 papers on the relationship between immunizations or vaccines and pervasive developmental disorder (PDD), which includes the diagnoses autistic spectrum disorder, autism, and Asperger's syndrome. After an initial review, a team of two IOM committee members determined that 12 papers focused on some aspect of the immunization schedule. Three of the papers either addressed only one vaccine or had methodological limitations. The other nine studies examined the association between thimerosal and autism and other neurodevelopmental problems (Andrews et al., 2004; Fombonne et al., 2006; Geier and Geier, 2003, 2004a,b, 2006; Hviid et al., 2003; Madsen et al., 2003; Young et al., 2008). Five of the studies had serious methodological limitations and were not helpful with examination of the association between thimerosal and vaccines. Each of the other four papers might help with a study of the schedule.

Fombonne et al. (2006) examined the prevalence of PDD in relation to two aspects of the immunization schedule in Canada: cumulative thimerosal dose and a change in the MMR schedule from one to two doses in birth cohorts from 1987 to 1998. Thimerosal was eliminated in 1996, and a second MMR (administered at age 18 months) was added to the schedule in 1996. Data on autism were from school records. Vaccine data were in part from a registry and in part from provider records. The dose of thimerosal was calculated from the recommended immunization schedule by year (not the dose received by individual children). A continuous increase in the incidence of PDD occurred over time, despite the elimination of thimerosal, and a decrease in MMR coverage was also detected. The increased rate of PDD was the same before and after the addition of a second required dose of MMR. The study was limited by reliance on administrative codes for the diagnosis of PDD. The study was also conducted in one school board (district), and some PDD cases may have moved into that board, which would have inflated the numbers. This was an ecological study, but the data were interpreted carefully and the differences in appropriate trends were noted.

Andrews et al. (2004) used the United Kingdom GPRD to evaluate the risk of a variety of neurodevelopmental disorders, including autism, tics, speech and language delay, attention deficit disorder, and other developmental delays, in association with the calculated cumulative exposure to thimerosal to up to 4 months of age in more than 100,000 children born between 1988 and 1997. The retrospective cohort study found no evidence for an increased risk of neurodevelopmental disorders, with the possible

exception of tics, in association with thimerosal exposure. For general developmental disorders, unspecified developmental delay, and attention deficit disorder, increasing thimerosal exposure had an apparent protective effect. Although the study was limited by an inability to adjust for several confounding factors, such as socioeconomic status and other medical conditions, in general, it had a sound methodology. GPRD is a good source of linked data that may be used to look at other aspects of the vaccination schedule in the United Kingdom. The aspect of the schedule covered by this study included the cumulative doses of thimerosal received by children immunized with DTP and DT and whether these were received, for example, on time or late.

Two studies examined aspects of the Danish immunization schedule. Hviid et al. (2003) studied the relationship between cumulative thimerosal exposure via the whole-cell pertussis vaccine and autistic spectrum disorder. The study included a cohort of children with a diagnosis of autistic spectrum disorder born between 1990 and 1996. The diagnoses were taken from the Danish Psychiatric Central Research Registry and linked with the immunization history of each child. The study covered a period (1990 to 1992) when only one thimerosal-containing vaccine was in use. The study found no association between a diagnosis of autism and the presence of thimerosal but noted that the incidence of autism may have been underascertained, especially in earlier birth cohorts. This study did not demonstrate a relationship between thimerosal administration via the pertussis vaccine and the development of autism in a small country (Denmark) with high immunization rates and a good system of record keeping. The only aspect of the schedule covered was thimerosal exposure specifically via the pertussis vaccine.

The other Danish study evaluating an association between immunization and PDD (Madsen et al., 2003) also used data from the Danish Psychiatric Central Research Registry. The authors sought to evaluate the vaccine history for all Danish children identified with autism between 1971 and 2000 to assess the incidence of autism among children between 2 and 10 years of age before and after the removal of thimerosal from vaccines in 1992. The annual incidence of autism increased rapidly starting in 1990 and continued to do so through 1999, even though thimerosal was eliminated from DTP in 1992. The study was limited, as was the study by Hviid et al. (2003), by the fact that before 1995, diagnoses of autism were made only for hospitalized patients, whereas after 1995, outpatient diagnoses of autism were included. This study failed to demonstrate a correlation between the discontinuation of thimerosal in DTP and the incidence of autism in Danish children. This was an ecological study and so it cannot confirm an association. The paper provided no real information about the immunization schedule.

In summary, the evidence of an association between autism and the overall immunization schedule is limited both in quantity and in quality and does not suggest a causal association. The committee found the literature to be most useful in suggesting study designs that might be adapted and extended for the committee's core task of suggesting further research.

Other Neurodevelopmental Disorders

Forty-one papers concerning a relationship among immunizations, immunization schedule, or vaccines and learning disorders, communication disorders, developmental disorders, intellectual disability, attention deficit disorder, disruptive behavior disorders, tics, and Tourette's syndrome were identified via an Ovid MEDLINE database search. This list was reduced to eight papers after use of the exclusion criteria described above, including exclusion of papers on vaccines not currently recommended for administration to children under age 6 years. After an initial review, five of the papers were believed to focus on some aspect of the immunization schedule and were selected for more in-depth review. Each of these five studies focused on possible adverse effects of thimerosal (given via different schedules). Importantly, with the exception of the influenza vaccine, since 2001 thimerosal has been either removed from or substantially reduced in amount in vaccines given to U.S. children under 6 years of age. Although thimerosal is no longer a component of U.S. childhood vaccines, these studies may suggest methods to study variations due to use of alternative schedules, or to changes to the recommended immunization schedule made over time. The committee identified a sixth study through its second search effort.

A study conducted by Tozzi et al. (2009) in Italy also evaluated the effects of different doses of thimerosal during infancy on neurodevelopmental outcomes. These investigators conducted a late follow-up evaluation at 10 to 12 years of age of subjects who were initially enrolled in a study of the efficacies of two formulations of pertussis vaccine that contained different amounts of thimerosal. Twenty-four neurodevelopmental outcomes were measured via 11 standardized tests. Only two statistically significant differences, which were believed not to have been clinically significant, were noted in the female subjects. Specifically, girls with higher thimerosal exposure had lower mean scores in the Boston Naming Test and on finger tapping with the dominant hand. Given the large number of comparisons, these significant differences could be attributable to chance. In this study, the cumulative dose of thimerosal was low compared with the doses that had been used in the United States.

In a cohort study of 1,047 subjects enrolled in three MCOs as part of the VSD, Thompson et al. (2007) evaluated the effects of cumulative exposure to thimerosal on 42 neurodevelopmental outcome measures (excluding

autism). The subjects were between 7 and 10 years of age. Immunization status was retrospectively assessed, and the assessment included exposure to thimerosal both prenatally (via maternal immunization or immunoglobulin administration) and then during the first 7 months of life. Few significant associations between cumulative thimerosal exposure and a particular neurodevelopmental outcome were noted. These associations were few in number and were equally divided between positive and negative effects. Most were gender specific. For example, in boys, higher exposure to thimerosal prenatally was associated with a higher score on the Stanford-Binet copying test and a lower score on the Wechsler Intelligence Scale for Children III (WISC-III) digit-span test of backward recall. In girls, higher thimerosal exposure at between birth and 7 months of age was associated with a better performance on the Grooved Pegboard Test in the nondominant hand as well as on the WISC-III digit-span test of backward recall. Although this study was limited by only a 30 percent participation rate, which may have resulted in selection bias, it failed to demonstrate a causal association between early exposure to mercury via thimerosal-containing vaccines or immunoglobulins and neurodevelopment.

Smith and Woods (2010) used secondary data from the VSD cohort study of Thompson et al. (2007) to determine if on-time immunization by 1 year of age was associated with neuropsychological outcomes. The researchers performed two analyses using immunization and outcomes data from the VSD. The first analysis compared children who had received all vaccinations on time with those who had not. Complete immunization was defined as having received within 30 days of the recommended age at least two doses of HepB, three doses of DTaP, three doses of Hib, and two doses of polio vaccine (referred to as the 2:3:3:2 series) during the first year of life. The second analysis stratified children into five groups by age at the time of completion of the 2:3:3:2 series. Children with on-time immunizations consisted of those who received at least 10 vaccinations in the first 7 months of life, whereas the least vaccinated group comprised those who had received less than seven vaccine doses of any type during the same time period. Using the outcomes data obtained from the research of Thompson et al. (2007), Smith and Woods (2010) found that children who had received their immunizations on time and also those who had received at least 10 doses did not have better neuropsychological outcomes in this study than those who had received fewer doses, and no significant differences were found between those who received the least vaccines and those with the greatest vaccine exposure during the first 7 months of life.

In a cohort study conducted in Brazil, Marques et al. (2007) evaluated the effects of thimerosal exposure during the neonatal period on neurodevelopment measured by use of the Gesell battery of tests at 6 months of age. In their study, 84 infants were immunized with a thimerosal-containing

HepB either on the day of birth or later in the neonatal period (between days 2 and 4 of life). Before the neurodevelopmental assessments at 6 months of age, these infants also received additional doses of vaccines containing thimerosal (two doses of HepB and three doses of DTP). The researchers did not report any difference in neurodevelopmental measures between the two groups. In addition to the small sample size, this research focused on a minimal alteration in the immunization schedule that may have been so minor that an effect on neurodevelopment would not be expected.

In a longitudinal study of 14,000 infants in the United Kingdom, Heron et al. (2004) evaluated the relationship between cumulative exposure to thimerosal and several neurodevelopmental outcomes, including behavioral difficulties, tics, deficits in speech and fine motor development, and other "special needs." At the time of this study, thimerosal-containing vaccines were administered in the United Kingdom at 2, 3, and 4 months of age, which represents an accelerated schedule of exposure compared with the schedule used in the United States. This study evaluated 69 specific behavioral and developmental outcomes via questionnaires that were sent to the parents of children born over a 15-month interval during 1991 and 1992. Only one outcome (poor prosocial behavior) was found to be associated with cumulative thimerosal exposure at 3 months of age. Interestingly, this study demonstrated that adverse neurodevelopmental outcomes were less likely in children who had higher thimerosal exposures.

In another VSD study, Verstraeten et al. (2003) also evaluated the association between the cumulative exposure to thimerosal at 1, 3, and 7 months of age and neurodevelopmental disorders such as autism, other speech and language disorders, disorders of attention, and tics. This was a large retrospective cohort study of subjects from three MCOs that participated in the VSD. In Phase 1 of the study, data from two MCOs were analyzed. A positive association between cumulative thimerosal exposure and the development of tics was found for subjects from one MCO, whereas a positive association with language delay was found for subjects from the other MCO. In Phase 2 of the study, the most common associations seen in Phase 1 were evaluated in a third MCO, and no significant associations were demonstrated. Therefore, no consistent significant association between cumulative thimerosal exposure and neurodevelopmental outcomes was found. Importantly, in no instance was a significant risk of cumulative thimerosal exposure and either autism or disorders of attention detected. This study was limited, as the investigators evaluated thimerosal only as opposed to the type of vaccine. Neurodevelopmental outcomes for the subjects were determined only by medical record designations (codes) and not by a review of the results of formal neuropsychological assessments.

In summary, the evidence regarding an association between the overall immunization schedule and other neurodevelopmental disorders is limited

in quantity and of limited usefulness because of its focus on a preservative no longer used in the United States.

Seizures, Febrile Seizures, and Epilepsy

Fifty-eight papers of studies of the association among immunizations, immunization schedule, or vaccines and seizures, epilepsy, or febrile seizure were identified via an Ovid MEDLINE search. This list was then reduced to 14 papers. After an initial review, four of the papers were believed to focus on some aspect of the immunization schedule and were selected for a more in-depth review.

A study from Denmark by Sun and colleagues (2012) determined the risk of cumulative doses of combined DTaP-inactivated poliovirus vaccine (IPV)-Hib on the development of both febrile seizures and the later development of epilepsy as well as the risk of these adverse events after pneumococcal vaccine was added to the combined DTaP-IPV-Hib. This was a self-controlled case series study based on children with febrile seizures during follow-up of the cohort. In Denmark, DTaP-IPV was introduced in 1997, Hib was added in September 2002, and pneumococcal vaccine was added in October 2007. Data were collected from January 1, 2003, to December 31, 2008, and the immunization schedule that was evaluated included vaccine administration at 3, 5, and 12 months of age. The analysis did not include the 5-year booster immunization. Compared with a reference cohort of children who were not within 0 to 7 days of receiving an immunization, the increased risk of febrile seizure on the day of immunization only (but not between days 0 and 7 after immunization) was minimal after the first or second dose of combined DTaP-IPV-Hib vaccine but not after the third dose. The overall incidence of febrile seizures in these cohorts was small. The vaccinated group had a lower risk of developing epilepsy in the first 15 months of life than the reference cohort of children did, whereas the risk of epilepsy later in life was unchanged. The estimates did not change when pneumococcal vaccine was added to the vaccination program. It is not clear why the immunized children had a decreased risk of epilepsy. This may have been due to unmeasured confounding factors, as the investigators did not address whether children with a high risk of developing febrile seizures or epilepsy (such as children with preexisting neurological disorders) were less likely to have been vaccinated.

A VSD surveillance study by Klein et al. (2010) evaluated the risk of development of febrile seizures after children received the combined measles, mumps, rubella, and varicella (MMRV) vaccine, MMR plus the varicella vaccine, MMR alone, or the varicella vaccine alone. The investigators compared the incidence of evaluations for seizures in the emergency department or hospital and for fever in the clinic that occurred in patients at between 12

and 23 months of age within 42 days of receiving any "measles-containing vaccine" as well as the varicella vaccine (either as a component of the measles vaccine, at the same time as the measles vaccine, or at a different time). The investigators determined that both MMRV and MMR, but not the varicella vaccine alone, are associated with increased outpatient visits for fever and seizures 7 to 10 days after vaccination, with MMRV increasing the risk of fever and seizures twice as much as MMR plus the varicella vaccine. A limitation of this study was that the cases of febrile seizure were determined by the presence of *International Classification of Diseases, Ninth Revision,* codes for febrile seizure within the medical record. This may have somewhat overestimated the risk of this adverse event.

Another VSD study (Tse et al., 2012) investigated the risk of febrile seizures that followed the receipt of trivalent inactivated influenza vaccine (TIV) which was administered during the 2010-2011 influenza season. The investigators conducted surveillance of adverse events in children between the ages of 6 and 59 months of age who had received a first dose of TIV. Cases of febrile seizures were identified through the analysis of ICD-9 codes and chart review, specifically for patients presenting to emergency departments or those who were hospitalized. In mid-November 2010, a signal was detected that indicated an increased risk of febrile seizures occurring between 0 and 1 days following the first dose of TIV. However, further analysis demonstrated that the risk of febrile seizure was higher after the concomitant administration of both TIV and 13-valent pneumococcal conjugate vaccine (PCV13) compared with the additive risk of febrile seizure after receiving either TIV or PCV13 alone. This risk was highest in children vaccinated at 16 months of age, which is not surprising as studies of the natural history of febrile seizures indicate that the background risk is greatest around this age and progressively falls off in older children. Limitations of this study were that the investigators did not evaluate the possible effects of the concomitant administration of other vaccines (such as DTaP), and due to limited information about attributable causes, the investigators were not able to exclude cases who had intercurrent infections as the cause of the febrile seizure. Importantly, given the results of this study, the vaccine information statement for TIV was updated for the 2011-2012 influenza season to include a statement about the possible increased risk of febrile seizure in young children who concomitantly receive both TIV and PCV13 (CDC, 2012).

A study conducted in The Netherlands (David et al., 2008) evaluated the frequency of adverse events that occurred after infants received pertussis vaccine. In The Netherlands, infants receive this vaccine at 2, 3, 4, and 11 months of age. The study compared the adverse events that occurred after patients received whole-cell pertussis vaccine, acellular pertussis vaccine, or acellular pertussis vaccine along with pneumococcal vaccine. The data were

acquired from 28,796 of approximately 53,000 questionnaires distributed to parents. The risks of prolonged crying, pallor, high fever, and "fits and jerks" were significantly reduced when the whole-cell pertussis vaccine was replaced by the acellular vaccine. The authors point out that although "fits and jerks" was meant to be an indicator for "seizures," upon review of their data, it was apparent that this category mainly included chills, shivering, jitteriness, and myoclonus. Possible febrile seizures were noted only after the fourth dose of vaccine, with only two cases occurring in the group receiving the whole-cell pertussis vaccine and one case occurring in the group receiving the acellular pertussis vaccine. This was not a statistically significant finding. The addition of pneumococcal vaccine to the schedule did not change the risk of any adverse events. This study was limited by the 54 percent questionnaire return rate, with a probable bias of an increased rate of return from parents of children who had had reactions. In addition, some at-risk children (children of mothers with hepatitis B) received HepB at the same time as pertussis vaccine, but this clinical feature was not factored into the analysis.

In summary, the literature associating the overall immunization schedule with seizures, febrile seizures, and epilepsy is limited and inconclusive. With the exception of the study suggesting the increased risk of febrile seizure after concomitant TIV and PCV13 immunization (Tse et al., 2012), there is no suggestion of a causal relationship between the administration of multiple vaccines and a single seizure or the later development of epilepsy.

Immunization of Premature Infants

The committee reviewed six papers on the immunization of premature infants published since 2002. Five papers examined postvaccination cardiorespiratory events, and two papers examined C-reactive protein levels following the immunizations at 2 months of age. All papers included at least some very premature infants (≤32 weeks of gestation), all examined aspects of the vaccines scheduled to be delivered at 2 months of age, and two reviewed longer-term effects. Because small numbers of infants were monitored for short periods of time, it is challenging to draw conclusions from this review. An increased risk of cardiorespiratory events after vaccination may exist, especially in infants with prior septicemia and the need for continuous positive airway pressure for a longer period of time earlier in their lives. The authors of several papers proposed that some infants be monitored in a hospital after the first and perhaps the second round of immunizations, but the authors had no consensus on how to identify which infants born prematurely are the most likely to benefit from monitoring. They did note, however, that risk factors include lower birth weight, ongoing complications, and underlying medical conditions.

CONCLUSIONS

The committee conducted a review directed by conventional electronic searches of the peer-reviewed literature, findings from searches conducted by committee members, committee member expertise, committee discussions, and information from public presentations at open committee meetings.

The committee's review confirmed that research on immunization safety has mostly developed around studies examining potential associations between individual vaccines and single outcomes. Few studies have attempted more global assessments of entire sequence of immunizations or variations in the overall immunization schedule and categories of health outcomes, and none has squarely examined the issue of health outcomes and stakeholder concerns in quite the way that the committee was asked to do in its statement of task. None has compared entirely unimmunized populations with those fully immunized for the health outcomes of concern to stakeholders.

Queries of experts who addressed the committee in open session did not point toward a body of evidence that had been overlooked but, rather, pointed toward the fact that the research conducted to date has generally not been conceived with the overall immunization schedule in mind.

The available evidence is reassuring, but it is also fragmentary and inconclusive on many issues. Nevertheless, the committee found in its literature review useful perspectives on how to define exposures and outcomes and how conventional study designs might be expanded and adapted to more clearly address the question of health outcomes after immunization with the overall immunization schedule.

A challenge to the committee in its review of the scientific literature was uncertainty as to whether studies published in the scientific literature have addressed all health outcomes and safety concerns. The field needs valid and accepted metrics of the entire schedule (the "exposure") and clearer definitions of the health outcomes linked to stakeholder concerns (the "outcomes") in research that is sufficiently funded to ensure the collection of a large quantity of high-quality data.

Recommendation 5-1: To improve the utility of studies of the entire childhood immunization schedule, the committee recommends that the National Vaccine Program Office develop a framework that clarifies and standardizes definitions of

- **key elements of the schedule,**
- **relevant health outcomes, and**
- **populations that are potentially susceptible to adverse events.**

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6

Methodological Approaches to Studying Health Outcomes Associated with the Current Immunization Schedule: Options, Feasibility, Ethical Issues, and Priorities

The current immunization schedule recommended by the Advisory Committee on Immunization Practices (ACIP) was developed after consideration of the safety and effectiveness of the component vaccines and the burden of the infectious diseases on the population targeted by each vaccine. The Food and Drug Administration's (FDA's) current protocol for approval of new vaccines requires an evaluation of the effect of administration of a new vaccine along with other vaccines within the preexisting schedule. Therefore, the burden of disease and evidence of adequate immunogenicity when vaccines are administered together with existing recommended vaccines are established at the time of FDA approval and development of a recommendation by the ACIP. Although the committee's review of the available scientific evidence revealed that no potential adverse health outcomes that may occur after immunization with the recommended immunization schedule rose to a level of concern or biological plausibility sufficient to justify a strong recommendation for immediate study, the committee was asked to recommend methodological approaches that could be implemented should the need arise.

To fulfill its appointed charge, the committee deliberated on five distinct topics to meet the requirements of its statement of task: (1) factors that should be used to determine that new research is needed; (2) major stakeholder concerns that the committee identified; (3) epidemiological evidence on the health effects of the current schedule; (4) major stakeholder concerns and available epidemiological evidence recast into testable research questions; and (5) possible research approaches to address priority research questions.

CONSIDERATIONS TO DETERMINE NEED FOR INITIATION OF NEW STUDIES

As discussed in Chapter 5, the committee noted that limited published data do not provide evidence that the recommended immunization schedule is associated with safety or health risks. Indeed, the available epidemiological data repeatedly indicate the health benefits associated with the recommended schedule (e.g., reduced infections and hospitalizations).

To undertake new studies on the immunization schedule beyond analyses with existing data from surveillance systems, researchers will need to carefully consider the current evidence, both epidemiological and biological, that supports the plausibility of their hypotheses. The decision to initiate further studies should depend on the results of an evaluation of three considerations that the committee identified through its review of stakeholder concerns and scientific findings:

1. epidemiological evidence of potential adverse health outcomes associated with elements of the immunization schedule (such as postmarketing signals or indications of an elevated risk from observational or experimental studies);
2. biological plausibility supporting hypotheses linking specific aspects of the immunization schedule with particular adverse health outcomes; and
3. expressed concerns from some stakeholders about the immunization schedule's safety, which should support efforts to evaluate the previous two considerations.

Currently, the U.S. Department of Health and Human Services (HHS) considers these criteria before initiating new studies through the Vaccine Safety Datalink (VSD). As discussed in Chapter 3, the Vaccine Adverse Event Reporting System (VAERS) allows parents and providers to report suspected adverse events after immunization. If an association is suspected on the basis of these signals, medical experts in the Clinical Immunization Safety Assessment (CISA) Network evaluate the pathophysiological basis of the suspected event. Researchers may also conduct, using VSD, population-based epidemiological studies on the basis of signals reported through VAERS and conclusions about biological plausibility reported by the CISA Network.

The committee concluded that stakeholder concerns have a role in guiding the research priorities of the Centers for Disease Control and Prevention (CDC), FDA, the National Institutes of Health, and the National Vaccine Program Office because they may point to potential research questions that need to be validated from their epidemiological signals and the plausibil-

ity of the suggested biological pathways. Given the safeguards already in place, stakeholder concerns alone are not sufficient reason to embark on costly clinical research, such as new randomized controlled trials (RCTs) or prospective cohort studies, without the existence of supporting signals or evidence of biological plausibility.

Recommendation 6-1: The committee recommends that the Department of Health and Human Services incorporate study of the safety of the overall childhood immunization schedule into its processes for setting priorities for research, recognizing stakeholder concerns, and establishing the priorities on the basis of epidemiological evidence, biological plausibility, and feasibility.

Animal Models

Animal models play a critical role in preclinical studies during development of all medications, including vaccines (Kanesa-thasan et al., 2011). For example, rats and mice are used for investigations into fundamental basic science issues to establish ranges of dosing, to explore immunogenicity, and even to provide perspectives on some clinical outcomes. Studies of acute toxicity, tolerability, and causes of fever have been performed in guinea pigs and rabbits (Kanesa-thasan et al., 2011). Subsequent studies of safety may be carried out in rats or primates, as appropriate (Kanesa-thasan et al., 2011). Animal models may also be useful for studies exploring novel vaccines, the extent of interference with vaccine immunogenicity by concurrently administered vaccines, and the bactericidal qualities of antibodies. In its review of the existing evidence of the immunization schedule and safety, the committee did not explicitly review mechanistic evidence for any health outcomes, such as case studies or existing animal models, and instead points to the excellent work of previous committees in their reviews of individual vaccines (IOM, 2002, 2012). However, various stakeholders expressed interest in the potential use of animal models, and the committee therefore also considered the potential of studies with animal models of disease to advance knowledge of the biological mechanisms by which the childhood immunization schedule might be associated with adverse events.

To use animal models for the biological study of the recommended immunization schedule, however, many challenges must be overcome and limitations must be appreciated. For example, if one is interested in events that are purported to occur long after vaccine administration, such as asthma or food allergy, one must establish the generalizability of animal models of those diseases to the human context. Furthermore, spontaneously occurring models of diseases in animals would have to be developed before

studies exploring the safety of the aggregate immunization schedule could be performed.

To the committee's knowledge, realistic animal models that could provide information on the potential of long-term health outcomes of the full immunization schedule in humans are not available. Furthermore, an assessment of the long-term effects of multiple immunizations in, for example, rats 3 months after they receive those immunizations would not be applicable to humans because the onset of such chronic diseases takes years to arise in humans.

An example of an animal model is the model of allergic hypersensitivity to dust mites and *Ascaris* in monkeys, which has resulted in studies of asthma (Hogan et al., 1994). However, few such primate colonies with relevance to asthma in humans exist. Furthermore, the cost to establish and maintain a primate colony is extremely high, and the availability of allergic monkeys is therefore extremely limited.

In the absence of animal models of the spontaneous onset of chronic diseases such as Guillain-Barré syndrome, studies of the effects of multiple vaccinations on aspects of airway hyperreactivity in mice or monkeys could be performed, but such studies would be limited in their ability to answer questions about the aggregate immunization schedule.

The key limitation to the use of animal models for evaluation of the immunization schedule therefore is not the availability of science or resources but the limited ability of models to produce results generalizable to the human experience. Given the committee's recognition of the complexity of the immunization schedule, the importance of family history, the role of individual immunologic factors, and the complex interaction of immunization with the health care system, the committee determined that it would be more appropriate to focus future research efforts on human research rather than research involving animal models.

In summary, it is not possible to recommend studies with animals to inform the notion that the aggregate childhood immunization schedule results in the onset of chronic diseases. The committee also recognized the role of animal models in understanding neurological diseases, which have made important contributions to the understanding of disease processes that affect the brain in terms of structural or motor changes, such as seizures. In addition to the limitations described above in relation to chronic diseases, the study of neurological diseases such as autism has limited use for animal models since "no animal embodies the repertoire of behaviors seen in the human, and in particular, no animal has language equivalent to that of the human" (IOM, 2012, p. 86). Thus, there are sizable barriers in using animal models to assess such neurological outcomes following administration of the childhood immunization schedule.

POTENTIAL RESEARCH QUESTIONS OF INTEREST

The complexity of the current immunization schedule, which includes variables such as the number of doses, the age of administration, and the time between doses, permits the examination of a large number of potential research questions. Nevertheless, the committee noted a general lack of consistent and integrated theories of biological mechanisms or pathways that link specific elements of the immunization schedule to specific health conditions in the vaccinated child.

Perhaps the most compelling hypothesis is that introduction of an excess of immune-stimulating agents into an immature or dysregulated immune system might result in a cascade of adverse immunological processes culminating in asthma, allergies, autoimmune disorders, and the like. Nevertheless, the biological evidence to support this line of reasoning was examined by an Institute of Medicine committee in 2002 as part of the *Immunization Safety Review* series, and that examination found no more than weak justification for such a hypothesis (IOM, 2002).

Likewise, the committee's review of existing epidemiological studies of the immunization schedule was complicated by the effectively infinite number of variations for delivery of the recommended childhood immunization schedule that could be investigated. The literature summarized in Chapter 5 reflects the range of approaches that have been used to characterize departures from the recommended schedule, and no single approach prevailed across multiple investigations.

The committee struggled in its efforts to identify research questions that could be posed to evaluate the health outcomes after immunization with the recommended childhood immunization schedule because of a lack of well-defined exposures and biologically plausible outcomes. Thus, the primary research questions of interest that the committee identified and that are listed below are broad and most likely too general to be readily translated into new research studies, unless biologically plausible hypotheses emerge.

Among the many questions about the current immunization schedule that could be posed, the committee identified what it viewed to be the leading research questions of interest on the basis of a review of stakeholder concerns. The committee parsed the phrase "this question" in Part 2 of the statement of task into four broad research questions. These questions are listed in Box 6-1.

The committee identified other potential gaps in research on the larger health care delivery system and policy-setting procedures that influence parents' knowledge of and decisions about their immunization choices for their children. For example, several stakeholders identified the need for additional research on effective provider-patient communications on the risks and benefits of vaccinations. Others suggested the value of additional re-

BOX 6-1
Leading Research Questions of Interest to Select Stakeholders

1. How do child health outcomes compare between those who receive no vaccinations and those who receive the full currently recommended immunization schedule?
2. How do child health outcomes compare between (a) those who receive the full currently recommended immunization schedule and (b) those who omit specific vaccines?
3. For children who receive the currently recommended immunization schedule, do short- or long-term health outcomes differ for those who receive fewer immunizations per visit (e.g., when immunizations are spread out over multiple occasions), or for those who receive their immunizations at later ages but still within the recommended ranges?
4. Do potentially susceptible subpopulations—for example, children from families with a history of allergies or autoimmune diseases—who may experience adverse health consequences in association with immunization with the currently recommended immunization schedule exist?

search on patient barriers to obtaining vaccinations. Although the committee acknowledges that these subjects are of interest and indeed are merely two examples of a large number of potential questions about the system of delivery of the immunization schedule that research could evaluate (see Chapter 4), they are beyond the scope of this committee's task. Therefore, the committee makes no recommendations regarding further research aimed at addressing such concerns; however, the committee encourages HHS to make continued efforts to identify populations facing barriers to immunization and consider stakeholder concerns on the safety, efficacy, and delivery of the immunization schedule and communication about the immunization schedule, as detailed in Recommendation 4-1.

This chapter focuses on potential health benefits or concerns about the recommended schedule at the individual level (e.g., the vaccinated child) and population-level considerations, including monitoring of community immunity (also called "herd immunity," which is the indirect protection afforded to unimmunized individuals, e.g., infants too young to be vaccinated against pertussis when a sufficient fraction of the population is vaccinated), that are necessary for study of the recommended immunization schedule.

The next section focuses on research questions that directly address the individual health benefits and risks of the recommended immunization schedule for the vaccinated child and describes a number of research approaches that could be pursued. The chapter then highlights the critical point that the consequences of individual vaccination choices can be considered only in light of the level of immunization in the larger population, to which the individual is invariably linked.

The committee recognized the vital importance of considering the population health impacts of any studies of the childhood immunization schedule. As the immunization schedule exists within a complex system consisting of individual-level protection and community immunity, studies that require any variations to the immunization schedule may have a profound impact on broader population health. After the discussion of methods to study individual health outcomes, the committee describes methods to monitor and maintain community immunity.

GENERAL RESEARCH APPROACHES TO ADDRESS PRIMARY RESEARCH QUESTIONS OF INTEREST

Each of the primary research questions of interest to stakeholders concerned about the safety of the immunization schedule described in Box 6-1 could be investigated by a range of study methods that vary considerably according to their cost, feasibility, and ethical propriety. At the one end are secondary analyses of existing data sets that could be initiated immediately; at the other end are primary research efforts involving the collection of new data, most notably, large, new RCTs.

This section describes the range of research approaches that could be pursued to investigate the leading questions of interest, with attention given to each approach's potential according to cost, feasibility, and anticipated scientific yield and utility. The research strategies broadly include

- initiation of new RCTs,
- initiation of new observational studies, and
- secondary analyses of data from current vaccine safety surveillance systems in the United States (such as VSD) and comparable international systems.

Each of these approaches has some potential to advance knowledge of the four primary research questions identified. The following sections discuss the strengths, limitations, cost, and feasibility of each approach.

Randomized Controlled Trials

It is widely acknowledged that when it is possible to randomize study participants, the RCT is the preferred design for evaluating the effectiveness and safety of health interventions. Data obtained from RCTs are often touted as the "gold standard" for clinical evidence, and results from a properly conducted clinical trial are considered to be of superior quality and reliability to evidence from most observational studies. The committee deliberately considered the form that an RCT of the immunization schedule could take and explored whether such a design would be both ethical and practical.

The critical advantage of the RCT is its ability to randomly assign participants to follow one of two or more different immunization schedules. Such a design would enable researchers to be reasonably certain that any observed difference in outcomes would be free of bias that could result from unequal allocation to treatment groups and would create reasonably comparable groups. The outcomes observed in a well-conducted RCT thus should accurately reflect an actual causal effect of treatment rather than results that could arise from population differences (Friedman et al., 2010).

Although it is well established that vaccines prevent a vast burden of disease among immunized as well as unimmunized or underimmunized people via community immunity, data suggest that some children continue to receive no vaccinations. One could argue that it would be ethical to recruit this population to an RCT comparing a group that receives the standard vaccination schedule with a group that receives no immunization. Because participants would be randomly placed in one of these study arms, at least half of the participating children, who otherwise would receive no vaccination, would receive all or part of the recommended immunization schedule. The other half would receive no benefit, except for a possible improvement in community immunity that would increase their chances of avoiding vaccine-preventable diseases. They would also avoid any hypothetical risk of receiving immunizations according to the ACIP-recommended schedule.

The committee considered and rejected this logic on the basis that any child, even the child of a parent who staunchly rejects vaccination, who is randomized to a no-vaccination arm is essentially consigned to an elevated risk of severe illness and even possible death should the child contract a vaccine-preventable disease. Moreover, should a child in the no-vaccination arm contract a preventable disease, the risk to other unprotected people in the community would increase. Randomization of such a child would also place the child's pediatrician in the position of having to go against professional medical guidelines. Likewise, parents of intentionally unvaccinated children are unlikely to allow their children to be randomized to receive vaccines. Similarly, the committee believes that any study stipulating that

some children receive less than the recommended immunization schedule would not be ethical. The ethics of human experimentation always trump scientific and other considerations, and no study that needlessly endangers children is acceptable. As the committee did not find evidence to suggest that the current schedule is unsafe, the committee concludes that any RCT comparing the current schedule with an alternative schedule that does not provide full and timely coverage of all the currently recommended vaccines would offer an unacceptable risk of vaccine-preventable diseases in individuals and in the population.

The committee believes that it may be ethical to use the RCT design to evaluate the third research question, which seeks to determine how health outcomes differ for those who receive the full recommended schedule in unconventional ways. A potential schedule that might be feasible as a comparative intervention is one that would disperse the vaccinations within the recommended window so that children are visiting their health care providers more often but receiving fewer doses at each visit. An example of such a study would be one that compares the health of infants who receive their five immunizations at the 4-month visit during one encounter with a health care provider with the health of infants who receive the same immunizations after age 4 months over the course of five separate visits. Because such a dispersed vaccination schedule would require an increased number of visits, often in rapid succession over a period of a few weeks, such a study would add substantial costs to both parents and providers and, moreover, may be unacceptable to insurers if its effectiveness—measured as a decreased rate of adverse outcomes—is negligible. Although it is unobjectionable ethically, the committee considered the time and financial strains resulting from immunization on a dispersed schedule to be too prohibitively costly to recommend pursuing this line of research and, thus, does not endorse this method as a feasible option for studying the recommended immunization schedule.

Certain segments of the population, including premature infants, children born into families with histories of autoimmune disease, and children with genetic traits not yet identified that confer an increased chance of developing diseases having autoimmune features, could be vulnerable both to putative harmful effects of vaccination and, conversely, to the absence of protection from vaccine-preventable diseases should they not be vaccinated. The benefits of immunization to such possibly vulnerable populations could surpass those to children in nonvulnerable groups, allowing them to avoid vaccine-preventable diseases that, although mild for others, could be severe for them. One might hypothesize, however, that the risk of a severe adverse effect of immunization is elevated in this group if, for example, administration of several vaccines causes an immune overload that precipitates the onset of an immunological disease.

If observational data suggest that a particular element of the schedule is associated with a particular adverse outcome in an identifiable subgroup, it could be ethical to conduct a randomized trial of the schedule with such a population, if such a trial does not require some children to receive a reduced schedule that would put them at risk for vaccine-preventable disease. However, as both the potential risks and the benefits are elevated and, moreover, the research community does not currently have a sound idea of the magnitudes of those risks and benefits, it is premature to propose RCTs to evaluate differences in outcomes between these hypothesized groups.

General Feasibility Issues

As detailed in Chapter 3, RCTs to evaluate the introduction of individual vaccinations are conducted within the context of the currently recommended childhood immunization schedule. The committee found no evidence that a trial has ever been conducted to evaluate the entire immunization schedule, for example, to compare administration of the recommended schedule of vaccines with administration of an alternative schedule. To conduct such a trial would require careful consideration of multiple factors. For instance, it has been established that some vaccines are associated with fevers, febrile convulsions, anaphylaxis, and other syndromes, which in some cases are similar to the symptoms of the diseases that they are intended to prevent. These adverse reactions are mostly rare. For example, febrile seizures occur for only 1 of every 3,000 measles, mumps, and rubella (MMR) vaccine doses (IOM, 2012), but a sufficiently large study of the safety of a schedule that omits or delays MMR would likely show an increased risk of seizures in the group receiving the regular doses of MMR. Unless researchers somehow accounted for the occurrence of the more serious preventable diseases, it may appear that nonvaccination is "safer" in this respect. To further complicate matters, the rare unvaccinated child in an otherwise heavily vaccinated area will benefit from community immunity and may thus appear to have done better than his or her peers, some of whom will develop adverse effects, such as fever.

Because vaccination in the United States essentially begins at birth, an RCT of the immunization schedule would have to randomize children either before birth or shortly thereafter. In addition to the many practical difficulties that this raises, randomization before birth means that the trial cannot be conducted solely through interactions with child health care providers, as pregnant women will typically be seeing a pregnancy care provider in the months preceding delivery. Such a trial would also require parents to adhere to their child's assigned schedule for at least 6 years and to avoid catch-up immunizations in the years that follow to evaluate hypothesized long-term health outcomes, all of which would likely add up to

an impractically long study commitment, likely much longer than 10 years. Compliance with this study protocol may prove difficult for parents over this length of time.

Clinical trials commonly mask participants and evaluators to the identity of the randomized treatments to prevent bias in the evaluation of treatment effects. In an RCT comparing the recommended schedule with an alternative schedule, masking of subjects would involve administration of placebo injections at the recommended vaccination times (for the alternative arm) and at the alternative times (for the recommended arm). Such a scheme would be cumbersome and difficult to implement, potentially causing errors in treatment administration and discouraging good compliance. It would also be unacceptable to parents, who would object to their children being repeatedly injected.

One key limitation of RCTs, which was discussed in Chapter 2 in the context of RCTs already performed to evaluate vaccine safety, is that they generally require large sample sizes to have adequate power. The power critically depends on the incidence rate of the adverse outcome in question. For example, a 90 percent power to detect a halving of the rate of an adverse event that occurs in 8 percent of children would require a relatively small sample size, likely no more than 2,000 participants. With disorders that are less common, for example, those that occur in only 1 percent of a population, one would need about 15,000 subjects to achieve a 90 percent power of detection. For events that occur very rarely, for example, in 0.25 percent of children, a trial would need upward of 50,000 participants to have the same level of power. Given the weak biological justification for the association of the immunization schedule with any adverse outcome, an RCT would have to include tens or hundreds of thousands of participants to be powered to look for a range of outcomes simultaneously, including those that are very rare (see Appendix D).

Only if observational studies suggest specific hypotheses to address could researchers use smaller sample sizes in follow-on RCTs. Given the large number of participants that would be required, the cost of such trials would also be prohibitive. Tens of millions of dollars would likely be required to adequately study the identified hypotheses. A federal investment in an RCT of the immunization schedule would therefore be infeasible, and unless further epidemiological evidence of safety problems from observational studies reveals a safety problem, such an investment could be considered wasteful.

Overall, the committee recognizes the value of the RCT in providing definitive data on the potential effects of the immunization schedule on adverse outcomes and asserts that the RCT should have a role in the overall research program on the safety of the schedule. Even though RCTs on individual and combination vaccines are part of the federal research

infrastructure, in the absence of data to suggest that the current schedule is unsafe, the committee must reject on ethical grounds any RCT design that compares the current schedule with an alternative that does not involve full vaccination within the permitted time windows. The committee believes that if clearly defined, biologically plausible hypotheses emerge from observational studies—either studies based on current resources, such as VSD, or studies with newly recruited cohorts—then these could serve as the basis for further research by the use of studies with the RCT design. Before HHS initiates further research on the entire immunization schedule, a thorough review of the biological plausibility of the association of a particular outcome with an aspect of the schedule should be conducted.

Recommendation 6-2: The Department of Health and Human Services should refrain from initiating randomized controlled trials of the childhood immunization schedule that compare safety outcomes in fully vaccinated children with those in unvaccinated children or those vaccinated by use of an alternative schedule.

New Observational Studies

Observational studies are the cornerstone of epidemiological science and are often used to evaluate associations between exposures and outcomes in situations in which randomization to a treatment arm would be unethical or in which it would not be feasible, either because of costs or other factors, to directly assign and monitor an intervention in the study population. Observational studies can involve either primary data, in which new data are obtained by the investigators to examine study hypotheses, or secondary data analysis, in which instances investigators analyze data that have been previously collected. In its consideration of the use of observational methods to address the four research questions of interest to stakeholders concerned about the safety of the immunization schedule identified in Box 6-1, the committee discussed potential options and challenges for studies with both primary data (in this section), and secondary data (in the section that follows).

Prospective Cohort Studies

Prospective cohort studies, which monitor—forward in time—populations selected on the basis of their exposure status, would be the most ambitious options involving primary data collection to address research questions, such as comparison of the health outcomes between children who receive no vaccinations and those who receive the full, currently recommended immunization schedule. As was mentioned earlier in

this report, a small percentage of the U.S. population receives no recommended childhood immunizations for reasons ranging from religious or philosophical beliefs, such as followers of Christian Science and some in U.S. Amish communities, to health reasons, such as children with certain conditions, to personal convictions about the safety of vaccines. Given the above-average proportion of unimmunized children in these populations, ranging from 4 to 16 percent in surveys of different communities (Smith et al., 2004; Wenger et al., 2011), it has been suggested that such a population could serve as a naturally occurring unimmunized group in designing a new prospective cohort study. However, such a study would have limited utility to accurately assess differences in health outcomes between unimmunized and fully immunized children. First, there are questions regarding the potential size and resulting statistical power for such a study. As with RCTs, sufficiently large numbers of participants would need to be recruited for each study arm—those who are unimmunized and those who are fully immunized. Because some Amish communities and other potential naturally occurring unimmunized populations have relatively so few unvaccinated children, the sample population of unimmunized children who could be recruited would likely be too small to provide adequate statistical power, particularly for very rare outcomes (see Appendix D).

Furthermore, the study would need to account for the many confounding variables that distinguish distinct subgroups of naturally occurring unimmunized populations from the rest of the U.S. population, including lifestyle factors and known genetic variables that may play a role in the development of allergies, asthma, and other conditions. For example, data from the National Immunization Survey have shown that unimmunized children are characteristically different from children who are underimmunized or fully immunized on the basis of race, gender, socioeconomic status, and parental concerns (Smith et al., 2004). For all these reasons, the committee does not recommend the pursuit of prospective cohort studies with distinct subgroups of naturally occurring unimmunized populations (such as those who decline immunizations due to membership in specific religion or cultural groups).

One option warranting additional investigation would involve embedding a new prospective cohort study of nonvaccinated and fully vaccinated families within the VSD surveillance system. If adequate numbers of fully unvaccinated children were included within VSD, it might be possible to identify comparable, well-matched, fully vaccinated children and actively monitor both groups over time with direct assessments of health functioning. In contrast to a study of, for instance, Amish families only, this study would likely include a more diverse and less highly-selective group of unimmunized children (with reduced potential for confounding) and with a larger sample size.

Further investigation of the number and characteristics of fully unvaccinated children or children vaccinated by use of alternative schedules within VSD appears warranted. It would be important to ensure an adequately comparable comparison group of fully vaccinated children. The committee raised some concerns that differences between the comparison groups of interest might constrain the utility of such a study, for reasons discussed below in regards to secondary analyses.

Furthermore, to be of sufficient scientific quality, such a study would require considerable effort to retain study participants. Additional consideration should be given to the feasibility of assessing long-term health outcomes for participants in VSD and the cost of doing so. This information would be essential to adequately assess the feasibility and cost of initiating a new prospective cohort study nested within VSD.

In addition to studies focused on existing unimmunized populations, the committee recognized that other longitudinal cohort studies of infants and children could be informative for evaluating long-term health outcomes after immunization, if a large sample size was available and accurate recording of immunization coverage was possible. One such opportunity is the National Children's Study (NCS), which is funded by both the U.S. Congress and the National Institutes of Health through the Children's Health Act of 2000 and which received total funding of $744.6 million from fiscal years 2007 to 2011. The budgetary request for fiscal year 2013 is $165 million, which will fund the continuation of the pilot study and introduction of data collection for the main study (National Children's Study, 2012).

The main NCS will be a multicenter effort that will examine the effect of a child's environment—including variables such as air and water quality, diet, family dynamics, and cultural influences—on his or her general health and well-being from birth through age 21 years. With a target population of 100,000 children, the NCS will be adequately powered to evaluate rare health outcomes and will aim to prioritize the investigation of environmental determinants of neurodevelopmental disorders and asthma, among other outcomes. Once begun, the main study will actively collect immunization histories. NCS therefore affords an opportunity to study potential health outcomes among children with a range of immunization histories, and the committee encourages such efforts through NCS and other similar cohorts to create a rich set of data for continued research.

Given the opportunity available through NCS, the limits of studying distinct subgroups of naturally occurring unimmunized populations, and the high cost of pursuing prospective data collection, the committee does not consider the initiation of new prospective cohort studies to be the most feasible or fruitful approach to studying the recommended immunization schedule at this time.

Case-Control Studies

Although they are less demanding in time and cost than a cohort study, the committee concluded that studies with case-control designs are unlikely to advance knowledge and provide answers to the four primary research questions of interest to concerned stakeholders presented in Box 6-1. The main reasons for this conclusion are that (1) the major variations in immunization history of interest are relatively uncommon, necessitating the enrollment of a large number of affected cases and unaffected study participants, and (2) it is not clear how accurately investigators would be able to retrospectively reconstruct details of the child's vaccination history. In addition, case-control studies can be used only if the adverse event of interest is known (see Appendix D for further discussion). Additional methodological work designed to determine the accuracy of retrospective ascertainment of vaccine histories and known adverse events may well be warranted.

Secondary Analyses of Existing Databases

U.S. Databases

Unlike prospective observational studies, which require the collection of new data, secondary analyses of accumulated data, such as retrospective cohort or case-control studies, are traditionally less resource intensive because they generally rely largely on information previously or routinely collected in existing databases. Given the comprehensive state of immunization data systems in the United States, the committee considered secondary analyses with data from existing data sets to be the most feasible option for the study of the safety of the childhood immunization schedule. In particular, a number of questions about variations in the current immunization schedule could be further investigated by the use of VSD.

VSD is the premier electronic health record (EHR)-based vaccine safety data system in the United States (Baggs et al., 2011; Chen et al., 1997; DeStefano, 2001). As noted in Chapter 3, VSD is a collaboration between the CDC and nine health plans that serve about 9.5 million members and that have an annual birth cohort of more than 100,000. In recent years, funding for VSD has totaled approximately $9 million per year, with additional funding being provided for special projects, making VSD a relatively low-cost and effective data system for investigating immunization safety (Frank DeStefano, CDC, personal communication, September 25, 2012).

VSD could be valuable for answering the research questions that the committee identified in Box 6-1 because it includes information on the immunization histories of participants that can be used to identify

1. individuals vaccinated according to some alternative immunization schedules;
2. variations in immunization schedules because of different immunization policies in the participating health plans, variations in clinical practice, vaccine shortages, problems with access, or parental decisions to delay vaccinations;
3. multiple outcomes, including adverse events, diagnoses, and procedures as well as mortality;
4. covariates, including race, age, gender, and zip code–level demographics; and
5. global indices of shorter-term child health and service utilization, including numbers of days hospitalized, numbers of emergency room visits, and so forth.

Accordingly, secondary analyses of the data in VSD databases would add to current knowledge and help answer the four primary research questions listed in Box 6-1. For example, in a review of alternative immunization schedules in the Kaiser Permanente Colorado system, VSD researchers initiated a retrospective matched cohort study to examine patterns and trends for children defined as undervaccinated at ages 2 to 24 months and compared the health care utilization rates between undervaccinated children and children vaccinated at the appropriate age.

Eight sites in the VSD participated in this study. Of 323,247 children born (within the participating managed care organization sites) between 2004 and 2008, 48.71 percent were considered undervaccinated for at least 1 day before age 24 months. The prevalence and specific patterns of undervaccination significantly increased across the study duration. In a matched cohort analysis, undervaccinated children had a significantly lower outpatient visit rate (11 percent) than did children who were vaccinated in an age-appropriate manner. In contrast, undervaccinated children had significantly greater (25 percent more) inpatient hospital admission rates than did children vaccinated at the appropriate age.

In a second matched cohort analysis, children who were undervaccinated because of parental choice had fewer outpatient visits and emergency room encounters than did children vaccinated at the appropriate age. In this second matched cohort analysis, no significant detectable difference in inpatient visit rates was detected between the two groups. Among children considered undervaccinated for any reason, 1,399 instances of undervaccination (variations in immunization history that could indicate alternative schedules) were detected. Among children undervaccinated because of parental choice, 756 distinct instances of undervaccination were detected (Glanz et al., 2013). More study will clearly be needed to draw conclusions

from these early results, but the potential of this study addressing alternate schedules and of other VSD research is promising.

As already mentioned, families electing different immunization schedules presumably differ in meaningful ways (e.g., according to their access to health care providers, attitudes toward vaccines, health care utilization, and sociodemographic factors). Although these differences may not affect reported incidence of adverse events or the presence of disease, they could be related to individual beliefs or to access to health care. Although confounding can ultimately be reduced by explicit adjustment for covariates, it cannot be fully addressed through analysis of existing study variables.

Moreover, the VSD system has limitations, including a population limited to children in private health care plans and therefore not representative of the entire U.S. population, loss of children to follow-up when families move or switch insurers, and an occasional need for additional data not routinely collected by VSD. These limitations may be addressed by the collection of supplementary data, including through patient interviews or medical record reviews.

To address the adequacy of long-term follow-up data, the magnitude of patient attrition from VSD would need to be fully investigated. For example, preliminary evidence suggests that among children born in 2001, over half continue to be included in the VSD database (Frank DeStefano, CDC, personal communication, August 28, 2012).

Collection of Additional Data on VSD Participants

One potential enhancement to VSD would be to collect additional demographic and, possibly, family history data for current participants. Basic information on vaccination history, child gender, race/ethnicity, and birth status (e.g., gestational age or birth weight) could be systematically collected for all participants. New approaches to the collection of additional data on a family history of allergies, autoimmune disorders, neurological disorders, and the like should be considered. These data would permit analyses of the fourth research question (about potentially susceptible subpopulations) that cannot be readily conducted at this time.

Collection and banking of blood samples with appropriate informed consent from VSD participants would support subsequent analyses of subpopulations that are potentially susceptible to adverse events according to genetic and epigenetic characteristics.

A more costly enhancement to the current system would be to attempt to capture additional data on child health, possibly including additional data on participants' use of health care services that are not already in the database.

Finally, it might be conceivable to conduct direct assessments of subgroups of interest (e.g., those who receive no vaccinations and a comparable group that receives the full immunization schedule). This option is discussed further below, but it is more feasible to study children who have had incomplete immunizations by a specified age than to identify children considered vaccine refusals because the population which falls into the latter category is generally very small.

Extending the Length of Follow-Up of VSD Patients

A limitation of VSD is that it includes data only from individuals in the nine participating health plans. Families with young children may move and switch health plans, resulting in limited follow-up information after their immunizations. This shortcoming is largely overcome in comparable systems in Scandinavia and the United Kingdom because of their universal health care systems and patient registries that contain information on medical services received from primary care providers. The use of strategies to collect health care utilization data through EHRs or provider reports after a participant has left the original health plan may warrant consideration.

Increasing the Number and Variety of VSD Participants

With an annual birth cohort of more than 100,000 participants, the total number of children monitored through VSD is substantial. However, national estimates derived from a representative sample of all U.S. children, including those in public health plans, suggest that less than 1 percent of children receive no vaccines. Data from VSD (Jason Glanz, University of Colorado–Denver, personal communication) suggest that the number of unvaccinated children within VSD is generally consistent with national values. Approximately 1.23 percent of children participating in VSD had no vaccinations recorded by age 1 year, and 1 percent of children had no vaccinations recorded by age 2 years. These estimates are limited to children who were born between 2004 and 2008 and who had a minimum period of enrollment in VSD of 12 months and a maximum enrollment of 36 months. It is not clear how commonly other variations of the recommended immunization schedule occur among the children in VSD.

In addition, the diversity of the participants represented in VSD is limited by the fact that managed care organizations in the Southwest and rural South are not currently among the managed care organizations participating in VSD. Furthermore, because VSD does not now include any public insurance plans, its population has fewer low-income and minority individuals than the number in the U.S. population as a whole. Options to broaden the diversity of VSD participants would enhance the utility of this

system to address the primary research questions of interest and increase the generalizability of research results.

Further discussion would be required to assess the feasibility and cost of such efforts. The committee noted that although VSD represents the most promising system for investigating outcomes after immunization with the recommended childhood immunization schedule, other resources discussed in Chapter 3, such as VAERS, the National Immunization Survey, and immunization information systems, are highly valued resources for monitoring vaccine safety and coverage as well. The Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program, which has been used to evaluate vaccine safety in a larger cohort than the VSD, may have the capability to monitor rare adverse events potentially associated with the childhood immunization schedule. However, the data are not yet well-characterized.

Analyses of comparable international immunization surveillance systems in countries including Denmark, the United Kingdom, and Canada have historically been better suited for these purposes for the reasons described below. Although consideration of international immunization surveillance systems was not central to the committee's task, analyses in Denmark, the United Kingdom, Canada, and other countries also hold considerable promise for advancing knowledge about the health outcomes associated with the immunization schedule. First, as discussed in Chapter 3, these countries often collect and maintain full immunization histories for the entire population, greatly increasing the total sample size and the number of children immunized with less common combinations of vaccines (including no vaccines). Second, many of these countries have comprehensive health and educational registries permitting linkage to longer-term and less severe child outcomes. Third, these systems include a richer set of variables on sociodemographic characteristics and family history, permitting analyses of potentially susceptible subpopulations.

The committee considered but does not recommend cross-national comparisons because of the potential bias and lack of generalizability from results that must account for different environments, vaccine antigens, or immunization schedules. The U.S. population differs from the populations in other countries in important ways, including on the basis of genetics and health care history. Even vaccine efficacy can vary among populations, as has been demonstrated in separate studies of a *Haemophilus influenzae* type b conjugate vaccine in two different populations (Eskola et al., 1990; Ward et al., 1990). A cross-national comparison to study child health outcomes related to recommended childhood immunization schedules would require careful and extensive consideration of the possible covariates, many of which may not be known at this time. Ecological comparisons may be useful for monitoring disease trends and detecting epidemiological signals; however, the information gathered from such studies could not be

extrapolated to inferences of individual risk of adverse events related to each immunization schedule, and thus would not be useful for shaping U.S. immunization policy.

The major limitations of U.S. surveillance systems to address the primary research questions identified in this report are (1) the potentially limited number of families included in these systems who will have used the major alternative immunization schedules of interest; (2) potentially high rates of migration from the participating health care organizations, resulting in varying and often short-term follow-up after vaccination; (3) limits on how much information on less severe health outcomes is collected from participating children; and (4) limited ancillary information routinely collected about participating children, such as premature birth or a family history of allergies.

Despite these limitations, VSD is currently the best available system for the study of the safety of the immunization schedule in the United States and holds tremendous promise for advancement, including the potential for future prospective cohort studies. Furthermore, continuing to move toward the increased use of EHRs (as encouraged by federal funding), which are what allow VSD to capture and link large amounts of immunization and health data on children, will help the United States establish richer data sets that are more comparable to those in other high-income countries.

To further enhance the data collected by VSD, the system should strive to obtain complete demographic information to strengthen its functions and generalizability to the whole U.S. population. Secondary analyses with data from other existing databases similar to VSD would be feasible, ethical, and a lower-cost approach to investigating the research questions that the committee identified, including research on alternative immunization schedules. To date, the data obtained from VSD have already been used to study health outcomes of children with incomplete immunizations or who may follow alternative schedules, as described above. In addition, the VSD system has a large enough proportion of unvaccinated children to investigate differences in health outcomes of unvaccinated and vaccinated children. Increased efforts to collect information on individual medical histories could lead to a fruitful source of data for studying which populations are potentially susceptible to vaccine adverse events. The committee recognizes that the currently funded managed care organizations' commitment to VSD studies needs to remain high to continue and build upon existing efforts. Additionally, VSD's utility will be expanded with the addition of more detailed demographic data and family medical histories.

Recommendation 6-3: The committee recommends that the Department of Health and Human Services (HHS) and its partners continue to

fund and support the Vaccine Safety Datalink project to study the safety of the recommended immunization schedule. Furthermore, HHS should consider expanding the collaboration with new health plan members and enhancing the data to improve its utility and generalizability.

METHODS TO MONITOR COMMUNITY IMMUNITY AND MEASURE POPULATION-LEVEL IMPACTS OF STUDIES OF THE IMMUNIZATION SCHEDULE

If large numbers of children avoided immunization, community immunity would be eroded and this protective effect would disappear for those who are not or who cannot be fully vaccinated. Thus, any analysis of vaccine safety data needs to consider the community immunity aspect of the milieu in which the study is conducted. Such complications would affect both clinical trials and observational studies.

Consideration of Population Impacts of Alternative Schedules

Attempts to quantify the relative safety of contrasting immunization schedules need to take into account at least two separate health outcomes: (1) adverse events related to the administration of specific vaccines and the overall immunization schedule, and (2) the respective impacts of alternative schedules on the circulation of vaccine-preventable diseases and the consequent adverse outcomes associated with infection. Secondary effects (such as longer waiting times and the greater cost of care if more visits are needed for immunization) and potential medical errors in provider offices accustomed to the routine schedule would also have to be measured.

Previously, high-profile analyses have focused on calculation of the number of serious reactions either per vaccine or over the immunization schedule compared with the per child risk of hospitalization associated with vaccine-preventable diseases (Sears, 2011). Although such analyses are intuitively appealing, they overlook the intimate association between immunization and age-specific disease incidence. Specifically, any shifts in the immunization schedule that lead to a net increase in the time spent vulnerable to these diseases will inevitably increase the circulation of these pathogens. The population-level impacts of such an outcome will be a simultaneous rise in the incidence of the affected infectious diseases and a reduction in the age at which they are contracted. Thus, not only is the risk of exposure to vaccine-preventable diseases increased but so is the likely severity of infection, which may be most acute in younger children (Heiniger et al., 1997).

A clear manifestation of the dual impact of immunization on the incidence and age distribution of vaccine-preventable diseases has been documented in Sweden, where the pertussis vaccine was removed from the

national pediatric immunization schedule in 1979 because of concerns over the reactogenicity of the whole-cell vaccine (Gangarosa et al., 1998; Romanus et al., 1987). After a 17-year hiatus, the acellular pertussis vaccine was added to the immunization schedule in 1996 (Carlsson and Trollfors, 2009). Analyses of age-stratified incidence reports highlighted both a sharp decline in the incidence and a marked increase in the age distribution of pertussis cases as a result of the resumption of immunization against pertussis (Rohani et al., 2010). Importantly, Swedish data also illustrate the concept of community immunity.

A pattern similar to that seen in Sweden has been observed in England and Wales, where declines in the uptake of MMR after controversy instigated by a subsequently retracted paper questioning the vaccine's safety were associated with a rise in measles notifications and a shift in the incidence of measles toward younger age groups (Jansen et al., 2003).

Predicting Changes to Community Immunity

As outlined in the commissioned paper (see Appendix D), a variety of designs may be used to compare the safety of alternative schedules. It is, unfortunately, difficult predict the long-term population-level consequences of disease transmission as a result of changes to the immunization schedule. It is possible, however, to use mathematical and computational models to predict the impacts of changes in the administration of any one specific vaccine on the incidence of the infectious disease affected by that vaccine. This process involves three distinct steps: model formulation, parameterization, and model validation. These and other elements of the models are described below.

Model Formulation

The development of a disease-specific transmission model begins with determination of the model structure and key processes, which are informed by the known immunology and epidemiology of the system. For instance, a loss of immunity may be a necessary ingredient for a model of pertussis transmission, whereas a latent carrier stage may be appropriate for varicella (Anderson and May, 1992; Keeling and Rohani, 2008). The model also needs to explicitly consider age-dependent heterogeneities in contact rates, susceptibility to complications, and reporting.

A number of age-specific models have been proposed for many of the key childhood infections, including measles (Anderson and May, 1992; Schenzle, 1984), pertussis (Hethcote, 1998; Rohani et al., 2010), *Streptococcus pneumoniae* infection (Cobey and Lipsitch, 2012), rubella (Metcalf et al., 2011), and chickenpox (Ferguson et al., 1996).

Parameterization and Model Validation

The usefulness of any model and the reliability of its predictions depend on its veracity. Thus, models need to be carefully based on ground truths, a process that is made particularly challenging for high-dimensional age-structured models because a fundamental challenge to the effective parameterization of age-specific models is determination of the appropriate patterns of contact by age. It is fortunate that recent studies have addressed this problem, and detailed information on the typically age-stratified patterns of contact in the United States (Del Valle et al., 2007) and a number of European countries (Mossong et al., 2008) is now available. Synthesis of this information together with historical incidence data to formulate validated transmission models is made possible by the use of modern inference techniques, including sequential Monte Carlo methods for hypothesis testing (Ionides et al., 2006). An example is the age-structured pertussis model developed by Rohani et al. (2010) and parameterized with data from incidence reports from Sweden.

Data Needs

The production of fully validated transmission models requires access to age-specific incidence reports. This is often a critical bottleneck in such an endeavor, as public health agencies (e.g., CDC) do not routinely provide such complete data via, for instance, the National Notifiable Diseases Surveillance System (Goldwyn and Rohani, 2012). When detailed incidence reports, stratified by age, county, and immunization status (e.g., through the Supplementary Pertussis Surveillance System), do become available, requests for access to such data are not always granted in a timely manner, and may be answered with the provision of data that was not obtained using the best-available methods (Thacker et al., 2012).

Quantifying Uncertainty and Sensitivity

The predictions of any formal modeling analyses need to be evaluated within the context of their inherent variability and should be subject to extensive sensitivity analyses (Blower, 2000). Uncertainty in predictions can be quantified by use of a wide array of rigorous probabilistic approaches to model execution, whereby the system of equations is translated into a Markov chain process (Gibson and Bruck, 2000; Gillespie, 1977; Keeling and Rohani, 2008). Such an approach would permit a detailed situational analysis, whereby the model could provide policy makers with information on the most likely (i.e., the median) outcome, for example, the size of the focal vaccine-preventable disease outbreak given a specific change in the

immunization schedule. This approach would also provide information about extreme outcomes or the 95th percentile of predicted outbreak sizes (Park et al., 2009; Rohani et al., 2009). Examination of sensitivity involves extensive repetition of the model simulation as a critical parameter of interest (e.g., the efficacy of the first dose of diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed administered at 3 months of age) is systematically varied.

The development, appropriate parameterization, and scrutiny of mechanistic transmission models have been adopted by a number of governmental agencies, and this process has been influential for determination of the implementation of specific immunization practices in countries such as the United Kingdom. In 2002, for example, Edmunds et al. used an approach similar to that outlined here to examine the potential cost-effectiveness of introduction of an acellular pertussis booster vaccine to the schedule in England and Wales (Edmunds et al., 2002). Similarly, Jit et al. (2008) carried out extensive analyses of detailed transmission models to inform the policy decision of the government of the United Kingdom on the effectiveness of routine vaccination of 12-year-old schoolgirls against human papillomavirus. Other examples include identification of the optimal targeting of age groups to contain the influenza pandemic (Medlock and Galvani, 2009), as well as pinpointing the most effective immunization schedule for meningococcal serogroup C (Trotter and Edmunds, 2006).

CONCLUSIONS

The committee deliberated on many potential research approaches and worked to determine which were feasible, ethical, and cost-effective. The commissioned paper in Appendix D helped identify methods that could be considered. Many questions can be answered by use of the methods described above, although they are not currently well integrated.

Chapter 7 summarizes the committee's judgment on its statement of task. Setting of priorities for research will be challenging. For example, the committee does not recommend a study comparing the recommended immunization schedule and no immunization at this time because a high-quality randomized trial is not ethical and a prospective observational study could be complex, lengthy, and expensive and would potentially provide inconclusive results about key health outcomes after immunization. Thus, the committee proposes establishment of a process for setting priorities incorporating epidemiological and other evidence (on the basis of formal systematic reviews), biological plausibility, feasibility, and stakeholder concerns.

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7

Conclusions and Recommendations

COMMITTEE RESPONSE TO ITS STATEMENT OF TASK

This final chapter highlights selected findings and conclusions and presents recommendations for each section of the committee's statement of task. The preceding chapters, especially Chapter 6, include many assessments that may be construed as the committee's preferences among the alternatives presented but that fall short of formal recommendations.

Vaccine safety is critically important, but a determination of safety is ultimately a value judgment. For example, some might believe that a serious adverse event that occurs once in 1 million doses is "safe enough" relative to the benefit of preventing a serious disease, whereas others may consider that risk unacceptably high. The committee did not set a specific numerical target or goal for what should be considered "safe enough." Instead, the committee made a judgment based on the literature that failed to link adverse effects to schedule exposures or multiple immunizations, concluding that there is no evidence that the schedule is not safe.

The committee recognized that final decisions about research studies must await knowledge of further evidence, including biological plausibility and/or epidemiological evidence, feasibility, cost, and the exact circumstances of stakeholder concerns, before the planning and conduct of specific research projects. In turn, the committee believes that it would be inappropriate to make unqualified recommendations without this knowledge. The committee notes that stakeholder concerns may be used to drive a search for scientific evidence (biological or epidemiological), although such concerns would not be sufficient motivation to embark

on costly clinical research, such as new randomized controlled trials or cohort studies.

The committee thus decided to make five general recommendations. Three recommendations focus on improvements to understanding stakeholder concerns, harmonizing research methods, and sequencing the process for selecting research questions. Two recommendations focus on research methods, including randomized controlled trials and data systems that would enable ongoing and improved observational studies.

> Statement of Task (Part I): Review scientific findings and stakeholder concerns related to the safety of the recommended childhood immunization schedule.

Summary of Stakeholder Concerns

The committee's findings and conclusions about stakeholder concerns are presented in Chapter 4. Although the committee identified the concerns of some parents about the number, frequency, and timing of immunizations in the overall immunization schedule, the committee did not find in its literature review that clinicians, public health personnel, or policy makers have similar safety concerns. Among the latter groups, the childhood immunization schedule is considered to be among the most effective and safe of the public interventions available to prevent serious disease and death. However, although health care professionals have much information about individual vaccines, they have much less information about the effects of administration of multiple vaccines at a single visit or the timing of the immunizations. Additionally, the cited concerns of health care professionals include efficacy of certain vaccines as well as appropriate delivery and communication regarding the recommended childhood immunization schedule.

Although the 2010 National Vaccine Plan addresses the need to provide health care providers with more timely, accurate, and transparent information about the benefits and risks of vaccines, the plan does not specifically address strategies to assist providers with questions about the safety of the immunization schedule (HHS, 2010). The committee concluded that parents and health care professionals would benefit from more comprehensive and detailed information with which to address parental concerns about the safety of the immunization schedule. Such information should clearly address vaccine-preventable diseases, the risks and benefits of immunizations, and the safety of the immunization schedule.

The committee's literature review highlighted the lack of high-quality evidence supporting stakeholder concerns (the priority stakeholders are listed in Box 4-1) about the immunization schedule. In its role to ensure

vaccine safety, the federal government has already prioritized the engagement of stakeholders in multiple activities, as detailed in the 2010 National Vaccine Plan and implementation efforts, as well as the Centers for Disease Control and Prevention's Immunization Safety Office scientific agenda (CDC, 2011; HHS, 2010). However, an effective national vaccine program will require more complete information on stakeholder concerns about the safety of the immunization schedule, the severity of vaccine-preventable diseases, individual- and population-level immunization rates, vaccine efficacy, and the delivery and supply of vaccines recommended in the childhood immunization schedule. Improved communication between public health authorities and parents requires improvements to the clarity of the information provided, as well as the building of trust and the use of a systematic approach to elicit public concerns. Further research into the type of questions that parents seek to answer by the use of the scientific methods of social, behavioral, and decision science is indicated.

On the basis of the committee's literature review and public testimony, the committee strongly endorses the need for research to understand the public's knowledge, beliefs, and concerns about vaccines and vaccine-preventable diseases in particular, which is a key strategy in the 2010 National Vaccine Plan (HHS, 2010). It must be acknowledged that the methods used in most immunization studies do not permit a detailed analysis of the impact of parental concerns on the decision to immunize their children. Although the committee found that the largest safety concerns exist among a subset of parents, the concerns of multiple stakeholders should be included as part of the efforts of the National Vaccine Program Office (NVPO). For example, health care providers have much knowledge about individual vaccines but less information about the effects of administering multiple vaccines at a single visit or the timing of the immunizations.

Recommendation 4-1: The committee recommends that the National Vaccine Program Office systematically collect and assess evidence regarding public confidence in and concerns about the entire childhood immunization schedule, with the goal to improve communication with health care professionals, and between health care professionals and the public regarding the safety of the schedule.

Summary of Scientific Findings

The committee's findings and conclusions about the safety of the immunization schedule on the basis of the information in the scientific literature are presented in Chapter 5. The committee encountered two major issues. First, the concept of the immunization "schedule" is not well developed in the scientific literature. Most vaccine research focuses on the health outcomes associated with single immunizations or combinations of vaccines

administered at a single visit. Even though each new vaccine is evaluated in the context of the overall immunization schedule that existed at the time of review, individual elements of the schedule are not evaluated once it is adjusted to accommodate a new vaccine. Key elements of the immunization schedule—for example, the number, frequency, timing, order, and age at the time of administration of vaccines—have not been systematically examined in research studies.

The second major issue that the committee encountered during the review of the scientific literature was uncertainty over whether the scientific literature has addressed all health outcomes and safety concerns. The committee could not determine whether its list of health outcomes was complete or whether a more comprehensive system of surveillance might identify other outcomes of potential safety significance. In addition, the conditions of concern to some stakeholders, such as immunological, neurological, and developmental problems, are illnesses and conditions for which the etiology, in general, is not well understood. Further research on these conditions may clarify their etiologies.

Finally, the committee found that evidence from assessments of health outcomes in potentially susceptible subpopulations of children who may have an increased risk of adverse reactions to vaccines (such as children with a family history of autoimmune disease or allergies or children born prematurely) was limited and is characterized by uncertainty about the definition of populations of interest and definitions of exposures and outcomes. Most children who experience an adverse reaction to immunization have a preexisting susceptibility. Some predispositions may be detectable prior to vaccination; others, at least with current technology and practice, are not (IOM, 2012, p. 82).

In summary, to consider whether and how to study the safety and health outcomes of the entire childhood immunization schedule, the field needs valid and accepted metrics of the entire immunization schedule (the "exposure") and clearer definitions of health outcomes linked to stakeholder concerns (the "outcomes") in rigorous research that will ensure validity and generalizability.

Recommendation 5-1: To improve the utility of studies of the entire childhood immunization schedule, the committee recommends that the National Vaccine Program Office develop a framework that clarifies and standardizes definitions of

- **key elements of the schedule,**
- **relevant health outcomes, and**
- **populations that are potentially susceptible to adverse events.**

Statement of Task (Part II): Identify potential research approaches, methodologies, and study designs that could inform this question, including an assessment of the potential strengths and limitations of each approach, methodology, and design, as well as the financial and ethical feasibility of doing them.

Summary of Methodological Issues

The committee's findings and conclusions about research approaches are presented in Chapter 6. The committee parsed the phrase "this question" in Part 2 of the statement of task into four broad research questions in Box 7-1.

The committee then discussed general research approaches with the potential to answer these questions: ongoing research with data from existing data systems, research with enhanced data from existing data systems, prospective observational studies, and randomized controlled trials. The committee also recognized that to advance the knowledge about the safety

BOX 7-1
Leading Research Questions of Interest to Select Stakeholders

1. How do child health outcomes compare between those who receive no vaccinations and those who receive the full currently recommended immunization schedule?
2. How do child health outcomes compare between (a) those who receive the full currently recommended immunization schedule and (b) those who omit specific vaccines?
3. For children who receive the currently recommended immunization schedule, do short- or long-term health outcomes differ for those who receive fewer immunizations per visit (e.g., when immunizations are spread out over multiple occasions), or for those who receive their immunizations at later ages but still within the recommended ranges?
4. Do potentially susceptible subpopulations—for example, children from families with a history of allergies or autoimmune diseases—who may experience adverse health consequences in association with immunization with the currently recommended immunization schedule exist?

of the immunization schedule, certain enhancements to the research infrastructure will be needed, as detailed in Chapter 6.

The committee recognizes that the establishment of priorities for research will be a challenge. Thus, the committee proposes a process for setting priorities that recognizes stakeholder concerns and establishes these priorities on the basis of epidemiological and other evidence (based on formal systematic reviews), biological plausibility, and feasibility.

Before the U.S. Department of Health and Human Services (HHS) initiates further research on the entire immunization schedule through its agencies—most notably CDC, FDA, the National Institutes of Health, and NVPO—the biological plausibility of the association of a particular outcome with an aspect of the immunization schedule must be thoroughly reviewed. Along these lines, previous IOM vaccine safety committees have assessed the mechanisms by which vaccines potentially cause adverse events by identifying and evaluating the clinical and biological evidence (from human, animal, and in vitro studies) for individual vaccines. Furthermore, the recent IOM Committee to Review Adverse Effects of Vaccines developed categories for a mechanistic assessment of the weight of the evidence. Each assessment considers clinical information from case reports and clinical and experimental evidence from other sources (IOM, 2012).

Recommendation 6-1: The committee recommends that the Department of Health and Human Services incorporate study of the safety of the overall childhood immunization schedule into its processes for setting priorities for research, recognizing stakeholder concerns, and establishing the priorities on the basis of epidemiological evidence, biological plausibility, and feasibility.

The decision to initiate further studies should be based on an evaluation of three considerations that the committee identified through its review of stakeholder concerns and scientific findings:

1. epidemiological evidence of potential adverse health outcomes associated with elements of the immunization schedule (such as postmarketing signals or indications of elevated risk from observational studies);
2. biological plausibility supporting hypotheses linking specific aspects of the immunization schedule with particular adverse health outcomes; and
3. concern about the immunization schedule's safety expressed by stakeholders, which should initiate efforts to explore the two previous considerations.

The committee acknowledges the evidence that reducing vaccine coverage is associated with increases in vaccine-preventable disease and found only inconsistent and anecdotal evidence to imply that the recommended immunization schedule is not safe. Furthermore, existing systems for the detection of adverse events provide confidence that the existing childhood immunization schedule is safe, and the committee recognizes that the federal government invests considerable resources to ensure vaccine safety. Nevertheless, some stakeholders have suggested that further work is warranted, such as a comparison of vaccinated children with unvaccinated children or children receiving immunizations on alternative immunization schedules.

The committee supports the National Vaccine Advisory Committee Safety Working Group statement that "the strongest study design, a prospective, randomized clinical trial that includes a study arm receiving no vaccine or vaccine not given according to the current recommended schedule, would be unethical and therefore cannot be done" (NVAC, 2009, p. 38). In Chapter 6, the committee presents the formidable ethical and feasibility problems associated with the conduct of randomized controlled trials of children who receive all recommended immunizations and children who receive none of them and randomized controlled trials of children who receive all recommended immunizations and children who receive the recommended immunization on an alternative schedule. There are very low observed rates of adverse events with vaccination, which is another factor sffecting feasibility of a randomized controlled trial. Because of these problems, the committee concludes that a randomized controlled trial comparing the recommended schedule with any alternative schedule would be unethical and infeasible and could increase the risk of vaccine-preventable diseases in individuals and in the community.

Furthermore, the committee found that a trial of a modified version of the ACIP schedule—one that would disperse the timing of vaccinations so that children are visiting health care professionals more often but receiving fewer shots at each visit—would be ethical; however, it would add substantial costs to both parents and providers and, moreover, may be unacceptable to insurers if its effectiveness—measured as a decreased rate of adverse safety outcomes—was negligible. This modified schedule would provide immunizations within the time intervals approved by ACIP and would address the concern about immunization with too many vaccines at one office visit, but the committee did not view this option to be feasible for study.

In light of the ethical and feasibility requirements and the available evidence, the committee concludes that new randomized controlled trials of the childhood immunization schedule are not justified at this time.

Recommendation 6-2: The Department of Health and Human Services should refrain from initiating randomized controlled trials of the child-

hood immunization schedule that compare safety outcomes in fully vaccinated children with those in unvaccinated children or those vaccinated by use of an alternative schedule.

The committee also reviewed opportunities to study groups that choose not to vaccinate their children by use of a prospective cohort study design. However, such a study would not conclusively reveal differences in health outcomes between unimmunized and fully immunized children for two main reasons. First, the sample populations often suggested for study (such as some religious populations) may be too small to adequately power such a comparative analysis, particularly for very rare adverse health outcomes. Such a study would also need to account for the many confounding variables that separate these naturally occurring unimmunized populations from the average U.S. child, including lifestyle factors and genetic variables.

The committee finds that secondary analyses of existing systems are more promising approaches to examination of the research questions that the committee identified in future studies of the childhood immunization schedule. The Vaccine Safety Datalink (VSD) is a useful collaborative project that could conduct both postmarketing surveillance and longer-term targeted research. The ability to augment routinely collected administrative data in VSD with data from parent interviews and reviews of medical records for a selected study population is an important strength.

VSD is currently the best available system for studying the safety of the immunization schedule in the United States. VSD should strive to improve the generalizability of its data to the U.S. population as a whole by enhancing the quality of its demographic information and by expanding its scope to include more diversity in its study populations. Secondary analyses with data from other existing databases (that might be modeled on VSD) could be a feasible, ethical, and cost-effective means of investigating several research questions that the committee identified. The committee recognizes that the commitment to VSD studies by the managed care organizations currently receiving funding through VSD needs to be sustained to continue to build on existing efforts. The committee concludes that VSD is a valuable component of the federal research infrastructure and will be the best-suited source of data for studying the childhood immunization schedule. Its utility will be expanded with the addition of more detailed demographic data and family medical histories.

Recommendation 6-3: The committee recommends that the Department of Health and Human Services (HHS) and its partners continue to fund and support the Vaccine Safety Datalink project to study the safety of the recommended immunization schedule. Furthermore, HHS should

consider expanding the collaboration with new health plan members and enhancing the data to improve its utility and generalizability.

CONCLUDING OBSERVATIONS

The committee's efforts to identify priorities for recommended research studies did not reveal a base of evidence suggesting that the childhood immunization schedule is linked to autoimmune diseases, asthma, hypersensitivity, seizures or epilepsy, child developmental disorders, learning disorders or developmental disorders, or attention deficit or disruptive behavior disorders. While the committee found that there is no scientific evidence to justify the majority of safety concerns, perceptions dictate parental support and actions. Therefore further study of the full immunization schedule as well as further study to understand stakeholder perceptions and how they are formed may help improve awareness and education efforts. Stakeholder concerns should be one of the elements used to drive searches for scientific evidence, but these concerns alone, absent epidemiological or biological evidence, do not warrant the initiation of new high-cost randomized controlled trials. The committee concludes that data from existing data systems may be used to conduct observational studies and offer the best means for ongoing research efforts of the immunization schedule's safety.

The committee found no significant evidence to imply that the recommended immunization schedule is not safe. Furthermore, existing surveillance and response systems have identified adverse events known to be associated with vaccination. The federal immunization research infrastructure is strong. A key component is the VSD project, which with ongoing support will be able to feasibly address the committee's identified key research questions. Although the committee concludes that protection of children from vaccine-preventable diseases is of higher importance than testing of alternative immunization schedules without epidemiological or biological evidence indicating a safety problem, VSD should continue to examine the health outcomes of people who choose alternative schedules.

Looking to the future, the committee supports the work of the federal research infrastructure in ensuring that stakeholders are involved in all stages of development, implementation, evaluation, and dissemination of the immunization schedule. As electronic medical records become more commonly used, they may provide an opportunity to capture complete immunization data linked with hospital discharge records that will be useful to future studies. Further, the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program may have the capability to monitor rare adverse events potentially associated with the childhood immunization schedule. Initiatives such as the National Children's Study also hold promise; it

will be one of the most comprehensive research efforts focused on studying children's health and development.

The childhood immunization schedule may become more complex over time as scientific advances are made and new vaccines are developed. Feasible research approaches to study potential adverse health outcomes will emerge only with a sustained and substantial federal commitment to research on vaccine safety.

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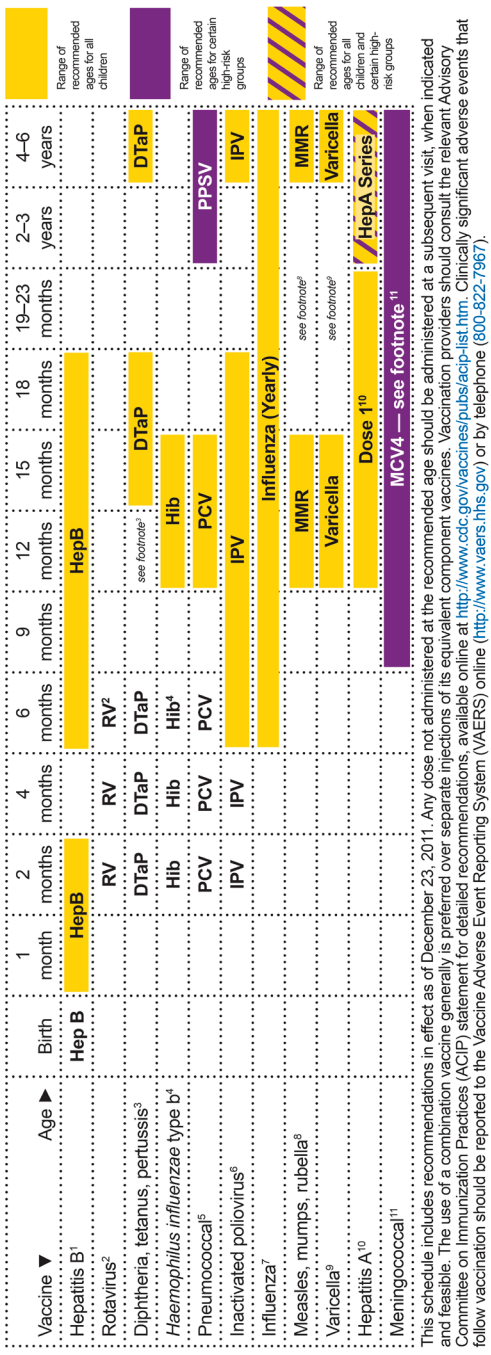
Appendix A

2012 Advisory Committee on Immunization Practices' Recommended Immunization Schedule for Children



This schedule includes recommendations in effect as of December 23, 2011. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/pubs/acip-list.htm. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967).

FIGURE A-1 Recommended immunization schedule for individuals aged 0 through 6 years, United States, 2012.
SOURCE: CDC (Centers for Disease Control and Prevention). 2012. *Immunization schedules.* Atlanta, GA: Centers for Disease Control and Prevention. http://www.cdc.gov/vaccines/ schedules/hcp/child-adolescent.html.

0-6 YEARS SCHEDULE

1. Hepatitis B (HepB) vaccine. (Minimum age: birth)

At birth:

• Administer monovalent HepB vaccine to all newborns before hospital discharge.

• For infants born to hepatitis B surface antigen (HBsAg)–positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of at least 3 doses of the HepB series, at age 9 through 18 months (generally at the next well-child visit).

• If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine for infants weighing ≥2,000 grams, and HepB vaccine plus HBIG for infants weighing <2,000 grams. Determine mother's HBsAg status as soon as possible and, if she is HBsAg-positive, administer HBIG for infants weighing ≥2,000 grams (no later than age 1 week).

Doses after the birth dose:

• The second dose should be administered at age 1 to 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.

• Administration of a total of 4 doses of HepB vaccine is permissible when a combination vaccine containing HepB is administered after the birth dose.

• Infants who did not receive a birth dose should receive 3 doses of a HepB containing vaccine starting as soon as feasible (see Figure A-2).

• The minimum interval between dose 1 and dose 2 is 4 weeks, and between dose 2 and 3 is 8 weeks. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose.

2. Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV-1 [Rotarix] and RV-5 [Rota Teq])

• The maximum age for the first dose in the series is 14 weeks, 6 days; and 8 months, 0 days for the final dose in the series. Vaccination should not be initiated for infants aged 15 weeks, 0 days or older.

• If RV-1 (Rotarix) is administered at ages 2 and 4 months, a dose at 6 months is not indicated.

3. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks)

• The fourth dose may be administered as early as age 12 months, provided at least 6 months have elapsed since the third dose.

4. *Haemophilus influenzae* type b (Hib) conjugate vaccine. (Minimum age: 6 weeks)

• If PRP-OMP (PedvaxHIB or Comvax [HepB-Hib]) is administered at ages 2 and 4 months, a dose at age 6 months is not indicated.

• Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years.

5. Pneumococcal vaccines. (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])

• Administer 1 dose of PCV to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.

• For children who have received an age-appropriate series of 7-valent PCV (PCV7), a single supplemental dose of 13-valent PCV (PCV13) is recommended for:
—— All children aged 14 through 59 months.
—— Children aged 60 through 71 months with underlying medical conditions.
• Administer PPSV at least 8 weeks after last dose of PCV to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant. See *MMWR* 2010; 59(No. RR-11), available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.

6. Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)
• If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years.
• The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

7. Influenza vaccines. (Minimum age: 6 months for trivalent inactivated influenza vaccine [TIV]; 2 years for live, attenuated influenza vaccine [LAIV])
• For most healthy children aged 2 years and older, either LAIV or TIV may be used. However, LAIV should not be administered to some children, including (1) children with asthma, (2) children 2 through 4 years who had wheezing in the past 12 months, or (3) children who have any other underlying medical conditions that predispose them to influenza complications. For all other contraindications to use of LAIV, see *MMWR* 2010; 59(No. RR-8), available at http://www.cdc.gov/mmwr/pdf/rr/rr5908.pdf.
• For children aged 6 months through 8 years:
—— For the 2011–12 season, administer 2 doses (separated by at least 4 weeks) to those who did not receive at least 1 dose of the 2010–11 vaccine. Those who received at least 1 dose of the 2010–11 vaccine require 1 dose for the 2011–12 season.
—— For the 2012–13 season, follow dosing guidelines in the 2012 ACIP influenza vaccine recommendations.

8. Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months)
• The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
• Administer MMR vaccine to infants aged 6 through 11 months who are traveling internationally. These children should be revaccinated with 2 doses of MMR vaccine, the first at ages 12 through 15 months and at least 4 weeks after the previous dose, and the second at ages 4 through 6 years.

9. Varicella (VAR) vaccine. (Minimum age: 12 months)
• The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose.
• For children aged 12 months through 12 years, the recommended minimum interval between doses is 3 months. However, if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

10. Hepatitis A (HepA) vaccine. (Minimum age: 12 months)
• Administer the second (final) dose 6 to 18 months after the first.
• Unvaccinated children 24 months and older at high risk should be vaccinated.

See *MMWR* 2006; 55(No. RR-7), available at http://www.cdc.gov/mmwr/pdf/rr/rr5507.pdf.

• A 2-dose HepA vaccine series is recommended for anyone aged 24 months and older, previously unvaccinated, for whom immunity against hepatitis A virus infection is desired.

11. Meningococcal conjugate vaccines, quadrivalent (MCV4). (Minimum age: 9 months for Menactra [MCV4-D], 2 years for Menveo [MCV4-CRM])

• For children aged 9 through 23 months (1) with persistent complement component deficiency; (2) who are residents of or travelers to countries with hyperendemic or epidemic disease; or (3) who are present during outbreaks caused by a vaccine serogroup, administer 2 primary doses of MCV4-D, ideally at ages 9 months and 12 months or at least 8 weeks apart.

• For children aged 24 months and older with (1) persistent complement component deficiency who have not been previously vaccinated; or (2) anatomic/functional asplenia, administer 2 primary doses of either MCV4 at least 8 weeks apart.

• For children with anatomic/functional asplenia, if MCV4-D (Menactra) is used, administer at a minimum age of 2 years and at least 4 weeks after completion of all PCV doses.

• See *MMWR* 2011; 60:72–76, available at http://www.cdc.gov/mmwr/pdf/wk/mm6003.pdf, and Vaccines for Children Program resolution No.6/11-1, available at http://www. cdc.gov/vaccines/programs/vfc/downloads/resolutions/06-11mening-mcv.pdf, and *MMWR* 2011; 60:1391–1392, available at http://www.cdc.gov/mmwr/pdf/wk/mm6040. pdf, for further guidance, including revaccination guidelines.

Persons aged 4 months through 6 years					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to dose 2	Dose 2 to dose 3	Dose 3 to dose 4	Dose 4 to dose 5
Hepatitis B	Birth	4 weeks	8 weeks and at least 16 weeks after first dose; minimum age for the final dose is 24 weeks		
Rotavirus[1]	6 weeks	4 weeks	4 weeks[1]		
Diphtheria, tetanus, pertussis[2]	6 weeks	4 weeks	4 weeks	6 months	6 months[2]
Haemophilus influenzae type b[3]	6 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose) if first dose administered at age 12–14 months No further doses needed if first dose administered at age 15 months or older	4 weeks[3] if current age is younger than 12 months 8 weeks (as final dose)[3] if current age is 12 months or older and first dose administered at younger than age 12 months and second dose administered at younger than 15 months No further doses needed if previous dose administered at age 15 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months	
Pneumococcal[4]	6 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older or current age 24 through 59 months No further doses needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months 8 weeks (as final dose for healthy children) if current age is 12 months or older No further doses needed for healthy children if previous dose administered at age 24 months or older	8 weeks (as final dose) This dose only necessary for children aged 12 months through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age	
Inactivated poliovirus[5]	6 weeks	4 weeks	4 weeks	6 months[5] minimum age 4 years for final dose	
Meningococcal[6]	9 months	8 weeks[6]			
Measles, mumps, rubella[7]	12 months	4 weeks			
Varicella[8]	12 months	3 months			
Hepatitis A	12 months	6 months			

FIGURE A-2 Catch-up immunization schedule for persons aged 4 months through 18 years who start late or who are more than 1 month behind—United States, 2012. The figure provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses.

SOURCE: CDC. 2012. *Immunization schedules*. http://www.cdc.gov/vaccines/schedules/hcp/child-adolescent.html.

CATCH-UP SCHEDULE

1. Rotavirus (RV) vaccines (RV-1 [Rotarix] and RV-5 [Rota Teq]).

• The maximum age for the first dose in the series is 14 weeks, 6 days; and 8 months, 0 days for the final dose in the series. Vaccination should not be initiated for infants aged 15 weeks, 0 days or older.

• If RV-1 was administered for the first and second doses, a third dose is not indicated.

2. Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.

• The fifth dose is not necessary if the fourth dose was administered at age 4 years or older.

3. *Haemophilus influenzae* type b (Hib) conjugate vaccine.

• Hib vaccine should be considered for unvaccinated persons aged 5 years or older who have sickle cell disease, leukemia, human immunodeficiency virus (HIV) infection, or anatomic/functional asplenia.

• If the first 2 doses were PRP-OMP (PedvaxHIB or Comvax) and were administered at age 11 months or younger, the third (and final) dose should be administered at age 12 through 15 months and at least 8 weeks after the second dose.

• If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a final dose at age 12 through 15 months.

4. Pneumococcal vaccines. (Minimum age: 6 weeks for pneumococcal conjugate vaccine [PCV]; 2 years for pneumococcal polysaccharide vaccine [PPSV])

• For children aged 24 through 71 months with underlying medical conditions, administer 1 dose of PCV if 3 doses of PCV were received previously, or administer 2 doses of PCV at least 8 weeks apart if fewer than 3 doses of PCV were received previously.

• A single dose of PCV may be administered to certain children aged 6 through 18 years with underlying medical conditions. See age-specific schedules for details.

• Administer PPSV to children aged 2 years or older with certain underlying medical conditions. See *MMWR* 2010; 59(No. RR-11), available at http://www.cdc.gov/mmwr/pdf/rr/rr5911.pdf.

5. Inactivated poliovirus vaccine (IPV).

• A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.

• In the first 6 months of life, minimum age and minimum intervals are only recommended if the person is at risk for imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).

• IPV is not routinely recommended for U.S. residents aged 18 years or older.

6. Meningococcal conjugate vaccines, quadrivalent (MCV4). (Minimum age: 9 months for Menactra [MCV4-D]; 2 years for Menveo [MCV4-CRM])

• See Figure 1 ("Recommended immunization schedule for persons aged 0 through 6 years") and Figure 2 ("Recommended immunization schedule for persons aged 7 through 18 years") for further guidance (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6105a5.htm).

7. Measles, mumps, and rubella (MMR) vaccine.

• Administer the second dose routinely at age 4 through 6 years.

8. Varicella (VAR) vaccine.

• Administer the second dose routinely at age 4 through 6 years. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

9. Tetanus and diphtheria toxoids (Td) and tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccines.

• For children aged 7 through 10 years who are not fully immunized with the childhood DTaP vaccine series, Tdap vaccine should be substituted for a single dose of Td vaccine in the catch-up series; if additional doses are needed, use Td vaccine. For these children, an adolescent Tdap vaccine dose should not be given.

• An inadvertent dose of DTaP vaccine administered to children aged 7 through 10 years can count as part of the catch-up series. This dose can count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11-12 years.

10. Human papillomavirus (HPV) vaccines (HPV4 [Gardasil] and HPV2 [Cervarix]).

• Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if patient is not previously vaccinated.

• Use recommended routine dosing intervals for vaccine series catch-up; see Figure 2 ("Recommended immunization schedule for persons aged 7 through 18 years," http://www.cdc.gov/vaccines/schedules/downloads/child/7-18yrs-schedule-pr.pdf).

Appendix B

Glossary

Acellular vaccine: a vaccine containing partial cellular material as opposed to complete cells.[1]

Adjuvant: a substance (e.g., aluminum salt) that is added during production to increase the body's immune response to a vaccine.[1]

Adverse event: undesirable experiences occurring after immunization that may or may not be related to the vaccine.[1]

Allergic rhinitis: rhinitis (inflammation of the mucous membrane of the nose marked especially by rhinorrhea, nasal congestion and itching, and sneezing) caused by exposure to an allergen.[2]

Allergy: a condition in which the body has an exaggerated response to a substance (e.g., food or drug). Also known as *hypersensitivity*.[1]

Anaphylaxis: an immediate and severe allergic reaction to a substance. Symptoms of anaphylaxis include breathing difficulties, loss of consciousness, and a drop in blood pressure. This condition can be fatal and requires immediate medical attention.[1]

Antibody: a protein found in the blood that is produced in response to foreign substances (e.g., bacteria or viruses) invading the body. Antibodies protect the body from disease by binding to these organisms and destroying them.[1]

Antigens: foreign substances (e.g., bacteria or viruses) in the body that are capable of causing disease. The presence of antigens in the body triggers an immune response, usually the production of antibodies.[1]

Arthritis: inflammation of joints due to infectious, metabolic, or constitutional causes.[2]

Asperger syndrome: a developmental disorder resembling autism that is characterized by impaired social interaction, by repetitive patterns of behavior and restricted interests, by normal language and cognitive development, and often by above-average performance in a narrow field against a general background of deficient functioning—also called *Asperger's disorder.*[2]

Asthma: a disorder that causes the airways of the lungs to swell and narrow, leading to wheezing, shortness of breath, chest tightness, and coughing.[3]

Atopy: a genetic disposition to develop an allergic reaction (as allergic rhinitis, asthma, or atopic dermatitis) and produce elevated levels of IgE upon exposure to an environmental antigen and especially one inhaled or ingested.[2]

Attention deficit disorder (ADD): a syndrome of disordered learning and disruptive behavior that is not caused by any serious underlying physical or mental disorder and that has several subtypes characterized primarily by symptoms of inattentiveness or primarily by symptoms of hyperactivity and impulsive behavior (as in speaking out of turn) or by the significant expression of all three.[2]

Attenuated vaccine: a vaccine in which live virus is weakened through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease. Attenuated vaccines currently licensed in the United States include measles, mumps, rubella, polio, yellow fever, and varicella. Also known as a *live vaccine.*[1]

Autism: a developmental disorder that appears in the first 3 years of life, and affects the brain's normal development of social and communication skills.[3]

Autoimmune Diseases Disorder: a condition that occurs when the immune system mistakenly attacks and destroys healthy body tissue. There are more than 80 different types of autoimmune disorders.[3]

Bacille Calmette-Guérin (BCG): an attenuated strain of tubercle bacillus developed by repeated culture on a medium containing bile and used in preparation of tuberculosis vaccines.[2]

Bias: systematic deviation of results or inferences from truth; processes leading to such deviation. An error in the conception and design of a study—or in the collection, analysis, interpretation, reporting, publication, or review of data—leading to results or conclusions that are systematically (as opposed to randomly) different from the truth.[4]

Case-control study: the observational epidemiological study of persons with the disease (or another outcome variable) of interest and a suitable control group of persons without the disease (comparison group, reference group). The potential relationship of a suspected risk factor or an attribute to the disease is examined by comparing the diseased and nondiseased subjects with regard to how frequently the factor or attribute is present (or, if quantitative, the levels of the attribute) in each of the groups (diseased and nondiseased).[4]

Cohort study: the analytic epidemiological study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or not exposed, or exposed in different degrees, to a factor or factors hypothesized to influence the occurrence of a given disease or other outcome. The main feature of cohort study is observation of large numbers over a long period (commonly years), with comparison of incidence rates in groups that differ in exposure levels. The alternative terms for a cohort study (i.e., follow-up, longitudinal, and prospective study) describe an essential feature of the method, which is observation of the population for a sufficient number of person-years to generate reliable incidence or mortality rates in the population subsets. This generally implies study of a large population, study for a prolonged period (years), or both. The denominators used for analysis may be persons or person-time.[4]

Community immunity: a situation in which a sufficient proportion of a population is immune to an infectious disease (through vaccination and/or prior illness) to make its spread from person to person unlikely. Even individuals not vaccinated (such as newborns and those with chronic illnesses) are offered some protection because the disease has little opportunity to spread within the community. Also known as *herd immunity*.[1]

Confounding: loosely, the distortion of a measure of the effect of an exposure on an outcome caused by the association of the exposure with other factors that influence the occurrence of the outcome. Confounding occurs

when all or part of the apparent association between the exposure and outcome is in fact accounted for by other variables that affect the outcome and are not themselves affected by exposure.[4]

Contraindication: a condition in a recipient which is likely to result in a life-threatening problem if a vaccine were given.[1]

Convulsion: see Seizure.

Cross-sectional study: a study that examines the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in a defined population at one particular time. The presence or absence of disease and the presence or absence of the other variables (or, if they are quantitative, their level) are determined in each member of the study population or in a representative sample at one particular time. The relationship between a variable and the disease can be examined (1) in terms of the prevalence of disease in different population subgroups defined according to the presence or absence (or level) of the variables and (2) in terms of the presence or absence (or level) of the variables in the diseased versus the nondiseased. Note that disease prevalence rather than incidence is normally recorded in a cross-sectional study. The temporal sequence of cause and effect cannot necessarily be determined in a cross-sectional study.[4]

Diabetes: a chronic health condition where the body is unable to produce insulin and properly breakdown sugar (glucose) in the blood. Symptoms include hunger, thirst, excessive urination, dehydration, and weight loss. The treatment of diabetes requires daily insulin injections, proper nutrition, and regular exercise. Complications can include heart disease, stroke, neuropathy, poor circulation leading to loss of limbs, hearing impairment, vision problems, and death.[1]

Diphtheria: a specific infectious disease due to the bacterium *Corynebacterium diphtheriae* and its highly potent toxin; marked by severe inflammation that can form a membranous coating, with formation of a thick fibrinous exudate, of the mucous membrane of the pharynx, the nose, and sometimes the tracheobronchial tree; the toxin produces degeneration in peripheral nerves, heart muscle, and other tissues, diphtheria had a high fatality rate, especially in children, but is now rare because of an effective vaccine.[5]

Ecological study: a study in which the units of analysis are populations or groups of people rather than individuals. Conclusions of ecological studies

may not apply to individuals; thus caution is needed to avoid the ecological fallacy. Ecological studies can reach valid causal inferences on causal relationships at the ecological level—i.e., on causal processes that occur at the group level of among groups. Ecological studies are necessary for decisions that affect entire groups.[4]

Eczema: an inflammatory condition of the skin characterized by redness, itching, and oozing vesicular lesions which become scaly, crusted, or hardened.[2]

Encephalopathy: a general term describing brain dysfunction. Examples include encephalitis, meningitis, seizures, and head trauma.[1]

Epilepsy: any of various disorders marked by abnormal electrical discharges in the brain and typically manifested by sudden brief episodes of altered or diminished consciousness, involuntary movements, or convulsions.[2]

Febrile seizures: a febrile seizure is a convulsion in a child triggered by a fever. Febrile seizures occur most often in otherwise healthy children between ages 9 months and 5 years. Toddlers are most commonly affected. Febrile seizures often run in families. Most febrile seizures occur in the first 24 hours of an illness and may not occur when the fever is highest. Ear infections or any cold or viral illness may trigger a febrile seizure.[3]

Guillain-Barré syndrome (GBS): an acute, immune-mediated disorder of peripheral nerves, spinal roots, and cranial nerves, commonly presenting as a rapidly progressive, areflexive, relatively symmetric ascending weakness of the limb, truncal, respiratory, pharyngeal, and facial musculature, with variable sensory and autonomic dysfunction; typically reaches its nadir within 2-3 weeks, followed initially by a plateau period of similar duration, and then subsequently by gradual but complete recovery in most cases.[5]

Haemophilus influenzae type b (Hib): a bacterial infection that may result in severe respiratory infections, including pneumonia, and other diseases such as meningitis.[1]

Hepatitis: inflammation of the liver, due usually to viral infection but sometimes to toxic agents.[5]

Hepatitis A: a viral disease with a short incubation period (usually 15-50 days), caused by hepatitis A virus, a member of the family Picornaviridae, often transmitted by fecal-oral route; may be inapparent, mild, severe, or occasionally fatal and occurs sporadically or in epidemics, commonly in

school-age children and young adults; necrosis of periportal liver cells with lymphocytic and plasma cell infiltration is characteristic, and jaundice is a common symptom.[5]

Hepatitis B: a viral disease with a long incubation period (usually 50-160 days), caused by a hepatitis B virus, a DNA virus and member of the family Hepadnaviridae, usually transmitted by injection of infected blood or blood derivatives or by use of contaminated needles, lancets, or other instruments or by sexual transmission; clinically and pathologically similar to viral hepatitis type A, but there is no cross-protective immunity; HBsAg is found in the serum and the hepatitis delta virus occurs in some patients. May lead to acute or chronic liver disease.[5]

Human papillomavirus (HPV): an icosahedral DNA virus, 55 nm in diameter, of the genus *Papillomavirus*, family Papovaviridae; certain types cause cutaneous and genital warts; other types are associated with severe cervical intraepithelial neoplasia and anogenital and laryngeal carcinomas.[5]

Immune thrombocytopenic purpura (ITP): a systemic illness characterized by extensive ecchymoses and hemorrhages from mucous membranes and very low platelet counts; resulting from platelet destruction by macrophages due to an antiplatelet factor; childhood cases are usually brief and rarely present with intracranial hemorrhages, but adult cases are often recurrent and have a higher incidence of grave bleeding, especially intracranial. Also known as *idiopathic thrombocytopenic purpura*.[5]

Immunoglobulins: see Antibody.

Inactivated vaccine: a vaccine made from viruses and bacteria that have been killed through physical or chemical processes. These killed organisms cannot cause disease.[1]

Influenza: an acute infectious respiratory disease, caused by influenza viruses, which are in the family Orthomyxoviridae, in which the inhaled virus attacks the respiratory epithelial cells of those susceptible and produces a catarrhal inflammation; characterized by sudden onset, chills, fever of short duration (3-4 days), severe prostration, headache, muscle aches, and a cough that usually is dry and may be followed by secondary bacterial infections that can last up to 10 days.[5]

Live vaccine: a vaccine in which live virus is weakened (attenuated) through chemical or physical processes in order to produce an immune response without causing the severe effects of the disease. Attenuated vaccines

currently licensed in the United States include measles, mumps, rubella, shingles (herpes zoster), varicella, and yellow fever. Also known as an *attenuated vaccine*.[1]

Measles: an acute exanthematous disease, caused by measles virus (genus Morbillivirus), a member of the family Paramyxoviridae, and marked by fever and other constitutional disturbances, a catarrhal inflammation of the respiratory mucous membranes, and a generalized dusky red maculopapular eruption; the eruption occurs early on the buccal mucous membrane in the form of Koplik spots, a manifestation useful in early diagnosis; average incubation period is from 10-12 days.[5]

Meningitis: inflammation of the membranes of the brain or spinal cord.[5]

Mumps: an acute infectious and contagious disease caused by a mumps virus of the genus Rubulavirus and characterized by fever, inflammation, and swelling of the parotid gland, and sometimes of other salivary glands, and occasionally by inflammation of the testis, ovary, pancreas, or meninges.[5]

Myoclonus: irregular involuntary contraction of a muscle usually resulting from functional disorder of controlling motor neurons.[2]

Nested case-control study: an important type of case-control study in which cases and controls are drawn from the population in a fully enumerated cohort. Typically, some data on some variables are already available about both cases and controls; thus concerns about differential (biased) misclassification of these variables can be reduced (e.g., environmental or nutritional exposures may be analyzed in blood from cases and controls collected and stored years before disease onset). A set of controls is selected from subjects (i.e., noncases) at risk of developing the outcome of interest at the time of occurrence of each case that arises in the cohort.[4]

Observational study: a study that does not involve any intervention (experimental or otherwise) on the part of the investigator. A study with random allocation is inherently experimental or nonobservational. Observations are not just a haphazard collection of facts; in their own way, observational studies must apply the same rigor as experiments. Many important epidemiological, clinical, and microbiological studies are completely observational or have large observational components.[4]

Otitis Media: a viral or bacterial infection that leads to inflammation of the middle ear. This condition usually occurs along with an upper respiratory infection. Symptoms include earache, high fever, nausea, vomiting, and

diarrhea. In addition, hearing loss, facial paralysis, and meningitis may result.[1]

Pertussis: an acute infectious inflammation of the larynx, trachea, and bronchi caused by Bordetella pertussis; characterized by recurrent bouts of spasmodic coughing that continues until the breath is exhausted, then ending in a noisy inspiratory stridor (the "whoop") caused by laryngeal spasm.[5]

Pneumonia: inflammation of the lung parenchyma characterized by consolidation of the affected part, the alveolar air spaces being filled with exudate, inflammatory cells, and fibrin.[5]

Poliomyelitis: an acute infectious virus disease caused by the poliovirus, characterized by fever, motor paralysis, and atrophy of skeletal muscles often with permanent disability and deformity, and marked by inflammation of nerve cells in the ventral horns of the spinal cord—called also *infantile paralysis, polio*.[2]

Randomized controlled trial (RCT): an epidemiological experiment in which subjects in a population are randomly allocated into groups, usually called study and control groups, to receive or not receive an experimental preventive or therapeutic procedure, maneuver, or intervention. The results are assessed by rigorous comparison of rates of disease, death, recovery, or other appropriate outcome in the study and control groups. RCTs are generally regarded as the most scientifically rigorous method of hypothesis testing available in epidemiology and medicine. Nonetheless, they may suffer serious lack of generalizability, due, for example, to the nonrepresentativeness of patients who are ethically and practically eligible, chosen, or consent to participate.[4]

Retrospective study: a research design used to test etiological hypotheses in which inferences about exposure to the putative causal factor(s) are derived from data relating to characteristics of the persons under study or to events or experiences in their past. The essential feature is that some of the persons under study have the disease or other outcome condition of interest, and their characteristics and past experiences are compared with those of other, unaffected persons. Persons who differ in the severity of the disease may also be compared. It is no longer considered a synonym for case-control study.[4]

Rotavirus: a group of viruses that cause diarrhea in children.[1]

Rubella: an acute but mild exanthematous disease caused by rubella virus (Rubivirus family Togaviridae), with enlargement of lymph nodes, but usually with little fever or constitutional reaction; a high incidence of birth defects in children results from maternal infection during the first trimester of fetal life (congenital rubella syndrome).[5]

Seizure: a violent spasm or series of jerkings of the face, trunk, or extremities. Also known as *convulsions*.[5]

Self-controlled case series study: the method, like the case-crossover method, uses cases as their own controls. However, the similarity stops there, as the case series method derives from cohort rather than case-control logic. In particular, ages at vaccination are regarded as fixed, and the random variable of interest is the age at adverse event, conditionally on its occurrence within a pre-determined observation period.[6]

Socioeconomic status (SES): descriptive term for a person's position in society, which may be expressed on an ordinal scale using such criteria as income, level of education attained, occupation, value of dwelling place, etc.[4]

Stroke: any acute clinical event, related to impairment of cerebral circulation, that lasts longer than 24 hours.[5]

Sudden death: unexpected death that is instantaneous or occurs within minutes or hours from any cause other than violence.[2]

Surveillance: systematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment to those who have the right to know so action can be taken. It is an essential feature of epidemiologic and public health practice. The final phase in the surveillance chain is the application of information to health promotion and to disease prevention and control. A surveillance system includes functional capacity for data collection, analysis, and dissemination linked to public health programs.[4]

Tetanus: a disease marked by painful tonic muscular contractions, caused by the neurotropic toxin (tetanospasmin) of *Clostridium tetani* acting upon the central nervous system.[5]

Thimerosal: thimerosal is a mercury-containing preservative used in some vaccines and other products since the 1930s. There is no convincing evidence of harm caused by the low concentrations of thimerosal in vaccines, except for minor reactions like redness and swelling at the injection site.

However, in July 1999, the Public Health Service agencies, the American Academy of Pediatrics, and vaccine manufacturers agreed that thimerosal should be reduced or eliminated in vaccines as a precautionary measure. Today, all routinely recommended childhood vaccines manufactured for the U.S. market contain either no thimerosal or only trace amounts with the exception of some flu vaccines. There are thimerosal-free influenza vaccines available.[1]

Thrombocytopenia: a condition in which an abnormally small number of platelets is present in the circulating blood.[5]

Toxoid vaccines: toxoid vaccines contain a toxin or chemical made by the bacteria or virus. They make you immune to the harmful effects of the infection, instead of to the infection itself. Examples are the diphtheria and tetanus vaccines.[3]

Type 1 diabetes: diabetes of a form that usually develops during childhood or adolescence and is characterized by a severe deficiency of insulin secretion resulting from atrophy of the islets of Langerhans and causing hyperglycemia and a marked tendency toward ketoacidosis—called also *insulin-dependent diabetes, insulin-dependent diabetes mellitus, juvenile diabetes, juvenile-onset diabetes, type 1 diabetes mellitus*.[2]

Vaccination: injection of a killed or weakened infectious organism in order to prevent the disease.[1]

Vaccine: immunobiological substance used for active immunization by introducing into the body a live modified, attenuated, or killed inactivated infectious organism or its toxin. The vaccine is capable of stimulating an immune response by the host, who is thus rendered resistant to infection. The word *vaccine* was originally applied to the serum from a cow infected with vaccinia virus (cowpox; from Latin *vacca*, "cow"); it is now used of all immunizing agents.[4]

Vaccine Adverse Event Reporting System (VAERS): a database managed by the Centers for Disease Control and Prevention and the Food and Drug Administration. VAERS provides a mechanism for the collection and analysis of adverse events associated with vaccines currently licensed in the United States. Reports to VAERS can be made by the vaccine manufacturer, recipient, their parent/guardian, or health care provider. For more information on VAERS call (800) 822-7967.[1]

Vaccine Safety Datalink (VSD) Project: to increase knowledge about vaccine adverse events, the Centers for Disease Control and Prevention have formed partnerships with nine large health management organizations (HMOs) to continually evaluate vaccine safety. The project contains data on more than 9 million people. Medical records are monitored for potential adverse events following immunization. The VSD project allows for planned vaccine safety studies as well as timely investigations of hypotheses.[1]

Varicella: an acute contagious disease, usually occurring in children, caused by the Varicella-zoster virus genus, Varicellovirus, a member of the family Herpesviridae, and marked by a sparse eruption of papules, which become vesicles and then pustules, like that of smallpox although less severe and varying in stages, usually with mild constitutional symptoms; incubation period is about 14-17 days.[5]

SOURCES

[1]Centers for Disease Control and Prevention as defined on the following webpage: http://www.vaccines.gov/more_info/glossary/index.html.

[2]*Merriam-Webster Medical Dictionary*, a source used by the National Institutes of Health's Medline Plus website, which is produced by the National Library of Medicine. The citation for the *Merriam-Webster Medical Dictionary* term is *Merriam-Webster Medical Dictionary* [Internet]. [Springfield (MA)]: Merriam-Webster, Incorporated; © 2003, and the specific term can be obtained on the following website: http://www.nlm.nih.gov/medlineplus/mplusdictionary.html.

[3]*A.D.A.M. Medical Encyclopedia*, a source used by the National Center for Biotechnology Information, a division of the National Library of Medicine at the National Institutes of Health. The citation for the *A.D.A.M. Medical Encyclopedia* term is *A.D.A.M. Medical Encyclopedia* [Internet]. [Atlanta (GA)]: A.D.A.M., Inc.; © 2010, and the specific term can be obtained on the following website: http://www.ncbi.nlm.nih.gov/pubmedhealth/s/diseases_and_conditions.

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Appendix C

Acronyms

AAFP	American Academy of Family Physicians
AAP	American Academy of Pediatrics
ACIP	U.S. Advisory Committee on Immunization Practices
BCG	bacillus Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CISA	Clinical Immunization Safety Assessment Network
CPRD	Clinical Practice Research Datalink (United Kingdom)
CRS	Danish Civil Registration System
DT	diphtheria and tetanus toxoids absorbed
DTaP	diphtheria and tetanus toxoids and acellular pertussis vaccine
DTP	diphtheria and tetanus toxoids and whole-cell pertussis vaccine
EHR	electronic health record
EMR	electronic medical record
FDA	Food and Drug Administration
GPRD	General Practice Research Database (United Kingdom)
GRADE	Grading of Recommendations Assessment, Development, and Evaluation

HCUP	Healthcare Cost and Utilization Project
HepB	hepatitis B vaccine
HES	Hospital Episode Statistics (United Kingdom)
HHS	U.S. Department of Health and Human Services
Hib	*Haemophilus influenzae* type B conjugate vaccine
HIPC	Human Immunology Project Consortium (NIH)
HPA	Health Protection Agency (United Kingdom)
IgM	immunoglobulin M
IIS	immunization information system
IMPACT	Immunization Monitoring Program, Active (Canada)
IND	Investigational New Drug
IOM	Institute of Medicine
IPV	inactivated poliovirus vaccine
IRB	Institutional Review Board
ISO	Immunization Safety Office (CDC)
ITP	immune thrombocytopenic purpura
KID	Kids' Inpatient Database
MCO	managed care organization
MeSH	medical subject headings
MMR	measles, mumps, and rubella vaccine
MMRV	measles, mumps, rubella, and varicella (chickenpox) vaccine
MMWR	*Morbidity and Mortality Weekly Reports*
NCS	National Children's Study
NHIS	National Health Interview Survey
NHS	National Health Service (United Kingdom)
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NIS	National Immunization Survey
NVAC	National Vaccine Advisory Committee
NVPO	National Vaccine Program Office
OPV	oral poliovirus vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PDD	pervasive developmental disorder
PRISM	Post-Licensure Rapid Immunization Safety Monitoring
RCT	randomized controlled trial

TIV	trivalent inactivated influenza vaccine
VAERS	Vaccine Adverse Event Reporting System
VAESCO	Vaccine Adverse Event Surveillance and Communication Network
VICP	National Vaccine Injury Compensation Program
VSD	Vaccine Safety Datalink
WHO	World Health Organization
WISC-III	Wechsler Intelligence Scale for Children III

Appendix D

Study Designs for the Safety Evaluation of Different Childhood Immunization Schedules

Martin Kulldorff[1]

SUMMARY

To date, there have been few comparative studies evaluating the safety of different vaccine schedules. A few of the existing studies have shown that there are cases in which the risk of adverse events can depend on the vaccination schedule used. Hence, it is both a feasible and an important area of study. As a relatively new field of investigation, the big question is what types of study designs will be most fruitful for evaluating different childhood vaccine schedules. A number of possible study designs are presented in this review to evaluate different features or components of the vaccine schedule. These include the timing of individual vaccines, the timing between doses of the same vaccine, the interaction effect between vaccines and concurrent health conditions or pharmaceutical medications, the interaction effects of different vaccines given on the same day, the ordering of different vaccines, and the effect of cumulative summary metrics such as the total number of vaccines or the total amount of some vaccine ingredient. Study designs for the comparative evaluation of one or more complete schedules are also considered. Methods are presented both for adverse events with an early onset, which are the easiest to study, and for adverse events with a late onset, including serious chronic conditions. It is concluded that a wide variety of different vaccine schedule components can be studied.

[1] Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute.

INTRODUCTION

Before approval by the Food and Drug Administration (FDA), vaccines are evaluated for efficacy and safety using large Phase III randomized controlled trials. For childhood vaccines, the number of children enrolled in these trials is typically in the thousands. That is sufficient to detect common but not rare adverse events. For the latter, there exist several postmarketing vaccine safety surveillance systems using observational data on children who receive the vaccines as part of their general care. In the United States, these include the Vaccine Adverse Event Reporting System (VAERS), the Vaccine Safety Datalink (VSD), and the Clinical Immunization Safety Assessment Network, all sponsored by the Centers for Disease Control and Prevention (CDC), as well as the Post-Licensure Rapid Immunization Safety Monitoring System (PRISM), which is part of the FDA-sponsored Mini-Sentinel Initiative. Internationally, there are other important vaccine safety surveillance systems such as the Epidemiology Vaccine Research Program at the National Institute for Health Data and Disease Control in Denmark; the Vaccine Adverse Event Surveillance and Communication (VAESCO) Network, coordinated by the European Center for Disease Control; the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring; and the Immunization Division at the Communicable Disease Surveillance Centre in England. All these vaccine safety systems have proven to be very useful and important. They have detected unsuspected adverse events leading to revisions in vaccine recommendations and, in other cases, established the safety of vaccines for which important safety concerns existed. Throughout their existence, there has been continuous and rapid development with respect to the types of questions studied and the epidemiological and statistical methods used. For example, for every new childhood vaccine approved by the FDA, VSD now conducts near real-time safety surveillance using weekly data feeds from electronic health records (Lieu et al., 2007; Yih et al., 2011). The credit for these continuously improved vaccine safety surveillance systems goes to the devoted scientists that are building the systems and using them for many important studies, to the government agencies supporting this work, and to the vaccine safety advocacy groups that are the key public voice for improved and expanded vaccine safety surveillance.

Most postmarketing studies evaluate the general question as to whether or not a vaccine causes an adverse event. Very few postmarketing studies have evaluated whether the risk of adverse events depends on the scheduling of the vaccines. For example, few postmarketing studies have evaluated whether the risk of adverse events depends on the age at which a vaccine is given, on the relative timing of two different vaccines, or on a combined cumulative effect generated by the timing of dozens of different vaccines.

These are all different components of the vaccine schedule, and any one of these could potentially be related to the number and severity of adverse events. When evaluating the safety of different vaccine schedules, it is hence important to study the whole range of issues, from the timing of a single vaccine to summary metrics based on the timing of dozens of vaccines.

The paper presented in this appendix was commissioned by the Institute of Medicine Committee on the Assessment of Studies of Health Outcomes Related to the Recommended Childhood Immunization Schedule. The paper considers different types of potential questions and concerns about the safety of vaccine schedules and describes different epidemiological study designs and statistical methods that can be used to answer such questions in a scientifically rigorous manner. The core of this paper is a set of proposals for the type of study designs and methods that would be appropriate for the comparative evaluation of vaccine adverse events under different vaccine schedules, and the paper is written in the context of the many difficulties raised by the speakers at the committee meetings held in February and March 2012. Note, though, that it is not a synthesis, an evaluation, or a review of the many excellent presentations made at those meetings. Instead, it should be viewed as complementary information. Note also that the paper does not say anything about the advantages or disadvantages about specific vaccines or vaccine schedules. Rather, the focus is on potential study designs and methods and their ability, or inability, to answer such questions.

DEFINITIONS OF KEY TERMS

Component of the vaccine schedule: some specific feature of the vaccine schedule, such as the age at which one of the vaccines is given or the total amount of immune-stimulating content received from all vaccines in the schedule. Not to be confused with different components of a single vaccine.

Early onset: an adverse event that manifests itself and can be detected within a few weeks after vaccination.

Late onset: an adverse event that does not manifest itself and/or cannot be detected until a few months or years after vaccination.

Potential adverse event: a health event under evaluation in a vaccine safety study, in order to determine if it is caused by the vaccine(s) or not.

VACCINE SCHEDULES, ADVERSE EVENTS, AND DATA SETS

Vaccine Schedules and Their Components

To study the safety of different childhood vaccine schedules is an important but complex task. With dozens of vaccines, many of which have

multiple doses, there are an almost infinite number of possible vaccine schedules that can be used. To scientifically evaluate the safety of different vaccine schedules, it is necessary to look at specific components of the schedule. Some such components are as follows:

Timing of Specific Vaccines

- The age at which a specific vaccine is given, such as the age at the first dose of the hepatitis B vaccine.
- The relative timing of different doses of the same vaccine, such as the number of months between the first and second doses of the 7-valent pneumococcal conjugate vaccine (PCV7).
- The interaction between the timing of a specific vaccine and time-varying health events or health status, such as a vaccination given to a child taking a temporary or seasonal medication.

Relative Timing of Two or More Different Vaccines

- The interaction among different vaccines given on the same day, such as the effect of giving the measles, mumps, and rubella (MMR) vaccine and varicella vaccines at the same health care visit or different health care visits.
- The order in which different vaccines are given, such as whether measles vaccine is given a few months before or after the diphtheria-tetanus-pertussis (DTP) vaccine.

Summary Metrics of a Vaccine Schedule

- The total number of vaccinations given to the child before a certain age, such as the 6th birthday.
- The average age at which the vaccines were given.
- The cumulative amount of immune-stimulating content present in all vaccines received.

In addition to specific components of the vaccine schedule, one can also try to compare complete vaccine schedules.

Comparison of Complete Vaccine Schedules

- Whether or not the child has approximately followed the CDC-recommended vaccine schedule.
- The comparative safety of a specific alternative vaccine schedule, such as Dr. Bob's (Sears, 2007), versus the one recommended by CDC.

The study design and statistical methods used depend on which vaccine schedule component is being evaluated. As they are quite different, each component of Components (a) to (e) is dealt with in separate sections of this paper. For cumulative summary metrics, the methods are similar irrespective of what component of the vaccine schedule the metric is designed to measure. Components (f) to (h) are treated together. Methods for comparing different complete vaccine schedules are discussed, and one vaccine schedule with completely unvaccinated children is evaluated. More general methodological issues and financial and ethical considerations are also discussed.

The different types of studies should not be done in isolation from each other. If it is found that one complete vaccine schedule has an excess number of adverse events compared to another, we do not know which component of the schedule caused the difference. Hence, it is not recommended that studies comparing complete schedules be conducted without also evaluating specific components of those schedules. Likewise, when a specific component is studied, results may be confounded by other components of the vaccine schedule. For example, a child receiving vaccine A at an early age may be more likely to also receive vaccine B at an early age, and the timing of vaccine A will then be correlated with the number of adverse events even if it is the timing of vaccine B that is the culprit. It could also be that there are two different vaccine schedule components that cause adverse events but that they cancel each other out when one looks at the difference between two complete schedules, making it impossible to detect the problem if only the complete schedules are studied.

Another reason for studying specific components of the vaccine schedule is that, if a problem is found, we need to know how to revise the schedule in order to reduce the number of adverse events. Just because one complete vaccine schedule is found to cause more adverse events than another, we do not necessarily have to revise all components of that schedule.

Adverse Events with Early Versus Late Onset

In vaccine safety studies, the goal is to evaluate if there is a causal relationship between the vaccine(s) and some health event of interest. The latter is denoted as a potential adverse event, as it may or may not be an actual adverse event caused by the vaccine(s). The type of health event under study determines the appropriate methodological methods for vaccine safety studies. This paper considers two main types. The first type consists of potential adverse events with an early onset that can be detected soon after the onset. The event itself could be either acute and of a passing nature without any permanent damage, such as a febrile seizure, or chronic, lasting many years, such as a stroke. The second type consists of potential adverse events with a late onset several months or years after vaccination

and events with an early or a gradual onset that cannot be detected until long after vaccination. For simplicity, all of these are denoted "late onset." These potential adverse events can also be either acute or chronic in nature.

The most suitable study designs and analysis methods are greatly dependent on whether the potential adverse event has an early or late onset, and in the description below, separate methods are proposed for the two outcome types. This is a little bit of a simplification, since there are, of course, also potential adverse events that fall somewhere in between on this spectrum. It should also be pointed out that an early-onset chronic condition can be studied by use of either of the methods described for early or late onset, but the early-onset methods are in most cases preferable.

Another key issue is whether there is a clear time at which the potential adverse event happened, as with, for example, a seizure, or whether the disease evolves more gradually, without a single clearly defined day of onset, as with, for example, narcolepsy or autism. This does not affect the study design as much as the time of onset, but it is an important consideration when defining and collecting the data.

For most potential adverse events, we are interested only in incident diagnoses, that is, the first time that a particular diagnosis has been made. For example, if a child is diagnosed with asthma at age 2 years and then has a follow-up visit for his/her asthma at age 4 years, we do not want to attribute the asthma to a vaccination given at age 3 years. Depending on the potential adverse event under study, one can define an incident diagnosis as a diagnosis that has not occurred during the previous D days. The value of D will depend on the adverse event, but a typical value is about 1 year.

The potential adverse event studied either can be very specific, such as febrile seizures or autism, or can be more general, such as all-cause outpatient physician visits, emergency department visits, or hospitalizations. The latter set of events may seem more desirable, as it includes the combined effect of the vaccine schedule on all important health events, but the opposite is true. Such general definitions are more prone to biases, and they are therefore more difficult to study. This is because people that follow the CDC-recommended vaccine schedule may be different from those that do not, in terms of their health care–seeking behavior. For example, parents that are more prone to take their children to the doctor when the child is sick may also be more prone to take their children to the well care visits during which most vaccines are given.

Data Sets for Postmarketing Vaccine Safety Studies

To facilitate the understanding of the study designs and methods described in subsequent sections, a brief background is first given concerning

some of the data sets that are available and currently used for postmarketing vaccine safety studies.

Premarketing Randomized Trials

Phase III randomized trials are primarily designed to evaluate the efficacy of vaccines. They are also able to find common adverse events, but their sample size is typically not large enough to evaluate rare but serious adverse events. Their primary use for postmarketing vaccine safety surveillance is to generate study hypotheses. For example, a single case of Kawasaki disease in the vaccine arm of a Phase III randomized trial is not evidence that the vaccine causes Kawasaki disease, since it could be pure coincidence, but it may warrant a postmarketing safety evaluation.

Spontaneous Reporting Systems

Most countries in the world have a vaccine safety surveillance system based on spontaneous reports. These are linked together through the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, so that it is possible to combine data from multiple countries. In the United States, CDC and FDA are joint sponsors of VAERS.

These systems contain spontaneous reports of suspected vaccine adverse events sent in by physicians, nurses, patients, parents, manufacturers, and others. The gender and age of the vaccinated person are some of the variables collected. There is often information about multiple vaccines given on the same day. Analyses are done by the use of proportional reporting ratios (Evans et al., 2001) and similar methods. For example, if 1.5 percent of all vaccine-related adverse event reports are for seizures and there are 1,000 reports for vaccine A, then we would expect 15 seizure reports for vaccine A. If, in reality, there are 45 such reports, the proportional reporting ratio is 3. That is more than what one would expect, and it may indicate that there is an excess risk of seizures after vaccination. Actual analyses are more complex, since it is necessary to adjust for age and other variables. There are also other more sophisticated methods used (Bate et al., 1998; DuMouchel, 1999; Rothman, 2011).

The major advantage of VAERS is that it receives reports from the whole country. The two major disadvantages are that there is underreporting and that there are no reliable denominator data. That is, while we have information about a number of vaccinated children with the potential adverse event of interest, we do not know the total number of children that were vaccinated, how many unvaccinated children had the same type of event, or how many vaccinated children had the event without it being reported.

Some reports to VAERS are studied further in the Clinical Immunization Safety Assessment Network. Among other things, this network aims to "improve the scientific understanding of vaccine safety at the individual patient level" by obtaining and evaluating detailed genetic and other information from each patient (LaRussa et al., 2011).

Electronic Medical Records

For 2011, it is estimated that 57 percent of office-based physicians used electronic medical records (EMRs), up from 24 percent in 2005 (Hsiao et al., 2011). The EMRs most useful for medical research are the ones from large health plans, as they contain medical records for a well-defined member population, including both inpatient and outpatient encounters. The VSD project is the premier EMR-based vaccine safety system in the United States (Baggs et al., 2011; Chen et al., 1997; DeStefano and the Vaccine Safety Datalink Research Group, 2001). Led by CDC, it is a collaboration with 10 health plans: Group Health in the State of Washington; Harvard Pilgrim/Atrius Health in Massachusetts; HealthPartners in Minnesota; Kaiser Permanente in Colorado, Georgia, Hawaii, Northern California, Oregon, and Southern California; and Marshfield Clinic in Wisconsin. Together, these health plans have about 9.5 million members and an annual birth cohort of more than 100,000. The VSD system is used both for retrospective studies and for near-real-time vaccine safety surveillance with weekly analyses of newly approved vaccines. Similar systems exist in a few other countries, including the Epidemiology Vaccine Research Program at the National Institute for Health Data and Disease Control (Statens Serum Institut) in Denmark.

The major advantage with EMR systems is that denominator data are available, as all vaccinated children can be identified. It is then possible to compare the number of adverse events in vaccinated and unvaccinated children or vaccine-exposed and unexposed time periods within the same child. A disadvantage is that the data are registered for purposes other than research, and there is sometimes miscoding of health events. Depending on the health outcome, manual chart review is therefore sometimes warranted.

Health Insurance Claims Data

Health insurance companies have medical information for millions of insured members and their families, which they receive when doctors and hospitals file their financial reimbursement claims. One such system in the United States is the PRISM program, run by FDA as part of its Mini-Sentinel project (Nguyen et al., 2012). Claims data are more limited than EMRs but can be used in much the same way for postmarketing vaccine

safety studies. The major advantage is the large sample size that can be achieved. The major disadvantage is that some health conditions are not captured. Depending on the potential adverse event under study and the confounders that need to be adjusted for, this may or may not be a problem.

Because of their similarities, EMRs and health insurance claims data will be treated as the same type of data in this appendix under the name "health plan data."

Study-Specific Data Collection

Sometimes, new data are collected specifically for vaccine safety studies, such as a self-controlled case series, a case-control study, a cohort study, or a postmarketing randomized trial. An intermediate option is to obtain some of the data from health plans, disease registries, and/or vaccine registries, while the remaining data are collected from study-specific patient surveys or measurements. The available options are too many to provide a detailed description of each.

TIMING OF SPECIFIC VACCINES

In a randomized childhood vaccine trial, the age at which the vaccine is given is tightly controlled by the study design, to correspond to the future planned vaccine schedule. This is appropriate, but once a vaccine is on the market, it is also given at a wide variety of other ages, for a variety of reasons. There are two scenarios in which it is of great interest to evaluate the risk of a vaccine as a function of the age at which the vaccine was given. (i) If a vaccine safety study has shown that there is a statistically significant excess risk of an adverse event, we want to know if the excess risk varies by the age at which the vaccine was given. (ii) Even if a general safety study covering all age groups has not shown a statistically significant excess risk of the adverse event, there could still be an excess risk if the vaccine is given at certain ages outside the recommended schedule. Such a safety problem could be masked by the noneffect among the most populous age group, and a special study looking at age-specific risks would be warranted.

Known Adverse Events with Early Onset

Background

Some vaccines have been shown to cause an acute adverse event within a few weeks after vaccination. Examples include intussusception 3 to 7 days after vaccination with rotavirus vaccine (RotaShield) (Kramarz et al., 2001; Murphy et al., 2001) and febrile seizure 7 to 10 days after vaccina-

tion with MMR and the measles, mumps, rubella, and varicella (MMRV) vaccine (Klein et al., 2010). There are also several such examples of less severe adverse events like fever and rash. The adverse event may be serious enough to warrant the withdrawal of the vaccine from the market, as with the rotavirus vaccine, or it may be mild enough to keep using the vaccine, as with MMR. A midlevel alternative option is to revise the vaccination schedule to minimize the number of adverse events or to contraindicate the vaccine in a certain age group. Knowledge of the relative and attributable risk of the adverse event as a function of age is one important component when deciding between these options, together with other important factors, such as how the immunogenicity varies by age. This paper discusses only methods for obtaining knowledge about the former and not how to weight different sources of information to arrive at a final decision.

Examples

In two different studies, Gargiullo et al. (2006) and Rothman et al. (2006) evaluated the effect of age on the excess risk of intussusceptions after vaccination with the rotavirus vaccine (RotaShield). In a more recent study, Rowhani-Rahbar et al. (2012) evaluated the effect of age on the risk of febrile seizures after vaccinations with MMR and MMRV. All three studies found that the risk of the adverse event varied greatly by age.

Data

EMRs from health plans and health insurance claims from health plans are ideally suited for studying this question. It is also possible to use data from a case-control study. VAERS data cannot easily be used since VAERS does not contain information about the age distribution of vaccinated children. Too few data are available from premarketing randomized because such trials are too small and typically do not include individuals over a wide enough range of ages. In light of existing observational data, specifically designed postmarketing randomized trials could be unethical, depending on the nature of the known adverse event.

Methods

The first key step is to determine the time between the vaccination and the adverse event as precisely as possible. Some children will, just by chance, have the adverse event soon after vaccination. To maximize the precision of our age estimates, we want to exclude as many of them as possible, by counting only the adverse events occurring in the true risk window. An efficient way to determine the appropriate risk window is to

use a temporal scan statistic. For a cohort of vaccinees with a subsequent event of interest, record the number of days from vaccination to the event. Ignore events that occur on the same day as the vaccination, as they may have a different background rate, as well as those that occur beyond an upper limit, such as 70 days after vaccination. If there is no relationship between the vaccine and the adverse event, we expect the adverse events to be uniformly distributed during the [1, 70]-day period. The temporal scan statistic scans the time period for any cluster of events, without any assumptions about their location or length. The method determines the statistical significance of such clusters, adjusting for the multiple testing inherent in the hundreds of overlapping time periods evaluated. As an example, temporal scan statistics were used to determine that the excess risk of seizures after vaccination with MMRV is confined to the 7- to 10-day postvaccination period (Klein et al., 2010).

The second step is to evaluate the relationship between age at vaccination and excess risk of the adverse event. The simplest and most common way to do this is to divide age into different groups, such as 6 to 12 months and 12 to 24 months, and compare the risk. It is unrealistic to assume that the risk suddenly jumps at a particular age, and for greater precision, it is better to model risk as a continuous function of age. This can be done by the use of either regression with first-, second-, and higher-degree polynomials or regression splines (Rothman et al., 2006).

In these analyses, it is important to take the underlying natural age-related risk into account. For example, the incidence of intussusceptions is very low immediately after birth, after which it gradually increases until about 5 months of age, after which it gradually decreases (Eng et al., 2012). There are a number of possible ways to adjust for this, depending on the exact study design. In a cohort study of vaccinated individuals, one can use historical data to estimate the age curve, using a polynomial function, and then use that as an offset term in the regression model. An alternative approach is to use both a risk and control interval for each individual, in a self-controlled analysis, evaluating whether the relative risk in these intervals varies by age of vaccination. Note, though, that if the natural incidence rate for the adverse event varies greatly by age in weeks rather than years, it is still necessary to incorporate an offset term based on the natural age curve even when a self-controlled analysis is conducted. In a case-control study, matching by age ensures that the age-based incidence curve is adjusted for.

Vaccine Risk for Specific Age Groups: Early-Onset Adverse Events

Background

Most childhood vaccines are given according to the recommended schedule, but some children may get the vaccine at a much earlier or a much later age. There are many potential reasons for this, including a high risk of exposure due to a current disease outbreak or because family members have the disease, or due to missed well care visits, shortages of the vaccine, parental or physician concerns about the recommended vaccine schedule, misunderstanding of the recommended schedule, or medical errors, etc. As an example, while the first dose of MMR is recommended at age 12 to 15 months, in one health plan, 22 percent of children were recorded to have received it later and 0.7 percent to have received it before their first birthday, with 0.3 percent receiving it before 6 months of age. Nationwide, even half a percent adds up to a fairly large number, and it is important to evaluate the safety of the vaccine for those children, so that a contraindication warning can be issued if there is a major safety problem.

Example

After the 2004 recommendation to give influenza vaccines to 6- to 23-month-old children, Hambidge et al. (2006) used data from VSD to conduct an influenza vaccine safety study specific to this age group, looking at a wide variety of potential adverse events.

Data

Health plan data capture all vaccinations at whatever age they occurred, so such data are useful not only for evaluating the safety of vaccines in special age groups but also for characterizing the real-world age distribution of vaccinated children.

With its national coverage, VAERS data can also be used to monitor vaccine safety in specific age groups. While no denominator data are directly available, a large number of adverse event reports in children outside the recommended age range could be the first indication that an age-specific problem exists.

If a change in the recommended age that a vaccine should be given is anticipated, a randomized trial may be warranted. For that to occur, there needs to be some uncertainty as to whether the currently recommended time is safe and some evidence, based on, for example, observational data, that an alternative age is safer. If the question is simply whether the vaccine should be contraindicated for certain age groups or whether the vac-

cine is also safe outside the recommended age of vaccination, without any evidence of harm at the recommended age, then a randomized trial would not be ethical.

Methods

For health plan data, there are a few different analysis options. For early-onset events, a self-controlled risk interval design can be used. First, decide on a risk window, such as 1 to 21 days after vaccination, and a control window, such as 22 to 42 days after vaccination. For each vaccinated child in the age group of interest, count how many of them had an adverse event in the risk and control windows, respectively. Suppose that the two windows are of the same length and that there are a total of n adverse events in the two windows combined. The number of adverse events in the risk window then has a binomial distribution with parameters n and $p = ½$.

Since this is a self-controlled analysis, it is only time-varying confounders that may need to be adjusted for, and there is no need to worry about gender, genetics, stable environmental factors, study site, etc. For some adverse events where the incidence rate changes rapidly from one week of age to the next, an age adjustment must be made. If the age distribution of the disease is know, this can easily be done by use of an offset term in a logistic regression model. The same is true if there are strong seasonal trends in the incidence rate. An alternative way to adjust for seasonality is to use a case-centered approach, as proposed by Fireman et al. (2009).

The choice of risk and control windows depends on the vaccine and the adverse event. Sometimes, it is worthwhile to have a washout period between the two windows. To avoid day-of-week effects, the two windows should have the same number of days in any modulus of seven. For example, the risk window may be 1 to 14 days and the control window 22 to 70 days or the risk window may be 1 to 2 days and the control window days 8 to 9 together with days 15 to 16. Theoretically, it is also possible to use a comparison window before vaccination, but that can introduce confounding by indication or contraindication.

In VAERS data, the age of the vaccinated child is one of the variables collected. To evaluate whether a vaccine is safe outside the recommended schedule, it is hence possible to look at specific predefined age groups. This can be done by the same methods that are used for all age groups combined, such as proportional reporting ratios (Evans et al., 2001).

TIME BETWEEN VACCINE DOSES

Background

Almost all childhood vaccines are given in multiple doses a few months or years apart. It is conceivable that the length of the time interval between vaccine doses could increase or decrease the risk of adverse events.

Example

Using a randomized trial, Pittman (2002) showed that the risk of adverse events was reduced if the second dose of subcutaneous anthrax vaccine, adsorbed, is given 4 months rather than 2 weeks after the first dose.

Early-Onset Adverse Events

Data

The use of electronic health data is suitable for vaccine doses that are at most a few years apart. If the time between doses is too long, health plan data are less suitable, as only some members will have been enrolled long enough to have information about all the doses of interest.

Methods

For simplicity's sake, first consider the situation where we want to evaluate the length of the time interval between the first two doses of the vaccine with respect to early-onset adverse events after the second dose. First, identify a cohort of children who received the first two doses of the vaccine. Exclude children that do not have a sufficiently long enrollment in the health plan to ensure that these are truly the first two doses. Note the number of days between the doses and whether they had an adverse event during a prespecified risk window after the second dose. For the statistical analysis, use logistic regression. The dependent variable is whether the potential adverse event was present in the risk window or not. The independent variable of interest is the number of days between the two doses. Adjust for gender, age at the second dose, calendar year, seasonality, study site, and any other potential confounders by including these as additional independent variables.

When one is looking at early-onset adverse events after the third dose, the same methods can be used for evaluating the length between the first and third dose or between the second and third dose. A single logistic regression can be used to evaluate both the time from the first to the third

dose and the time from the second to the third dose, by including both of them as two separate independent variables. The same applies for early-onset adverse events after subsequent doses.

If an excess risk is found, it is not clear from this design whether it is an excess risk due to the time length between the vaccinations or if there is an excess risk driven purely by the first dose and where the timing of the adverse event is such that it happens soon after the second dose in children that receive the second dose sooner. By estimating the temporal function of any excess risk due to dose number 1 alone, this can be adjusted for by including it either as an offset term or as an additional variable in the regression model, which then also may include children who never received dose two. An alternative, simpler approach is to limit the study to children where the doses are given at least x days apart, where x is chosen to be large enough that it is unlikely that there is any excess risk beyond that time that is purely due to the first dose.

If there is some evidence from the observational study that there is a differential risk depending on the time between vaccinations but it is not conclusive, then a randomized trial could be conducted. For example, in a study of a rotavirus vaccine, children may be randomized to receive the three doses at age 2, 4, and 6 months of age, according to the CDC-recommended vaccine schedule, plus a placebo dose at age 9 months, versus three doses at age 2, 6, and 9 months, plus a placebo dose at age 4 months. The results from the observational study, with its wide variety of schedules, can be used to inform the definition of the study arms in the randomized trial. Note, though, that if the adverse event is rare, a randomized trial is not a feasible approach, as the required sample size would be very large, and hence, the cost of the trial would be prohibitively expensive.

Late-Onset Adverse Events

Data

The use of electronic health data is suitable for late-onset adverse events that occur within a few years after the last dose and for vaccines for which all doses of interest are given within a year or two. For late-onset events and longer times between doses, health plan data may be less suitable, as only some members will have been enrolled long enough to be informative.

Methods

The same methods used for early-onset events can be used for late-onset adverse events, with some modifications. Most importantly, rather than defining adverse events in terms of a predefined risk window after the last

dose, it is more suitable to define them according to a predefined age range. For example, the study may include only children who had all the doses of interest before 18 months of age and would consider only adverse events for which the incident diagnosis occurred between ages 2 and 6 years. That will prevent bias due to age-varying incidence rates.

If suitable health plan data are not available, a case-control approach can be used instead. The first step is then to select children with an incident diagnosis during a predefined age range, together with a set of controls matched by age, gender, calendar month, study site, and other covariates of interest. The next, more challenging step is to obtain the vaccination history of each of the children. This could be done by contacting all the health plans or all the pediatricians that the child has had. The dose interval length is then compared between those children with and without the adverse event.

INTERACTION EFFECTS BETWEEN VACCINES AND HEALTH CONDITIONS

Background

Several vaccines are contraindicated for children with specific health problems. For example, live attenuated influenza vaccine should not be given to 2- to 4-year-old children who have had wheezing during the past 12 months (CDC, 2012). This means that the vaccine schedule may have to be modified for some children on the basis of their personal disease history. To know if and when that is necessary, one needs to study the interaction effects between vaccines and preexisting health conditions.

The study of interaction effects between vaccines and health conditions is especially important when there is a known excess risk of an adverse event. If it is possible to pinpoint that the adverse events are due to an interaction effect, then the number of adverse events can be reduced by contraindicating the vaccine for children with the health condition in question. For example, if the risk of seizures after vaccination with MMR is higher among children with a recent well-defined disease episode, then MMR may potentially be postponed by 3 months for those children.

Early-Onset Adverse Events

Data

Electronic health plan data are suitable for early-onset adverse events.

Methods

First consider the scenario in which there is a known increased risk of the adverse event in the population as a whole and we want to know if the excess risk is more severe among children in a specific group. By use of the temporal scan statistic, first determine the true risk window for the adverse event, as described above. Suppose that we have an excess risk in the 7 to 10 days after vaccination. We now define the study population as those who received the vaccine and who had an adverse event in some longer time period, such as 1 to 42 days after vaccination. In a logistic regression model, the dependent variable is whether they had the adverse event inside or outside the true risk window. The independent variables are the various health status variables that we want to examine as potential risk modifiers. Several of these can be included in the same logistic regression, but doing several univariate analyses may be a suitable first step. As long as the baseline risk for the adverse event is fairly constant over the longer time period, it is not necessary to adjust for age. Note that since all subjects had the vaccine and all subjects had the adverse event, there is no actual interaction term in the logistic regression model.

If we do not have a known adverse event but still want to evaluate possible vaccine–health status interaction terms, we can still use the same approach with a reasonable guess of a wider risk interval. For example, the risk interval may be 1 to 42 days, while the comparison interval is 43 to 84 days.

Late-Onset Adverse Events

The approach described above cannot be used to study late-onset adverse events. Instead, we first determine if a vaccinated child had the health condition of interest at the time of vaccination. We then compare the number of late-onset events between the children that did and those that did not. This design is more prone to bias than the self-controlled design described above. One way to partially adjust for this is to include only children that had both the vaccine and the potential adverse event of interest, at any time, and compare the children who had the vaccination at the same time as the health event with those that had them at different times.

VACCINE-VACCINE INTERACTION

Background

In the CDC-recommended vaccine schedule, many different vaccines are given on the same day. It is plausible that two vaccines, if given sepa-

rately from each other, do not increase the risk of adverse events, but if they are given on the same day, there is a vaccine-vaccine interaction effect, leading to increased risk. It could also be that one or both of the vaccines, when given separately, lead to a modest excess risk of the adverse event but, when given together, lead to a much higher excess risk.

Example

With data from VSD and separate self-controlled risk interval analyses, it was found that there was an increased risk of seizures 0 to 1 days after trivalent inactivated influenza vaccine (TIV) and also that there was an increased risk of seizures 0 to 1 days after the 13-valent pneumococcal conjugate vaccine (PCV13). To tease apart the effects from the two different vaccines and to evaluate the interaction between the two, the author of this paper suggested the approach mentioned below and worked out the formulas for the analysis. It was found that both vaccines had caused an excess risk of seizures 0 to 1 days after vaccination, irrespective of the presence of the other vaccines, and that the effects were independent of each other (Tse et al., 2012). This means that there was a positive additive interaction but no multiplicative interaction. Hence, the estimates obtained indicated that it is safer to give the two vaccines on separate days rather than on the same day.

Early-Onset Adverse Events

Data

Both VAERS and electronic health plan data can be used to evaluate early-onset adverse events due to vaccine-vaccine interaction.

Methods

For spontaneous reporting systems, Almenoff et al. (2003) have developed a proportionality-based version of DuMouchel's (1999) empirical Bayes multi-item gamma Poisson shrinker. Pairs of two drugs are treated as a separate unique drug, different from individual drug users. To signal a possible interaction-induced adverse event, the lower 5th percentile of the empirical base geometric mean estimate must be larger than the upper 95th percentile of the empirical base geometric mean estimate for both of the individual drugs. This approach makes sense in a data mining context, where it is necessary to have some form of formal or informal adjustment for the multiple testing.

Two other methods for evaluating interaction effects in spontaneous re-

ports have been proposed by Thakrar et al. (2007) and Norén et al. (2008). Both of these, as well as the previously described method by Almenoff et al. (2003), were proposed for drug-drug interactions, but they can also be used for vaccines.

For electronic health plan data, a different methodological approach is needed. With a self-controlled risk interval analysis, it is possible to evaluate the effect of a vaccine on an adverse event by comparing the number of adverse events in a risk interval right after the vaccine is given with the number in a control interval long after vaccination. Now, suppose we have two vaccines, such as PCV13 and TIV, and we want know to if there is an increased risk of seizure 1 to 2 days after vaccination. We can then do a self-controlled risk interval analysis for TIV and another one for PCV13, ignoring any other vaccines given on the same day. Suppose that we see an excess risk in both analyses. Since these particular vaccines are often given on the same day, it then is not clear if

- TIV causes an excess risk and PCV13 is just an innocent bystander with no excess risk.
- PCV13 causes an excess risk and TIV is just an innocent bystander with no excess risk.
- Both vaccines cause an increased risk of seizures independently of each other.
- There is either a positive or a negative interaction effect between the two vaccines.

To better understand the importance of different interaction effects, a few examples are given. Assume that TIV alone causes a twofold excess risk and that PCV7 alone also causes a twofold excess risk:

- If, when taken together, they also cause a twofold excess risk, then there is a negative interaction and it is safer to take the two vaccines on the same day.
- If, when taken together, there is a threefold excess risk, then there is a negative multiplicative interaction, while there is no additive interaction. In this scenario, it is equally safe to take the two vaccines on the same day or on separate days. This is because a threefold excess risk has twice as many excess cases than a twofold excess risk but there is only one rather than two times of exposure, which evens out the excess risk.
- If, when taken together, there is a fourfold excess risk, then the two vaccines act independently on a multiplicative scale (i.e., TIV doubles the risk and then PCV7 doubles the risk on top of that), while there is a positive interaction on an additive scale. In this

scenario, it is safer to give the two vaccines on separate days, since one time period with a fourfold excess risk is worse than two time periods with twofold excess risk.

- If, when taken together, there is a fivefold excess risk, then there is a positive interaction on both the multiplicative and the additive scales, and again, it is safer to take the vaccines on separate days.

While it is possible to do three separate self-controlled risk interval analyses for the vaccines when given alone and when given together, the best approach is to combine all the information into one logistic regression model that includes both the main effects and the interaction terms. This can be done, and it is then possible to formally test for a multiplicative interaction effect.

VACCINE ORDER

Background

While not a common concern, it has occasionally been suggested that the order in which vaccines are given may influence the risk of adverse events. Here, we are not thinking of vaccines given a couple of minutes apart at the same health care visit but of vaccines given a few days, weeks, or months apart. For example, in a study of DTP and the measles vaccine in a low-income African country, Aaby et al. (2004) hypothesized that "DTP as the last vaccine received may be associated with slightly increased mortality." Veirum et al. (2005) suggested that "it might be examined whether provision of BCG [bacille Calmette-Guérin] or measles vaccine shortly after the last dose of DTP could secure specific protection and prevent the negative immune stimulation associated with having received DTP," and that "different sequences of vaccinations" might have to be considered.

Example

In a three-arm randomized vaccine trial with a total of 1,027 children, Leonardi et al. (2011) compared both immunogenicity and safety for different orders of vaccination with MMRV and PCV7. In the study, MMRV was given 6 weeks prior to, on the same day, or 6 weeks after the fourth dose of PCV7. The incidence of local and systemic adverse events was comparable among the groups, while no serious adverse events were reported in any group.

Data

Electronic health plan data are ideally suited to study this question. Alternatively, children with the outcome of interest could be identified by the use of, for example, hospital data or data from a disease registry, followed by a vaccination history survey to their parents.

Late-Onset Adverse Events

Methods

The following is a study design for comparing the order of vaccines A and B with health plan data. For simplicity, this description assumes a single dose of each vaccine, but it can be generalized to multiple doses. First, identify children with the purported adverse event outcome of interest. Include only those children that had both vaccines A and B at least *x* days prior to the onset of the disease, except those that had both vaccines on the same day. With health plan data, the comparison group will be all other children. For each child with the purported adverse event, (i) note the exact age at disease onset, (ii) calculate how many of the comparison children of the same gender that also had both vaccines A and B at least x days before that age but not on the same day, and (iii) note the proportion of those that had vaccine A before vaccine B. Under the null hypothesis of no effect of vaccine order, this proportion is the estimated probability that the study child had vaccine A before vaccine B. The analysis is adjusted for age and gender, and other covariates can be adjusted for in the same way as gender.

The reason for excluding children that had one of the vaccines less than *x* days before the adverse event is to remove the effect of vaccine-specific early-onset adverse events that is caused by one of the vaccines independently of the presence of the other. The value of *x* will depend on the vaccines and adverse event studied. To avoid bias, it should be large enough so that any adverse events caused by one vaccine independently of the other do not vary in time on the basis of the number of days after vaccination.

An alternative is to use a case-control design. First, the children with the adverse event are selected as before. Second, identify a comparison group of children who did not have the adverse event outcome, matched by age, gender, and any other variables, and with the same inclusion criteria with respect to vaccination history. Then compare how many of the cases and how many of the controls had vaccine A before vaccine B, and vice versa.

Early-Onset Adverse Events

Methods

The above-described design cannot be used for acute adverse events because of the bias mentioned above. Instead, the following design can be used. By the use of health plan data, select children that had vaccine A at any time. Separate them by whether they have had vaccine B prior to vaccine A or not. Then compare these two groups in term of how many of them had the adverse event of interest on the 1 to *D* days after they received vaccine A. The value of *D* defines the risk window and will depend on the vaccines and adverse event studied. The analysis can be performed using unconditional logistic regression, adjusting for covariates such as age at vaccination, gender, calendar years, and study site.

This study design cannot in itself distinguish between an effect due to the order of the vaccines and an interaction effect, where the risk increases with the same amount after the second vaccine irrespective of their order. By collection of the above-described data both for vaccine A and then, in the corresponding manner, for vaccine B, it is possible to compare the two risk estimates. If the increased risk is due to vaccine-vaccine interaction but not the order of the vaccination, these estimates should be the same.

CUMULATIVE SUMMARY METRICS OF THE VACCINE SCHEDULES

Background

It is conceivable that it is neither the timing of individual vaccines nor the interaction between vaccines that is responsible for adverse events but, rather, some more general component of the vaccine schedule, such as the total number of vaccines given or the cumulative amount of immune-stimulating content, immunogenic adjuvants, or preservatives in all vaccines received. Similar study designs and statistical methods can be used for most of these types of summary measures or metrics of the vaccine schedule, so they are considered together.

Examples

The total amount of immunogens that a child has been exposed to is being used in studies of autism (DeStefano et al., 2012) and neuropsychological outcomes (Iqbal and DeStefano, 2012).

Cumulative Summary Metrics for General Features of Vaccine Schedules

The first and most critical step is to define one or more suitable metrics reflecting the general feature of the vaccine schedule that should be evaluated. The number of options is large. Here are some examples:

- The total number of vaccines received before the child's 6th birthday.
- The total number of health care visits before the child's 6th birthday on which the child received at least one vaccine.
- The total amount of immunogens (antibody-stimulating proteins and polysaccharides) that a child was exposed to from all vaccines combined (DeStefano et al., 2012).
- The total amount of immunogenic adjuvants that a child was exposed to from all vaccines combined.
- The total amount of the thimerosal preservative that a child was exposed to from all vaccines combined (Price et al., 2010).

For all the metrics listed above, completely unvaccinated children will have a value of zero. These children are at one end of the exposure spectrum, and together with the fully vaccinated children at the other end, they provide the most informative data points for statistical analyses. Hence, they should be included in these types of studies in order to ensure the highest possible statistical power.

All of the above metrics are continuous or ordinal in nature. Each one could be dichotomized into a 0/1 variable. For example, in the first example mentioned above, the children could be split into those receiving at least 10 vaccines and those receiving less than 10 vaccines. Such dichotomization is not recommended. If there is a difference in risks between receiving 9 and 10 vaccines, there is also probably a difference between 5 and 9 vaccines and between 10 and 15 vaccines. Such information is thrown away when the data are dichotomized, and hence, statistical power is lost. It may be tempting to compare only fully vaccinated and completely unvaccinated children, but that is not recommended either. By excluding the children in between, statistical power is lost, as they provide valuable information about the intermediate group. It also makes it impossible to look for a dose-response relationship, as described below.

Data

Electronic health plan data provide one of the best opportunities to study the safety of vaccine schedules with respect to cumulative summary metrics. As the complete vaccination history is needed to calculate the

metric of interest, population-based studies will be limited to children with a sufficiently long enrollment in the same health plan. In some European countries with a national health care system, such as Denmark, these studies are easier to conduct, as only a small percentage of children immigrate to or emigrate from the country. From the U.S. perspective, a drawback of doing these types of studies in foreign countries is, of course, that their recommended vaccine schedule is different from ours.

Methods

Once the outcome definition has been decided, the methods that one can use for these more general vaccine schedule components are very similar to those described above concerning the time between vaccine doses. With health plan data, first classify each child according to one or more of the metrics indicated above. Include only children with a sufficiently long enrollment period. As the next step, determine if they have the adverse event of interest during some predefined age period. For the statistical analysis, use logistic regression with the potential adverse event as the dependent variable and the vaccine schedule metric as the independent variable. More than one metric for the vaccine schedule can be included in the same regression model, by which it is possible to try to tease apart the relative influence of each one on the adverse event. Gender, calendar year, study site, and other covariates can be adjusted for by also including them as independent variables in the logistic regression.

To include as many children as possible in the study, irrespective of their length of enrollment, a survival analysis model could be used instead of logistic regression. Children leaving the health plan are then censored at the time of departure. Note, though, that the enrollment period must still be long enough to determine their vaccine schedule in sufficient detail to calculate the metric of interest. It is only the follow-up period that can be sensored.

The key strength of health plan data is the availability of detailed longitudinal vaccination and disease histories for millions of children. They do not contain all potential information of interest, though. If some of the exposure history is unavailable, such as the particular brand of a vaccine, one can instead conduct a case-control study. If the potential adverse event is rare, cases can be identified through the health plan data, together with a set of matched controls. Chart review can then be conducted on this limited population to obtain more detailed information about each of the vaccines given, about the exact nature of the potential adverse event, or about various potential confounders.

There is not necessarily a linear dose-response relationship between the metric of choice and the risk of a potential adverse event, but a linear

function can be used in the regression model as a test for trend. Quadratic and other nonlinear functions can then be explored and formally tested for statistical significance in order to get a better understanding about the dose-response curve.

When doing these types of studies, it is important to look for a dose-response relationship in which an excess risk observed is a monotonically increasing or decreasing function of the summary metric being evaluated. If it instead is, for example, a U-shaped function with a high risk among the least and most vaccinated and a low risk among the middle group, it is likely to be something else responsible for the differences, rather than the cumulative metric under study.

VACCINE SCHEDULE SUMMARY METRICS, INDEPENDENT OF VACCINES RECEIVED

A fundamentally different set of metrics compares children who receive the same set of vaccines, but through different schedules. The question is then exclusively focused on how the vaccinations are scheduled, and we want to adjust away any differences due to the different sets of vaccines received.

The number of potential vaccine schedule summary metrics is large. Here are some examples:

- The maximum number of vaccines received on a single day.
- The maximum amount of immunogens received on a single day (DeStefano et al., 2012).
- The maximum amount of adjuvants received on a single day.
- The average number of vaccines given at each visit. For example, if one child had 15 vaccines spread out over five visits, the average is 3. If another child had only 3 vaccines in total, all given at the same visit, the average is also 3.
- The number of days undervaccinated (Glanz, 2012). For each vaccine, calculate the number of days between the recommended age and the actual age of vaccination and then sum over all vaccines. For a perfectly compliant child, the value is zero.
- The age at which a certain portion of the recommended vaccine schedule was completed. For example, one could take the set of vaccines that CDC recommends for the first 18 months and determine the age at which all of them have been given.
- Average age at which vaccines were given.

None of these definitions is the "right" one, but they serve as examples of what could be used rather than recommendations of what should be

used. The choice will and must depend on the scientific hypothesis that the scientist is evaluating.

Data

Electronic health plan data are the most suitable for studying vaccine schedule metrics. Since the complete vaccination history is needed to calculate the metric of interest (such as average age at vaccinations), a sufficiently long enrollment in the same health plan is needed.

Methods

The methods described in the previous section can be used for these types of studies as well, with one critical modification. To truly evaluate the metric of the vaccine schedule and not the collection of vaccines received, the latter must be adjusted for. This can be done by classifying the children by the set of vaccines received and then conditioning the analysis on these sets. In this way, children are compared only with other children that received the same set of vaccines. All children who received at least one vaccine can be included in the same study, maximizing the statistical power. Children who did not receive any vaccines are not informative in this type of study and must be excluded.

COMPARISON OF COMPLETE VACCINE SCHEDULES

Background

Some parents have consciously decided to follow a specific alternative vaccine schedule other than the one recommended by the CDC. Hence, there is a natural interest in comparing the safety of these complete schedules as discrete entities rather than through the various components of the schedule, as discussed in previous sections. For example, one may compare the number of potential adverse events in (i) children that have followed the CDC-recommended vaccine schedule, (ii) children that have followed one of Dr. Bob's recommended schedules (Sears, 2007), and (iii) children that have not received any vaccines at all. The statistical methods are the same irrespective of which vaccination schedules are compared or whether vaccinated children are compared to completely unvaccinated children. Hence, we treat them together in this section.

Examples

In a pioneering study on vaccine schedules, Glanz (2012) used a matched cohort design where children on the CDC-recommended vaccine schedule were matched with children not on that schedule. It was then evaluated whether there were any differences in a few different outcomes: pertussis, upper respiratory infections, fever, sinusitis, outpatient physician visits, and hospitalizations. The data used were from VSD. In a companion study, Hambidge (2012) used the same data to look at febrile seizures.

Data

From a purely scientific perspective, the best design would be a double-blind placebo-controlled randomized trial with an intention-to-treat analysis where children are randomized to one of several vaccination schedules and/or no vaccinations at all. There are major financial, logistical, and ethical issues with conducting such trials, as discussed below.

To avoid ethical issues, observational health plan data can be used as an alternative to randomized trials. As in the previous section, complete vaccination histories are required to classify children into alternative vaccine schedules, so the length of enrollment must be long enough for a sufficiently large number of children.

Methods

Very few children are 100 percent compliant with any one particular schedule. Hence, the first challenge with these studies is to define some criteria of how divergent they can be from the schedule and still be considered compliant. For example, one could require that all the recommended vaccines have been received and that the average temporal divergence from the schedule is at most 1 month, taken over all the vaccines. Alternatively, one could require that the sum of the temporal divergences, taken over all vaccines, is at most, say, 1 year. If the criteria are too strict, the sample size will be too low and the statistical power will suffer. If the criteria are too wide, many of the children will not be appropriate representatives of the schedule that they are set to represent. In that case, the study is not actually evaluating the vaccines schedules that it is meant to evaluate.

Children with an incomplete vaccination history must be excluded from the study, together with children whose vaccine schedule is too divergent from either of the schedules being studied.

Once children in the health plan have been classified by the vaccine schedule, a variety of potential adverse events can be studied. A key difficulty here is to define the time period during which the events will be

counted. The cleanest option is to make the vaccine schedule classification based on data up to a certain age and consider only potential adverse events that occur after this age. This ensures that there is no bias if the adverse event studied causes subsequent changes in the vaccination schedule. It is not an ideal solution, though, since we must ignore either the adverse events occurring early during the vaccination schedule or the possible effect of later parts of the vaccination schedule. If the potential adverse event under study is such that there is little risk that its presence will change any aspect of the vaccination schedule, then one could include adverse events that occur before the end of the vaccine schedule considered, but such an approach is risky.

Since different children will have different lengths of follow-up, time-to-event data will best be analyzed by survival analysis methods, adjusting for possible confounders. When two alternative schedules are compared, an alternative way to adjust for covariates is to use a matched cohort design (Glanz, 2012), where each child with the recommended schedule is matched with a child with the alternative schedule having the same age, gender, study site, and calendar year of immunization. This is especially useful if additional health data that are not available in the health plan data sets are to be gathered from the children, since it is typically infeasible to collect such data for all children in a health plan.

To use observational health plan data to compare complete vaccination schedules, there must be enough children in the health plan that follow each schedule under study. That may be a problem if one of the comparison groups consists of followers of a very specific alternative schedule or of completely unvaccinated children. It may then be necessary to include a larger number of health plans or health plans with a larger number of members.

ADDITIONAL METHODOLOGICAL ISSUES

Bias and Confounding

The observational study designs described above are, like all observational studies, prone to various sources of bias. The type of bias is often different for different designs, and it is hence often wise to use multiple study designs for the same question. Of special concern in these types of studies is confounding due to the innocent bystander effect. This is when an adverse event that is seemingly due to one component of the vaccine schedule under study is actually due to another component that is correlated with the first one.

As a first step, it is natural to do a study considering a single component of the vaccine schedule, adjusting only for demographic variables. If

a significant relationship is observed, though, it is sometimes important to consider other aspects of the schedule as possible confounders. This is especially true for late-onset events. This can be tackled in one of several ways. As a second step, additional studies evaluating other components of the vaccine schedule can be conducted. One way to do this is to incorporate multiple components in the same regression model. For example, one regression model may include variables representing the age at which each vaccine was given, the total number of vaccines given, the total exposure to immune-stimulating content, and the total exposure to adjuvants. Such a design will provide information as to whether the component that is suspected of being the culprit still has a statistically significant relationship with the outcome after adjustment for other components of the schedule. It is important to note, though, that with many different correlated components in the same schedule, none may be statistically significant after adjustment for all the others. This does not mean that the risk of the adverse events does not depend on the vaccine schedule. It just means that it is not possible to determine which component is responsible, and that is important information.

Combining Health Plan Data with Study-Specific Data Collection

In the data sections presented above, health plans are often recommended as the best source of data to use. There are some potential adverse events that are not fully captured in the electronic health plan data, though, such as neuropsychological performance or immune function. Such outcomes must be measured specifically for a research study, but that can obviously not be done for all members of a health plan. Depending on the outcome, there are at least three different ways to go about doing this:

- Select a random sample of children from the health plan, measure the outcome of interest for each one, and evaluate the relationship between the relevant component of the vaccine schedule and the outcome measurement values. This is the simplest approach.
- Select a nonrandom sample of children from the health plan, oversampling children on both end of the metric used in the study. For example, if the variable of interest is the timing of the first dose of the hepatitis B vaccine, children who received it long after birth would be oversampled. After that, proceed as described above. This design will in many cases increase the statistical power. It is important that the probability of selection be unrelated to other health events.
- Select a nonrandom sample of children from the health plan, on the basis of a health outcome that is present in the health plan data

and that is correlated with the outcome of interest. The goal here is to get a larger variance in the health outcome being measured, thereby increasing the statistical power. It is important that the probability of selection be unrelated to any aspect of the vaccine schedule. After the study population has been selected, proceed as described for the first scenario.

Vaccine-Specific Versus General Components of Vaccine Schedules

The more general components of the vaccine schedule described above, as well as the comparison between complete schedules discussed earlier, are considerably more difficult to study than the more vaccine-specific components described above. There are several reasons for this.

First and foremost, there are many alternative vaccine schedules, and slightly different schedules have to be lumped together in the same comparison group. For the cumulative summary metrics, many different vaccination schedules will have the same value, for example, the average age at vaccination. If one vaccine schedule is safer than an alternative vaccine schedule in terms of a specific outcome but they both have the same average age at vaccination, then the effect size will be attenuated and go undetected.

If a statistically significant excess number of adverse events is found, a second problem with these designs is that it can be hard to know which aspect of the schedule caused the excess or reduced risk. Is it the timing of one specific vaccine, is it an interaction between two or more vaccines, or is it something else? Hence, any statistically significant findings will have to be followed up with studies concerning more specific vaccine schedule components.

A third issue is confounding. While confounding is present in all observational studies, it is likely to be a greater problem when complete vaccine schedules are studied. For example, children for whom most of the vaccines are delayed from the recommended schedule may be different in terms of both health care utilization and socioeconomic factors. This may bias the results, and the bias may exist whether the delayers are deliberately following an alternative schedule or not, and the bias may go in different directions for these two groups. The same type of confounding can be present when one is looking at more specific components of the vaccine schedule, but it is likely to be less strong, as such individual components are likely to have more random and less systematic variability than a complete schedule. A way to intuitively see this is to note that whatever it is that causes a general parental tendency to delay vaccinations, that will likely be more correlated with the average timing of all vaccinations than with the timing of a single vaccination.

To date, there have been few comparative studies evaluating the safety

of different vaccine schedules. For the above-mentioned reasons, it is suggested that, initially, the majority of such studies focus on the most vaccine-specific components of the vaccine schedule described earlier, as well as the content-defined components mentioned above. Information from such studies will greatly facilitate the design and understanding of subsequent studies evaluating the more general components discussed earlier as well as the comparison of complete vaccines schedules described above.

Cross-National Comparisons

Different countries have different recommended vaccine schedules, so it may seem natural to do cross-national studies to compare the safety of the schedules in an ecological study design. Unfortunately, this is very difficult to do well and generally not recommended. The problem is that the incidence of most diseases varies by geographical region for reasons other than the vaccine schedule, such as genetics, diet, physical exercise, or other environmental factors. Any such cross-national study may hence be heavily biased. This does not mean that one cannot do studies that include data from multiple countries or regions, as long as each one has a range of different exposures in each place. In such studies, the geographical region can easily be adjusted for in the analysis, in order to take the differential disease incidences into account.

Time Trend Evaluations

Another ecological study design is to take a particular country or region and compare time trends in disease incidence with temporal changes in the vaccination rate or vaccination schedule. This is also not recommended. In addition to vaccinations, there are many other reasons why the reported disease incidence may increase or decrease over time, including changes in environmental risk factors and changes in health care practice and diagnosis. Hence, an apparent temporal correlation between increasing disease incidence and increasing vaccine usage could be completely spurious. It should be pointed out that the bias can also go in the other direction. Even if there is no temporal correlation between disease incidence and vaccinations, a true relationship can be hidden by a compensatory effect from an unknown confounder.

Near-Real-Time Safety Surveillance

In what is called "rapid-cycle analysis," the VSD project has pioneered near-real-time vaccine safety surveillance (Lieu et al., 2007; Yih et al., 2011). For newly approved vaccines and selected adverse events, weekly

data feeds are received from the health plans and the data are analyzed by continuous sequential statistical methods (Kulldorff et al., 2011). If there are specific concerns regarding the newly revised vaccine schedule, such rapid-cycle analysis can also be implemented for many of the study designs described above.

Data Mining

Most vaccine safety studies evaluate a specific vaccine-event pair. For VAERS data, data mining methods are also used, where thousands of potential vaccine and adverse event pairs are evaluated simultaneously, without there being any prior hypothesis about their being an excess risk of the event. This is done to cast the net as wide as possible. Recently, data mining methods are also started to be used for health plan data. As vaccine safety data mining develops further, it may also be used to study questions regarding the vaccine schedule.

Disease-Causing Complications Versus Adverse Events

It should be noted that in these types of studies, it is not always clear what is an adverse event and what is not. For example, a child may have a febrile seizure that was caused by one or more of the vaccines or a febrile seizure caused by a disease, where the child got the disease because he or she was not immunized against it. Hence, an excess risk of seizures due to a particular vaccine schedule could be due either to vaccines given at a certain time when the child is more sensitive to adverse events or to vaccines not given at a certain time when the child needed the vaccine protection.

If the same type of health event is caused by the vaccine among one group of children as an adverse event and by the disease among the same or another group of children as a complication, then the vaccine may be found to cause an excess number of the adverse events in a vaccinated population, since the nonvaccinated children benefit from herd immunity. Hence, findings about the risk to individuals in a mostly vaccinated population cannot necessarily be generalized to the population level.

Vaccine Efficacy and Effectiveness

This paper covers only the study of potential adverse events after vaccination. If a study does not find an excess risk, all is fine and there is no need to worry about vaccine efficacy. On the other hand, if a true differential risk of adverse events is found with respect to some component of the vaccine schedule, vaccine efficacy and effectiveness must also be considered when contemplating a revised vaccine schedule. Some vaccines, such as MMR,

have a different immune response depending on the age of the child, and vaccine efficacy therefore depends on the vaccine schedule. The timing of a vaccination also influences the time period during which the child is protected from the disease and the herd immunity of the population at large. Herd immunity can also be affected if a parent refuses future vaccinations after his or her child has had an adverse event vaccine that could have been avoided with a different schedule. While such an analysis is outside the scope of this paper, all these factors must be considered in a joint cost-benefit analysis before the recommended vaccine schedule is revised, if and when there is a finding of a vaccine schedule-dependent adverse event.

FINANCIAL CONSIDERATIONS

When deciding what to study and what study design to use, cost is an important consideration. The study designs mentioned in this paper range from very cheap to very expensive. For some designs, the cost depends on how common the potential adverse event is. While we cannot do any precise sample size calculations, we will for illustrative purposes consider three classes of health outcomes: common, moderately rare, and very rare. Common events are those that affect more than 1 out of every 100 children, such as allergies and some learning disorders. Moderately rare outcomes are those that affect more than 1 out of 100 but less than 1 in 10,000, such as intussusception. Very rare outcomes are those affecting less than 1 in 10,000, such as Guillain-Barré syndrome,

The least expensive studies are those using VAERS data. Since those data are already collected, only the investigator's time needs to be covered. Unfortunately, VAERS data are of limited use when one is studying vaccine schedules. The cost is independent of the adverse event.

The second least expensive study designs are the ones based on fully automated health plan data. While they involve no new data collection, the extraction of data from large administrative databases is a complex activity involving detailed knowledge of the database structure and content, sophisticated computer programming, and thorough data quality control. To set up a new system from scratch is very costly, but the marginal cost of additional studies in existing systems is not. In most cases, the cost is independent of the potential adverse event under study. For common and medium-rare outcomes, a VSD-size study population of about 100,000 annual births should be enough for most study designs. For very rare outcomes, data from more and larger health plans may be needed in order to achieve sufficient power, resulting in additional expenses. Bigger datasets may also be needed for common events and moderately rare adverse events when complete vaccination schedules are evaluated, if only a small proportion of health plan members follow the particular schedule of interest. In

summary, the cost of these types of studies is similar to the cost of current vaccine safety studies conducted in VSD, PRISM, and similar systems.

With most health plan data, vaccine information has a high positive predictive value, but that is usually not the case for disease outcomes. For such adverse events, it is often necessary to conduct chart reviews to confirm whether or not a patient actually had the health event of interest, and that will increase the cost. For very rare adverse events, it is not a major additional cost, but for medium-rare and common adverse events, it can be. One way to reduce this cost is to first do a study on fully automated data and do chart review only when that study shows an excess risk of adverse events, to confirm or dismiss that finding.

The next level of cost is incurred by study designs that combine health plan data with specially collected outcome data that are not available as part of the EMRs. The cost will depend on the type of data collected but will in most situations be very high. For medium-rare and very rare outcomes, a very large number of health plan enrollees will have to be enrolled, potentially making such studies prohibitively expensive.

Randomized trials are the most expensive study design. For medium-rare and very rare adverse events, the study needs to have a very large sample size to detect a potential problem. For example, if a vaccine causes a specific adverse event in 1 of every 1,000 children, that is not something that can be detected in a randomized trial with 4,000 children in each arm, for a total of 8,000, even if the baseline rate of the event is very rare. To see this, suppose that there are four adverse events in the vaccinated arm and none in the control arm receiving the placebo. Under the null hypothesis, the probability of all four being in the vaccinated arm is $(1/2)^4 = 0.0625$, which is not statistically significant, and hence, we cannot conclude that it was the vaccine that caused the adverse events. So, for medium-rare and very rare adverse events, we need data with tens or hundreds of thousands of vaccinated children, and for such sample sizes, randomized trials are prohibitively expensive. A cost advantage of randomized trials over case-control studies is that multiple potential adverse events can be evaluated within the same study.

Irrespective of the design, studies evaluating late-onset events are more expensive than those evaluating early-onset events, since the individuals must be followed for a much longer time. With health plan data, this requires larger population sizes since many children will be lost to follow-up. When health plan data are augmented with specially collected data on health outcomes, children must be tracked and monitored for a longer time, which is costly. The same is true for randomized trials.

ETHICAL CONSIDERATIONS

As with all medical research, ethical considerations are very important when one is designing vaccine safety studies. With observational studies with health plan data, the key ethical issue is patient confidentiality, which can be ensured through existing research practices.

For randomized trials, ethical considerations play a much more important role. Depending on the vaccine component of interest, a randomized trial can sometimes be conducted in a way so that both arms fall within the recommended vaccination schedule, in which case there are no ethical concerns. An example of such a trial would be whether to give children two vaccines on the same day or a week apart. At the other extreme, it would be unethical to do a randomized trial where children in one arm are completely unvaccinated, since the scientist will then knowingly put some of the children at increased risk for vaccine-preventable diseases, some of which may result in death. Somewhere in between these two extremes there is a gray zone where randomized trials may or may not be ethical, depending on the vaccine schedules being compared and on the available strength of the evidence regarding efficacy and potential adverse events. Experts on medical ethics should then be consulted.

For more common adverse events, randomized trials have a potential role to play in postmarketing vaccine safety studies. There is little reason to use them to evaluate the general safety of a particular vaccine, since that evaluation is already covered by the Phase III trials. Questions for which randomized trials may be used include the order in which different vaccines are given, the exact timing between doses of the same vaccine, and whether two different vaccines are given on the same day or a week apart.

If a randomized trial is conducted, it is important to consider the effect on herd immunity. If the two arms differ by delaying one or more vaccines by at most a few weeks, it is not a major issue. If vaccination in one arm is delayed for a much longer time period or not given at all, it may reduce herd immunity. This may put children that are not participating in the study at increased risk for the disease, and this can be especially serious for immune-compromised children for which a vaccination is contraindicated. To minimize the negative effect on herd immunity, such randomized trials should be spread out geographically, so that there are at most a few additional unvaccinated children in any given location. In that way, nonparticipating children will not be at an increased risk of the disease, and equally important, those children randomized to the delayed vaccination will still have some protection against the disease from herd immunity.

CONCLUSIONS

Randomized trials are the "gold standard" for scientific studies, and premarketing Phase III randomized trials play an important role in the evaluation of vaccine-related adverse events. Because of their limited sample size, rare adverse events may not be detected, though. For financial and ethical reasons, the utility of randomized trials is more limited for postmarketing vaccine safety studies.

On the basis of utility and cost, health plan–based study designs are the most promising for the safety evaluation of different vaccine schedules. This is definitely true for medium-rare and very rare adverse events that cannot be detected in Phase III randomized trials, but such data can also be used to study common adverse events. The key is to always consider potential problems with confounding, and it is often a good idea to use different study designs with different potential biases for the same research question.

Hypotheses about potential adverse events may come from Phase III trials or from observational postmarketing studies with data from health plans or spontaneous reporting systems.

The comparative safety evaluation of different vaccine schedules is a complex and multifaceted task, and all aspects of the vaccine schedule are currently understudied with regards to potential adverse events. A number of different study designs and methods can be used to evaluate different components of the schedule. For all known and most potential adverse events, it is recommended that a wide variety of vaccine schedule components be evaluated. Direct evaluation of complete vaccine schedules is more difficult and probably less fruitful, but it is not impossible. Such studies are most useful when conducted in parallel with studies of specific components of the schedule. This is especially important when there is a significant adverse event finding, since it is otherwise impossible to know which of the many features of the complete schedule are actually causing the adverse events.

This paper should not be utilized as a cookbook where definite study designs and methods are obtained and used for different classes of problems in a black box–type approach. Each study is unique, depending on the vaccine(s) under study, the potential adverse event(s) of interest, the data used, and the scientific research question. All those aspects need to guide the methodology. The goal of this paper is simply to show that a wide variety of study designs and methods are available to study the comparative safety of different vaccine schedules, and the hope is that some of the proposed methods can serve as a starting point when thinking about the most suitable designs and statistical methods to use for different studies.

This paper does not present an exhaustive list of study designs and methods that can be used for the comparative evaluation of potential

adverse events due to different childhood vaccination schedules. As more such studies are performed, additional designs and methods will surely be developed and used. The paper should not be interpreted as a recommendation to use all of the study designs and statistical methods mentioned. The scientific question should drive which designs and methods are used, and while some of them may become widely used, others may not be used at all.

What the paper attempts to show is that the comparative safety evaluation of vaccine schedules is complex and multifaceted and that a wide variety of study designs and statistical methods are available to a scientist who wishes to conduct such studies.

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Appendix E

Agendas of Public Meetings Held by the Committee

February 9, 2012
The Pew Charitable Trusts
901 E Street, NW
Washington, DC 20004

Welcome and Overview
Ada Sue Hinshaw, Ph.D., R.N.
Committee Chair

Presentation of the Charge from the National Vaccine Program Office
Bruce Gellin, M.D., M.P.H.
Deputy Assistant Secretary for Health
Director, National Vaccine Program Office, U.S. Department of Health and Human Services

Review of the IOM Committee to Review Adverse Effects of Vaccines
Ellen Wright Clayton, J.D., M.D.
Chair of the IOM Committee to Review Adverse Effects of Vaccines
Craig-Weaver Professor of Pediatrics, Vanderbilt University

National Vaccine Information Center Perspectives
Barbara Loe Fisher
Co-Founder and President, National Vaccine Information Center

Provider Perspectives
Gary Freed, M.D., M.P.H.
Professor, Department of Health Management and Policy, University of Michigan School of Public Health
Director, Division of General Pediatrics
The Percy and Mary Murphy Professor of Pediatrics and Child Health Delivery

The Use of Clinical Trials for Childhood Vaccines
Susan Ellenberg, Ph.D.
Professor of Biostatistics and Associate Dean for Clinical Research
Perelman School of Medicine at the University of Pennsylvania

Ethical Issues in Clinical Trials
Robert (Skip) Nelson, M.D., Ph.D.
Senior Pediatric Ethicist/Lead Medical Officer, Food and Drug Administration

National Center for Immunization and Respiratory Diseases (NCIRD), Centers for Disease Control and Prevention (CDC)
Melinda Wharton, M.D., M.P.H.
Deputy Director, NCIRD, CDC
Captain, U.S. Public Health Service

Immunization Safety Office (ISO), CDC
Frank DeStefano, M.D., M.P.H.
Director, ISO, CDC

Data and Approaches in National and International Immunization Studies
Saad Omer, Ph.D., M.P.H., M.B.B.S.
Assistant Professor, Hubert Department of Global Health Epidemiology, Emory University Rollins School of Public Health
Assistant Professor, Emory Vaccine Center

Immune Profiling Research
Chuck Hackett, Ph.D.
Deputy Director, Division of Allergy, Immunology, and Transplantation
National Institute of Allergy and Infectious Diseases

OPEN SESSION—Opportunity for Attendee Comments

Adjourn

March 8, 2012
Talaris Conference Center
4000 NE 41st Street
Seattle, WA 98105

Welcome and Overview
Ada Sue Hinshaw, Ph.D., R.N.
Committee Chair

Welcome from Washington State Department of Health
Mary Selecky
Secretary of Health, Washington State Department of Health

Maxine Hayes, M.D., M.P.H.
State Health Officer, Washington State Department of Health

Washington State's Immunization Programs
Janna Bardi, M.P.H.
Office Director, Immunization and Child Profile Office
Washington State Department of Health

Findings on Alternative Immunization Schedule Practices
Douglas Opel, M.D., M.P.H.
Assistant Professor of Pediatrics, Adjunct Assistant Professor of Bioethics and Humanities
University of Washington
Treuman Katz Center for Pediatric Bioethics
Seattle Children's Research Institute

Assessing the Safety of Vaccines at the FDA: Pre- and Postlicensure Evaluations
Marion F. Gruber, Ph.D. (by phone)
Acting Director, Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Office of Medical Products and Tobacco
Food and Drug Administration

Karen Farizo, M.D. (by phone)
Acting Associate Director for Medical Policy and Safety
Office of Vaccines Research and Review
Center for Biologics Evaluation and Research
Office of Medical Products and Tobacco
Food and Drug Administration

Issues Leading to Vaccine Hesitancy
Douglas Opel, M.D., M.P.H.
Assistant Professor of Pediatrics, Adjunct Assistant Professor of Bioethics and Humanities
University of Washington
Treuman Katz Center for Pediatric Bioethics
Seattle Children's Research Institute

Process for Immunization Schedule Recommendations
Edgar Marcuse, M.D., M.P.H.
Professor of Pediatrics, Adjunct Professor of Epidemiology, University of Washington
Associate Medical Director, Quality Improvement, Seattle Children's Hospital

Decision Making at Advisory Committee on Immunization Practices in Response to Unanticipated Adverse Event Detection
Jeffrey Duchin, M.D.
Chief, Communicable Disease Epidemiology and Immunization Section
Public Health
Seattle and King County, Washington

Provider Self-Efficacy and Tools to Improve Immunization Rates
David Grossman, M.D., M.P.H.
Medical Director, Preventive Care
Group Health Cooperative

Group Health Research Institute and the Vaccine Safety Datalink
Michael L. Jackson, Ph.D., M.P.H.
Assistant Scientific Investigator
Group Health Research Institute

OPEN SESSION—Opportunity for Attendee Comments

Adjourn

May 29, 2012
The Pew Charitable Trusts
901 E Street, NW
Washington, DC 20004

Welcome and Overview
Ada Sue Hinshaw, Ph.D., R.N.
Committee Chair

U.S. Childhood Immunization Schedule Decisions
Margaret B. Rennels, M.D.
Professor of Pediatrics, University of Maryland School of Medicine (retired)
Independent Consultant

Question and Answer

Vaccine Policy and Safety Surveillance in the United Kingdom
Elizabeth Miller (by phone)
Head, Immunization Division
Communicable Disease Surveillance Centre
Health Protection Agency, Colindale, United Kingdom

Question and Answer

Vaccine Decisions: Policy Making and Priority Setting in Canada
Charlotte Moore Hepburn, M.D., F.R.C.P.C., F.A.A.P.
Lead, Child Health Policy Initiative
Assistant Professor, University of Toronto School of Medicine
Staff Paediatrician, Division of Paediatric Medicine, The Hospital for Sick Children

Question and Answer

Advisory Committee on Immunization Practices Decision Making
Melinda Wharton, M.D., M.P.H.
Deputy Director, National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention
Captain, U.S. Public Health Service

Question and Answer

Alternative Immunization Schedules: A Feasibility Study for Evaluating Vaccine Safety and the Risk of Pertussis

Jason Glanz, Ph.D.
Epidemiologist, Institute for Health Research
Kaiser Permanente Colorado

Question and Answer

Study Designs for the Safety Evaluation of Different Childhood Immunization Schedules

Martin Kulldorff, Ph.D.
Professor, Biostatistician, Department of Population Medicine
Harvard Medical School and Harvard Pilgrim Health Care Institute

Question and Answer

Commentary on Commissioned Paper and Other Committee Considerations

Michael A. Stoto, Ph.D.
Professor of Health Systems Administration and Population Health
Georgetown University School of Nursing and Health Studies

Question and Answer

OPEN SESSION—Opportunity for Attendee Comments

Adjourn

Appendix F

Biographical Sketches of Committee Members

Ada Sue Hinshaw, R.N., Ph.D. (*Chair*), is a professor and dean at the Graduate School of Nursing of the Uniformed Services University of the Health Sciences as well as a professor and dean emeritus of the University of Michigan's School of Nursing. She received her Ph.D. and master of arts in sociology from the University of Arizona, a master of nursing sciences from Yale University, and a bachelor of science from the University of Kansas. She is a member of the Institute of Medicine, a leader in nursing education and research, and a widely published scholar. Throughout her career, Dr. Hinshaw has conducted nursing research that focuses on the areas of quality of care, patient outcomes, measurement of those outcomes, and building positive work environments for nurses. Dr. Hinshaw was the first permanent director of the National Center for Nursing Research and the first director of the National Institute of Nursing Research at the National Institutes of Health. She led the institute in its support of disease prevention, health promotion, acute and chronic illness, and the environments that enhance nursing patient care outcomes. Dr. Hinshaw's awards include the Midwest Nursing Research Society Lifetime Achievement Award, the United States Public Health Service's Health Leader of the Year Award, the Elizabeth McWilliams Miller Award for Excellence in Nursing Research from Sigma Theta Tau, and the Nurse Scientist of the Year Award from the American Nurses Association. In addition, she has received 13 honorary doctorate degrees from universities in the United States and Canada.

Tomás J. Aragón, M.D., Dr.P.H., is the health officer of the city and county of San Francisco, California, director of population health and prevention

at the San Francisco Department of Public Health, and medical director of the Center for Infectious Diseases and Emergency Readiness at the University of California, Berkeley, School of Public Health. He specializes in the epidemiology and control of infectious diseases, population and community health, public health preparedness, and epidemiological computing. In San Francisco, he oversees disease control and prevention, public health laboratory, and environmental health. At the University of California, Berkeley, he teaches epidemiology and conducts research.

Alfred Berg, M.D., M.P.H., is a professor in the Department of Family Medicine at the University of Washington School of Medicine, Seattle. Dr. Berg received his professional education in family medicine and general preventive medicine and public health at Washington University, St. Louis, Missouri; the University of Missouri; and the University of Washington. He was elected to the Institute of Medicine in 1996. Dr. Berg's research has focused on clinical epidemiology in primary care settings. He has been active on many expert panels using evidence-based methods to develop clinical guidance, including chair of the United States Preventive Services Task Force, cochair of the Otitis Media Panel convened by the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality), chair and moderator of the Centers for Disease Control and Prevention's (CDC's) Sexually Transmitted Disease Treatment Guidelines panel, a member of the American Medical Association/CDC panel producing Guidelines for Adolescent Preventive Services, and founding chair of CDC's Evaluation of Genetic Applications in Practice and Prevention working group. He was recently appointed to the Methodology Committee of the Patient Centered Outcomes Research Institute. Dr. Berg has served on the Institute of Medicine's Immunization Safety Review Committee (member), the Committee on the Treatment of Post Traumatic Stress Disorder (chair), the Committee on Standards for Systematic Reviews of Clinical Effectiveness Research (chair), and the Committee on Preventive Services for Women (member) and is currently on the Committee on the Governance and Financing of Graduate Medical Education.

Stephen L. Buka, M.S., M.A., Sc.D., is a professor in and chair of the Department of Epidemiology at Brown University and also directs Brown's Center for Population Health and Clinical Epidemiology and Center for the Study of Human Development. He received a Sc.D. in epidemiology from the Harvard School of Public Health in 1988 and was a faculty member in its Departments of Maternal and Child Health, Epidemiology, and Society, Human Development and Health before moving to Brown in 2005. With training in epidemiology and developmental psychology, his research focuses on the causes and prevention of major psychiatric

and cognitive disorders. Current studies include investigations of prenatal risks for schizophrenia, attention deficit disorder, learning disabilities, and addictive disorders; work on the long-term effects of maternal smoking on offspring health and behavior; community-level influences on youth substance use and delinquency; and community-based strategies for the prevention of adolescent drinking and drug use. He has served on multiple panels for the National Institutes of Health and other federal organizations.

R. Alta Charo, J.D., is the Warren P. Knowles Professor of Law and Bioethics at the University of Wisconsin at Madison (UW), where she is on the faculty of the Law School and the Department of Medical History and Bioethics at the medical school. She also serves on the faculty of the UW Masters in Biotechnology Studies program and lectures in the master's of public health program of the Department of Population Health Sciences. Alta Charo (B.A., biology, Harvard, 1979; J.D., Columbia, 1982) is an elected member of the World Technology Network (2004) and the Wisconsin Academy of Sciences, Arts and Letters (2005). In 2006 she was elected to membership in the National Academies' Institute of Medicine. Professor Charo served on President Obama's transition team, where she was a member of the U.S. Department of Health and Human Services review team, focusing her attention particularly on transition issues related to the National Institutes of Health (NIH), the Food and Drug Administration (FDA), bioethics, stem cell policy, and women's reproductive health. She was on leave from 2009 to 2011 to serve as a senior policy adviser on emerging technology issues in the Office of the Commissioner at FDA. Professor Charo offers courses on public health law, bioethics, biotechnology law, food and drug law, reproductive rights, torts, and legislative drafting. In addition, she has served on the UW Hospital clinical ethics committee, the University's Institutional Review Board for the protection of human subjects in medical research, and the University's Bioethics Advisory Committee. Professor Charo's advisory committee service for the federal government includes the 1994 NIH Human Embryo Research Panel and President Clinton's National Bioethics Advisory Commission (1996 to 2001), where she participated in drafting its reports *Cloning Human Beings* (1997), *Research Involving Persons with Mental Disorders that May Affect Decision-making Capacity* (1998), *Research Involving Human Biological Materials: Ethical Issues and Policy Guidance* (1999), *Ethical Issues in Human Stem Cell Research* (1999), *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (2001), and *Ethical and Policy Issues in Research Involving Human Participants* (2001). From 2001 to 2008 she was a member of the Board on Life Sciences of the National Academy of Sciences and the National Academies. She served as its liaison to the

Committee on Research Standards and Practices to Prevent Destructive Applications of Biotechnology as well as its committee to develop national voluntary guidelines for stem cell research. She also served as a member of the Institute of Medicine's Committee on Smallpox Vaccination Program Implementation, and since 2006 she has served on the Board on Population Health and Public Health Practice of the Institute of Medicine. In 2005 and 2006, she was a member of the committee to review FDA and the U.S. national system for the assurance of drug safety.

Gerry Fairbrother, Ph.D., is a senior scholar at AcademyHealth, an adjunct professor of health policy at the George Washington University, and professor of pediatrics at the University of New Mexico and the University of Cincinnati. Dr. Fairbrother's research areas include measuring quality of care, the impact of churning in Medicaid and the Children's Health Insurance Program, and effects of health information technology on health care outcomes. She is currently examining the impact of health information technology on performance in the Cincinnati Beacon Communities Project and the impact of an improvement intervention in School-Based Health Centers as part of one demonstration project of the Children's Health Insurance Program Reauthorization Act. She has led investigations on gaps and patterns of enrollment in child health insurance, barriers and cost to enroll in these programs, the impact of Medicaid managed care on preventive screening for children, and the impact of financial incentives on physician behavior. Dr. Fairbrother holds a Ph.D. from The Johns Hopkins University, is a fellow of the New York Academy of Medicine and of the Ambulatory Pediatric Association, and is a member of the National Association of Social Insurance. She serves on the Centers for Medicare & Medicaid Services (CMS) Technical Expert Panel on National Impact Assessment of CMS Quality Measures and on the National Policy Advisory Committee of the National Institute of Children's Healthcare Quality. In recognition of her work, she received the Best Ohio Health Policy Award for Independent Scholar or Practitioner from the Health Policy Institute of Ohio.

Elena Fuentes-Afflick, M.D., M.P.H., is professor of pediatrics, epidemiology, and biostatistics and Vice Dean for Academic Affairs in the School of Medicine at the University of California, San Francisco (UCSF). Dr. Fuentes-Afflick completed her residency and chief residency in pediatrics at UCSF, followed by training in epidemiology and health policy. Dr. Fuentes-Afflick joined the faculty at UCSF in 1993. Dr. Fuentes-Afflick has served on the National Advisory Council of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the Agency for Healthcare Research and Quality as well as the National Advisory Committee of the Robert Wood Johnson Foundation's Clinical

Scholars Program. In 2009 she was president of the Society for Pediatric Research. Her research focuses on Latino health, with a specific interest in the impact of acculturation, immigration status, perinatal outcomes, and body mass. Dr. Fuentes-Afflick was elected to the Institute of Medicine in 2010.

Sidney M. Gospe, Jr., M.D., Ph.D., holds the Herman and Faye Sarkowsky Endowed Chair and is the head of the Division of Pediatric Neurology at the University of Washington and Seattle Children's Hospital. Prior to joining the faculty of the University of Washington in 2000, he served on the faculty of the University of California, Davis, for 13 years. Dr. Gospe received his undergraduate education at Stanford University and M.D. and Ph.D. degrees from Duke University. He completed his postgraduate medical education in both pediatrics and child neurology at the Baylor College of Medicine. Dr. Gospe's laboratory research has focused on neurotoxicology, in particular, the neurodevelopmental effects of maternal exposure to certain toxicants during pregnancy. He has conducted studies designed to help determine the effects of exposure to environmental tobacco smoke on brain development and whether the fetal brain is more vulnerable during certain periods of development. His earlier work focused on the effects of maternal exposure to the organic solvent toluene on fetal growth and development. Dr. Gospe's clinical research concerns pyridoxine (vitamin B_6)-dependent epilepsy (PDE), a rare familial cause of infantile seizures and associated developmental disability. He collaborates in biochemical and molecular studies of patients with PDE and has established a national registry for patients with this uncommon inherited disorder.

Paul A. Greenberger, M.D., is an attending physician at Northwestern Memorial Hospital and professor of medicine in the Division of Allergy-Immunology, Department of Medicine, Northwestern University Feinberg School of Medicine. He served as Fellowship Program Director from 1992 to 2007 and has helped oversee the postgraduate education for 128 allergy-immunology fellows over the past 33 years. Dr. Greenberger received an undergraduate degree from Purdue University with highest distinction and a medical degree from Indiana University in Indianapolis, where he did his internship at the Methodist Hospital. He completed an internal medicine residency at the Jewish Hospital of St. Louis, Washington University. He was a fellow in allergy-immunology at Northwestern University, where he has been a faculty member since 1977. Dr. Greenberger's research interests include reduction of allergic antibody reactivity utilizing the neuropeptide substance P, idiopathic anaphylaxis, drug allergy, severe and fatal asthma, and allergic bronchopulmonary aspergillosis. Dr. Greenberger has published 260 original articles and 90 reviews and book chapters. He is coeditor of

Patterson's Allergic Diseases and all three editions of the Northwestern University Allergy-Immunology Syllabus: Residents and Students and Drug Allergy and Protocols for Management of Drug Allergies. Dr. Greenberger reviews manuscripts for many journals and was co-editor in chief of *Allergy and Asthma Proceedings* for 12 years. He has contributed to various practice parameters in the field of allergy-immunology and served as chair of the Allergy-Immunology Residency Review Committee of the Accreditation Council on Graduate Medical Education. Dr. Greenberger is a recipient of the Special Recognition and Distinguished Service Award of the American Academy of Allergy, Asthma and Immunology, of which he served as president during 2009 and 2010.

Daniel F. Heitjan, Ph.D., M.Sc., is professor of biostatistics and statistics and director of the Biostatistics Core Facility in the Abramson Cancer Center at the University of Pennsylvania. After earning a Ph.D. in statistics from the University of Chicago in 1985, he served on the faculties of the University of California, Los Angeles (1985 to 1988), Pennsylvania State University (1988 to 1995), and Columbia University (1995 to 2002) before moving to the University of Pennsylvania. He was the 1994-1995 Stanley S. Schor Visiting Scholar at Merck & Co., Inc., and was elected a fellow of the American Statistical Association in 1997 and a fellow of the Institute of Mathematical Statistics in 2012. Dr. Heitjan is an associate editor of *Statistics in Biopharmaceutical Research* and *Clinical Trials* and a statistical editor of the *Journal of the National Cancer Institute*. He was formerly a member of the Agency for Healthcare Research and Quality Healthcare Technology and Decision Sciences study section and is a regular reviewer of grants for the National Institutes of Health, Susan G. Komen for the Cure, and other agencies. He was program chair of the 2005 Joint Statistical Meetings, the largest annual statistical conference in the world; was 2009 chair of the American Statistical Association's Biometrics Section, the largest and oldest of the American Statistical Association's sections; and is currently president-elect of the Eastern North American Region of the International Biometric Society. Dr. Heitjan's research interests include the theory and methodology of statistical analysis with incomplete data, clinical trial design, Bayesian statistics, health economics, and statistical methods for smoking cessation studies. His recent research in smoking cessation involves microsimulation modeling of the cost-effectiveness of smoking cessation treatment strategies, statistical methods for the analysis of rounded daily cigarette counts, comparison of cigarette counts recorded by time line follow back and electronic momentary assessment, and statistical modeling of time-to-event data on repeated smoking quits and lapse.

Annette C. Leland, M.B.A., graduated from Occidental College in 1980 with an A.B. in economics with an emphasis in econometrics. She received an M.B.A. in 1984 from the University of Southern California. Ms. Leland began her career as an economic forecaster at General Telephone before returning to graduate school. She subsequently held leadership roles in marketing for Redken Laboratories and for the Nutrition Counseling Institute, a start-up nutrition/weight-loss venture, where she coordinated with various local hospitals, developed a marketing campaign, and marketing materials. Ms. Leland then moved on to work as a liaison between Clinique Cosmetics and the Kaufmanns Department Store chain, overseeing branch performance, training new employees, and coordinating special events. In 1989, Ms. Leland had her first child and made the choice to be a stay-at-home parent. In 1995, her family moved to the Washington, DC, area and she became active in volunteering as a reading and art class assistant at the local elementary school and volunteering in several capacities at the Washington Waldorf School. Her second child required intensive occupational, speech, and vision therapies, which inspired Ms. Leland to dedicate her time to learning more about these issues. Ms. Leland continued to be involved in her children's schools as the family moved to Connecticut, to Italy, and then back to Washington, DC. Ms. Leland graduated from the Northern Virginia Institute Waldorf Teacher Training program while continuing to volunteer extensively at the Washington Waldorf School, both in and out of the classroom. She has continued to actively educate herself on the medical challenges that her children encounter. Her youngest child has participated in a 2-year clinical drug trial for type 1 diabetes at the Children's Hospital of Pennsylvania, and she has dedicated significant time to learning about the disease and how clinical drug trials operate. Currently, she serves as Annual Bazaar Chairperson, Parent Organization Steering Committee Chair, and 2nd Grade Class Reading Assistant for the Washington Waldorf School.

Pejman Rohani, Ph.D., is a professor of ecology and evolutionary biology, epidemiology, and complex systems at the University of Michigan. His training was in mathematics (B.Sc., University of Manchester, Manchester, United Kingdom) and population ecology (Ph.D., Imperial College, London, United Kingdom). He has held posts at the University of Georgia (2002 to 2009) and was a Royal Society University Research Fellow at the University of Cambridge (1996 to 2002). His research focuses on the population biology of infectious diseases, with a strong emphasis on the use of mathematical, computational, and statistical approaches to the elucidation of host-pathogen interactions. Currently, research in his lab focuses on the epidemiology and evolution of pertussis, dengue viruses, polio, and avian influenza viruses. He has published more than 75 papers, including 4 in *Sci-*

ence, 1 in *Nature*, 2 in the *Proceedings of the National Academy of Sciences of the United States of America*, and 1 in *Lancet*. He has also coauthored a book on modeling infectious disease published by Princeton University Press. He has worked on numerous occasions in an advisory capacity with the World Health Organization's Quantitative Analysis of Vaccine Related Research and served on the scientific advisory board of the Center for Zoonotic, Vector-Borne and Enteric Diseases at the Centers for Disease Control and Prevention.

Lainie Friedman Ross, M.D., Ph.D., is the Carolyn and Matthew Bucksbaum Professor of Clinical Medical Ethics; professor in the Departments of Pediatrics, Medicine, and Surgery and the College; associate director of the MacLean Center for Clinical Medical Ethics; and codirector of the Clinical and Translational Science Award at the University of Chicago. Dr. Ross has published two books on pediatric ethics: *Children, Families and Health Care Decision Making* (Oxford University Press, 1998), and *Children in Medical Research: Access Versus Protection* (Oxford University Press, 2006). She has also published more than 100 articles in peer-reviewed journals in the areas of pediatric ethics, transplantation ethics, research ethics, and genetics and ethics. Dr. Ross earned an A.B. from the Woodrow Wilson School at Princeton University (1982), an M.D. from the University of Pennsylvania School of Medicine (1986), and a Ph.D. in philosophy from Yale University (1996). She did her residency at the Children's Hospital of Philadelphia (1986 to 1988) and at Columbia University (1988 to 1989). She currently serves as the chair of the Executive Committee of the American Academy of Pediatrics Section on Bioethics and is a member of the U.S. Department of Health and Human Services Secretary's Advisory Committee on Human Research Protections.

Pauline A. Thomas, M.D., F.A.A.P., is associate professor in the Department of Preventive Medicine and Community Health at the New Jersey Medical School (NJMS) and in the School of Public Health of the University of Medicine and Dentistry of New Jersey. She is codirector of the NJMS Preventive Medicine Residency. Previously, Dr. Thomas spent 23 years at the New York City Department of Health and Mental Hygiene (DOHMH), where she served as director of AIDS Surveillance, director of the Immunization Program, and assistant commissioner for surveillance. Her work at DOHMH included development of the World Trade Center Health Registry, studying the health effects of more than 70,000 people exposed to the aftermath of the disaster at the World Trade Center on September 11, 2001. Dr. Thomas received undergraduate and medical degrees from Yale University. She completed a residency in pediatrics at the University of Rochester and after her residency joined the Centers for Disease Control

and Prevention's Epidemic Intelligence Service. She is chair of the Epidemiology Section of the American Academy of Pediatrics (AAP). She recently served on the Institute of Medicine Committee to Review Adverse Effects of Vaccines. Dr. Thomas has authored more than 60 journal articles and maintains a small part-time private pediatric practice in a multispecialty medical group in New Jersey.

Appendix G

Institute of Medicine Publications on Vaccines

- *Adverse Effects of Vaccines: Evidence and Causality* (2012)
- *Ranking Vaccines: A Prioritization Framework: Phase I: Demonstration of Concept and a Software Blueprint* (2012)
- "A Perspective on Vaccines," President's Address, Institute of Medicine Annual Meeting, Washington, DC (2011)
- *The 2009 H1N1 Influenza Vaccination Campaign: Summary of a Workshop Series* (2010)
- *The Domestic and International Impacts of the 2009-H1N1 Influenza A Pandemic: Global Challenges, Global Solutions: Workshop Summary* (2009)
- *Live Variola Virus: Considerations for Continuing Research* (2009)
- *Priorities for the National Vaccine Plan* (2009)
- *Initial Guidance for an Update of the National Vaccine Plan: A Letter Report to the National Vaccine Program Office* (2008)
- *Battling Malaria: Strengthening the U.S. Military Malaria Vaccine Program* (2006)
- *John R. La Montagne Memorial Symposium on Pandemic Influenza Research: Meeting Proceedings* (2006)
- *The Smallpox Vaccination Program: Public Health in an Age of Terrorism* (2005)
- *Vaccine Safety Research, Data Access, and Public Trust* (2005)
- *Immunization Safety Review: Influenza Vaccines and Neurological Complications* (2004)
- *Immunization Safety Review: Vaccines and Autism* (2004)

- *Financing Vaccines in the 21st Century: Assuring Access and Availability* (2003)
- *Immunization Safety Review: Vaccinations and Sudden Unexpected Death in Infancy* (2003)
- *Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 1* (2003)
- *Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 2* (2003)
- *Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 3* (2003)
- *Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 4* (2003)
- *Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 5* (2003)
- *Review of the Centers for Disease Control and Prevention's Smallpox Vaccination Program Implementation, Letter Report 6* (2003)
- *Setting the Course—A Strategic Vision for Immunization. Part 3: Summary of the Los Angeles Workshop* (2003)
- *Setting the Course—A Strategic Vision for Immunization. Part 4: Summary of the Washington, DC, Workshop* (2003)
- *The Anthrax Vaccine: Is It Safe? Does It Work?* (2002)
- *An Assessment of the CDC Anthrax Vaccine Safety and Efficacy Research Program* (2002)
- *Considerations for Viral Disease Eradication: Lessons Learned and Future Strategies* (2002)
- *Immunization Safety Review: Hepatitis B Vaccine and Demyelinating Neurological Disorders* (2002)
- *Immunization Safety Review: Multiple Immunizations and Immune Dysfunction* (2002)
- *Immunization Safety Review: SV40 Contamination of Polio Vaccine and Cancer* (2002)
- *Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military* (2002)
- *Scientific and Policy Considerations in Developing Smallpox Vaccination Options: A Workshop Report* (2002)
- *Setting the Course—A Strategic Vision for Immunization Finance. Part 1: Summary of the Chicago Workshop* (2002)
- *Setting the Course—A Strategic Vision for Immunization. Part 2: Summary of the Austin Workshop* (2002)
- *Immunization Safety Review: Measles-Mumps-Rubella Vaccine and Autism* (2001)
- *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders* (2001)

- Statement from the IOM Council on Vaccine Development (2001)
- *An Assessment of the Safety of the Anthrax Vaccine: A Letter Report* (2000)
- *Calling the Shots: Immunization Finance Policies and Practices* (2000)
- *Urgent Attention Needed to Restore Lapsed Adenovirus Vaccine Availability: A Letter Report* (2000)
- *Vaccines for the 21st Century: A Tool for Decisionmaking* (2000)
- *Assessment of Future Scientific Needs for Live Variola Virus* (1999)
- *Preliminary Considerations Regarding Federal Investments in Vaccine Purchase and Immunization Services: Interim Report on Immunization Finance Policies and Practices* (1999)
- *Detecting and Responding to Adverse Events Following Vaccination: Workshop Summary* (1997)
- *Research to Identify Risks for Adverse Events Following Vaccination: Biological Mechanisms and Possible Means of Prevention: Workshop Summary* (1997)
- *Risk Communication and Vaccination: Workshop Summary* (1997)
- *Options for Poliomyelitis Vaccination in the United States: Workshop Summary* (1996)
- *Vaccines Against Malaria: Hope in a Gathering Storm* (1996)
- *The Children's Vaccine Initiative: Continuing Activities* (1995)
- *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* (1994)
- *DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis* (1994)
- *Research Strategies for Assessing Adverse Events Associated with Vaccines: A Workshop Summary* (1994)
- *The Children's Vaccine Initiative: Achieving the Vision* (1993)
- *Adverse Effects of Pertussis and Rubella Vaccines* (1991)
- *The Potential Value of Research Consortia in the Development of Drugs and Vaccines Against HIV Infection and AIDS (report of a workshop)* (1989)
- *An Evaluation of Poliomyelitis Vaccine: Policy Options* (1988)
- *Prospects for Vaccines Against HIV Infection* (1988)
- *Temperature-Stable Vaccines for Developing Countries: Significance and Development Strategies* (1987)
- *New Vaccine Development: Establishing Priorities. Volume II, Diseases of Importance in Developing Countries* (1986)
- *New Vaccine Development: Establishing Priorities. Volume I, Diseases of Importance in the United States* (1985)
- *Vaccine Supply and Innovation* (1985)
- *Evaluation of Poliomyelitis Vaccines* (1977)

EXHIBIT E

RICHARD JAFFE, ESQ.

Lawyer
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THE DENMARK SCHEDULE HYSTERIA MISSES THE POINT: IT'S ABOUT SHARED CLINICAL DECISION-MAKING

December 23, 2025 (Https://Rickjaffeesq.Com/2025/12/23/The-Denmark-Schedule-Hysteria-Misses-The-Point-Its-About-Shared-Clinical-Decision-Making/) Richard Jaffe (Https://Rickjaffeesq.Com/Author/Rickjaffe/)

The vaccine establishment went into full panic mode last week when CNN reported that HHS was planning to align the U.S. childhood vaccine schedule with Denmark's. The headlines screamed: Denmark recommends only 11 vaccine doses targeting 10 diseases; the U.S. recommends 72 doses targeting 18 diseases. Scott Gottlieb warned we'd need to "build new pediatric hospitals." The AAP predicted "devastating results." Paul Offit accused HHS of wanting children to suffer.

But CNN missed half the story.

The next day, the Washington Post reported what CNN had overlooked: "Unlike Denmark, the U.S. is planning a more limited approach for recommending vaccines to children known as shared clinical decision-making, which has not been reported."

That's the buried lede. The plan isn't just about fewer vaccines, it's about moving childhood vaccines to "shared clinical decision-making" (SCDM), shifting from mandatory universal recommendations to individualized parent-physician decisions.

That's what this piece is about. Not the Denmark comparison (though it's worth noting that Denmark has better childhood health outcomes than we do). The real story is SCDM, what it actually means, what it changes, and why the vaccine establishment is so terrified of it.

Let me explain what actually changes, and what doesn't, if childhood vaccines move to SCDM.

But first, let's talk about why this discussion is happening at all.

Why SCDM, Why Now?

COVID changed everything.
For three years, Americans were told the COVID vaccines were "safe and effective," would "stop transmission," and that anyone who questioned the narrative was an anti-science conspiracy theorist. The vaccine establishment—CDC, FDA, AAP, the whole alphabet soup—spoke with one voice: Trust us. Don't ask questions. Just comply.

Then the truth started leaking out. The vaccines didn't stop transmission—Pfizer never even tested for it. The "95% effective" claim was relative risk reduction, not absolute risk reduction. Exposed, it turned out to be more like 0.85 percent effective. Myocarditis in young men wasn't "rare"—it was systematically undercounted. Natural immunity was dismissed as irrelevant, then quietly acknowledged. The six-foot rule? Made up. Exposed as not based on science. Masks for toddlers? No evidence.

All of this only came to the public's attention because, and only because, of the courageous doctors and scientists who called it out during the pandemic, like Piere Kory, MD (lead plaintiff in Kory v. Bonta, one of my Covid misinformation cases presently pending before the Supreme Court, Richard Eggleson and Thomas Siler, plaintiffs in another one of my Covid misinformation First Amendment cases also pending before the Supreme Court,. And to those, I must add the person I would call "doctor zero" (like in patient zero in mass infection cases), Simone Gold (double trouble because she's both a doctor and a lawyer).

The COVID debacle might not have created the public's district of public health authorities, but it surely reinforced that the public's mistrust was justified.

The lying didn't start with COVID, but it did reveal for all to see how they operate. More to the point, unlike mandatory school vaccination, COVID restrictions and mandates hit everyone, not just parents with school aged kids in the states without a religious exemption.

The Foundational Lie: "Vaccines Conquered Infectious Disease"

The vaccine establishment's origin story goes like this: Before vaccines, children died in droves from infectious diseases. Then vaccines came along and saved us all. Anyone who questions this narrative wants children to die.
It's a powerful story. It's also mostly false.

In September 2025, Senator Maria Cantwell waved a chart at HHS Secretary Robert Kennedy claiming vaccines had saved "154 million lives" by nearly eradicating infectious disease mortality. Kennedy's response should be required viewing for every American.
The data tells a different story. A CDC-funded study from Johns Hopkins—Guyer et al., published in Pediatrics in 2000—analyzed 100 years of U.S. mortality data. The conclusion: nearly all the mortality reductions from infectious diseases occurred BEFORE vaccines were introduced.

The numbers are stark:

Measles: Deaths fell from 13,000 annually in 1900 to a few hundred by 1960. The vaccine wasn't introduced until 1963—three years later. A 98% reduction before a single dose was administered.

Pertussis (whooping cough): The largest mortality drop happened before the vaccine.

Polio: Mortality fell 90% between 1923 and 1955, before the Salk vaccine.

Tuberculosis: Deaths virtually eliminated in the U.S. without mass vaccination.

Scarlet fever: Mortality plummeted along the same timeline. No vaccine ever developed.

What actually caused these dramatic declines?

Clean water. Sanitation. Refrigeration. Better nutrition. Chlorination. Flush toilets. The mundane infrastructure of modern civilization—not pharmaceutical products.

McKinlay and McKinlay's landmark 1977 study estimated that medical interventions—including vaccines AND antibiotics—accounted for less than 3.5% of the total mortality decline. Three and a half percent.
Yet the vaccine establishment has spent decades taking credit for the other 96.5%. That's not science. That's marketing.

So, What Does SCDM Actually Threaten?

Not children's health. The data proves that.

What SCDM threatens is the mythology—the carefully constructed narrative that vaccines are responsible for modern civilization's triumph over infectious disease, and therefore must never be questioned.

If parents can have real informed consent conversations with their doctors—if they can weigh actual risks and benefits for their individual child—the whole edifice starts to crumble. Not because parents will stop vaccinating (they won't, as we'll see), but because they'll start asking questions. And the vaccine establishment has never had good answers.

That's what the hysteria is really about. Now let's look at what SCDM actually does and doesn't change.

Insurance Coverage: No Change

The loudest claim is that SCDM vaccines won't be covered by insurance. This is false, and the people saying it know it's false.

Here's the CDC's own FAQ:
"This coverage requirement includes shared clinical decision-making recommendations when they have been adopted by CDC and are listed on the immunization schedules."
https://www.cdc.gov/acip/vaccine-recommendations/shared-clinical-decision-making.html
(https://www.cdc.gov/acip/vaccine-recommendations/shared-clinical-decision-making.html)

KFF confirms:
"The insurance requirement extends to vaccines with 'individual decision-making' (also known as 'shared clinical decision-making') recommendations as well, which are those 'individually based and informed by a decision process

between the health care provider and the patient or parent/guardian'."
https://www.kff.org/other-health/recent-changes-in-federal-vaccine-recommendations-whats-the-impact-on-insurance-coverage/ (https://www.kff.org/other-health/recent-changes-in-federal-vaccine-recommendations-whats-the-impact-on-insurance-coverage/)

The Avalere Guide to Vaccine Coverage Policies states that payers must cover without cost-sharing "all on-schedule products with routine and SCDM."
https://advisory.avalerehealth.com/wp-content/uploads/2023/10/Guide-to-Vaccine-Coverage-Policies.pdf (https://advisory.avalerehealth.com/wp-content/uploads/2023/10/Guide-to-Vaccine-Coverage-Policies.pdf)

CHOP's Vaccine Education Center:
"For children, the Vaccines for Children (VFC) program is designed to ensure payment for all vaccines on the childhood immunization schedule, including those that are recommended with SCDM. For adults, most private insurance plans pay for routinely recommended vaccines as well as those with SCDM, under Affordable Care Act (ACA) regulations."
https://www.chop.edu/vaccine-update-healthcare-professionals/newsletter/shared-clinical-decision-making-what-it-and-why-it-matters (https://www.chop.edu/vaccine-update-healthcare-professionals/newsletter/shared-clinical-decision-making-what-it-and-why-it-matters)

We already have SCDM vaccines. MenB for adolescents 16-23. HPV for adults 27-45. Hepatitis B for adults 60+ with diabetes. All covered. The sky hasn't fallen.

The insurance argument is simply wrong.

Manufacturer Immunity: Genuinely Unclear

What about liability? Does SCDM affect the manufacturer immunity created by the 1986 National Childhood Vaccine Injury Act?
This is where it gets legally interesting and frankly murky.

The liability shield in 42 U.S.C. § 300aa-22(b)(1) applies to vaccines covered by the Vaccine Injury Compensation Program. For a vaccine to be covered, 42 U.S.C. § 300aa-14 requires that CDC recommend it for "routine administration to children." The Vaccine Injury Table, maintained by the Secretary, lists covered vaccines.

The untested legal question: Does "routinely recommended for children" include Category B/SCDM recommendations, or only Category A routine recommendations?

Current SCDM vaccines like MenB remain on the VICP table—but they also have routine recommendations for high-risk populations. A vaccine that went to pure SCDM for everyone, with no routine recommendation for any childhood population, would present a novel question.
The statute doesn't define "routine administration." No court has interpreted whether SCDM qualifies. If it doesn't, vaccines moved to pure SCDM might fall outside VICP coverage—and outside the liability shield.

It is no secret that in his past, pre-government days, Secretary Kennedy repeatedly complained about vaccine manufacturer's immunity and called for its end. The question is whether he has administrative pathways to do so, or whether it requires congressional action.

The cleanest path would be legislation—Representative Gosar's "End the Vaccine Carveout Act" (H.R. 9828) would directly repeal the immunity provisions in § 300aa-22(b)(1). But Congress is Congress, enough said.

Administratively, the Secretary could potentially:
– Change CDC recommendations to pure SCDM, creating the legal ambiguity described above
– Attempt to remove vaccines from the VICP table through rulemaking under his authority to "modify" the table (42 U.S.C. § 300aa-14(c))

Either path would trigger immediate litigation. Post-Loper Bright, courts would most likely interpret "routine administration" de novo, giving no deference to agency interpretation. And the Major Questions Doctrine would loom over any attempt to strip immunity from a multi-billion-dollar market.

But "would face litigation" isn't the same as "would lose."

This is genuinely unsettled legal territory. The uncertainty itself may be significant; manufacturers facing years of litigation over their liability status is not nothing.

More importantly, after 39 years of living with manufacturer immunity for the products which seem to have played a significant role in the dramatic deterioration in the health of American children (my view), it is well past time we have this serious discussion about whether this whole immunity thing is doing American children more harm than good.

And Let's Put the Immunity Question into World Perspective

Care to guess how many other countries in the world give manufacturers immunity from lawsuits for vaccine injury? You got it: NONE, ZERO.

No other country gives immunity from civil liability and prohibits civil tort suits against vaccine manufactures (with one exception which I'll discuss). Many countries have administrative remedies in addition to civil tort suits, but the U.S. is the only country in the world that has a civil liability system that prohibits the vaccine injured from accessing it. (New Zealand, like the US, forces the vaccine injured into an administrative process, but that is because that country has done away with civil tort remedies for all injuries.)

So, circling back to the main question:

Unlike the insurance question, which is clearly settled in favor of SCDM coverage, the immunity question is open. Moving childhood vaccines to SCDM might create a pathway to challenge manufacturer immunity. However, it's untested, and anyone who tells you they know the answer is guessing.

State Mandates: No Direct Federal Effect

The federal government doesn't mandate vaccines. States do, under 10th Amendment police powers. ACIP recommends; states decide whether to require.

Forty-six states have religious exemptions. Only California, Connecticut, Maine, and New York have medical-only exemptions. And California has already decoupled from ACIP through AB 144.

So, in the vast majority of states, parents who want to decline vaccines for their kids, already can. Moving from Category A to Category B changes nothing for them.

The International Evidence: We're Not Just Talking About Denmark

Critics dismiss comparisons to Denmark with the repartee "We're not Denmark, a homogeneous country of 6 million people." Fair enough. So, let's look at the full picture.

A 2024 study in Vaccines (Farina et al.) systematically mapped childhood vaccination policies across all 30 EU/EEA countries. The findings are striking:

Countries with NO mandatory childhood vaccinations—recommendation-only (17 countries): Austria, Cyprus, Denmark, Estonia, Finland, Greece, Iceland, Ireland, Liechtenstein, Lithuania, Luxembourg, Netherlands, Norway, Portugal, Romania, Spain, Sweden

In these countries, all childhood vaccines are offered and covered, but parents decide. That's functionally identical to what ACIP calls "shared clinical decision-making." But there's a critical difference: these European nations have full sovereign authority to mandate vaccines—and chose not to. Per the above, in the U.S., the federal government cannot mandate vaccines; under the 10th Amendment, that power belongs exclusively to states. So, when ACIP "recommends," it's the only a recommendation to the states and has no direct force, unless state law couples their mandates to CDC/ACIP recommendations. When Denmark or Spain "recommends," it's a deliberate policy choice by governments that could mandate but decided parental choice works better.

Countries with LIMITED mandates—one to three vaccines mandatory, rest recommendation-only (3 countries):
– Belgium: Only polio mandatory; all other vaccines parental choice
– Germany: Only measles mandatory; all other vaccines parental choice
– Malta: Only tetanus, diphtheria, and polio mandatory; all other vaccines parental choice

Countries with COMPREHENSIVE mandates—most vaccines mandatory (10 countries): Bulgaria, Croatia, Czech Republic, France, Hungary, Italy, Latvia, Poland, Slovakia, Slovenia

So, even among the 13 countries with "at least one mandate," three of them—Belgium, Germany, and Malta—operate essentially on shared clinical decision-making for the vast majority of their vaccine schedule. Germany, Europe's largest economy with 84 million people, mandates only measles and recommends everything else.

That means 20 out of 30 EU/EEA countries either have no mandates at all or operate primarily on a recommendation basis with only limited mandates for specific high-concern vaccines. Only 10 countries have comprehensive mandate systems like the U.S. model.

Add the UK (67 million, recommendation-only with 92% DTP coverage) and Japan (125 million, abolished mandates in 1994, 98% coverage), and the picture is clear: the majority of the developed world trusts parents with vaccine decisions and achieves excellent coverage.

The international data demolishes the CDC's premise that eliminating parental choice is necessary for public health. Countries respecting medical freedom have lower infant mortality, less chronic disease, and comparable vaccination rates. American exceptionalism has produced exceptionally sick children.

AND HERE ARE TWO FACTS THAT SHOULD STOP EVERY VACCINE MANDATE DEFENDER IN THEIR TRACKS:

Russia's federal law explicitly allows parents to refuse childhood vaccinations. No exemption required. Just say no.

China's "mandatory" vaccination system? No penalties for refusal. The decision-making process is required; the actual vaccination isn't.

Meanwhile, in New York and California, parents have zero choice. Vaccinate or your child doesn't attend school. No religious exemption. No philosophical exemption.

Let that sink in:

On childhood vaccine choice, Vladimir Putin's Russia and Xi Jinping's China offer parents more freedom than New York or California.
In those states (and in Connecticut and Maine) The "land of the free" has become the land of "inject your kids with whatever Pfizer is selling this year or we'll lock them out of kindergarten; if something goes wrong, too bad, you can't sue."

To me, that sounds like a criminal protection racket. One of these days, I might just do something to push back.

Vaccination Rates: No Change

Here's the data point that demolishes the hysteria: Massachusetts has a religious exemption and a 95%+ kindergarten vaccination rate. New Jersey, Virginia, Rhode Island—same story. Religious exemptions available, rates above 95%.

If SCDM would cause parents to stop vaccinating, we'd see it in these states. We don't.
Parents in states where they can already opt out are choosing to vaccinate anyway. Clearly, the mandates aren't driving compliance; Parental choice is.

So why not formalize what's already happening? If informed consent doesn't reduce vaccination rates, why fight it so hard?

What SCDM Actually Changes

If insurance stays, immunity is uncertain but probably unchanged, mandates aren't federally controlled, and vaccination rates don't change—what's the point?

Three things matter:

First, the clinical encounter changes. Doctors must actually discuss risks and benefits with each patient. Informed consent becomes real, not theater.

Second, physician protection. Doctors who individualize care—who look at a particular child's history and make a judgment call—can no longer be hauled before medical boards for "deviating from the standard of care." The standard of care becomes individualized assessment.

Third, practice coercion weakens. "Vaccinate or leave our practice" becomes harder to justify when ACIP itself says it's an individual decision.

These aren't nothing. They're a step in the right direction—treating vaccines like every other medical intervention, subject to informed consent and professional judgment.

The Hepatitis B Proof of Concept

We just watched this play out in real time. On December 5, 2025, ACIP voted 8-3 to recommend "individual decision-making" for the hepatitis B birth dose in low-risk infants. That's 99.6% of U.S. births—infants born to mothers who test negative for hepatitis B.

The response from AAP was immediate and hysterical. President Susan Kressly called it "irresponsible and purposely misleading," warning of "thousands" of infections and "devastating results." Committee members predicted "children will die preventable deaths" and "liver cancers."

Paul Offit told CNN there would be a "four-fold increase" in infections and claimed 30,000 children under 10 contracted hepatitis B annually before universal vaccination.

The actual CDC data? Approximately 400 cases annually in that age group. Offit overstated by 75-fold.
Meanwhile, the UK and Canada already delay the birth dose. No infection surge. No liver cancer epidemic. No devastation.

This is what SCDM panic looks like: fabricated statistics, invented catastrophes, and complete disregard for what other developed countries do safely.

The Real Fear

They're not afraid SCDM will change vaccination rates. The data proves it won't.
They're afraid of losing the narrative of compulsion. That "CDC and AAP say so, shut up and comply." The authority to punish dissenting physicians. The power to label questioning parents as "anti-vax."

SCDM treats vaccines like the medicines they are. And apparently, that's intolerable to the vaccine mafia.

So, it seems that all the hysteria isn't about protecting children; it's about protecting a system that doesn't tolerate questions.

Rick Jaffe, Esq. (more to come soon I hope.)

Disclosure: As some may know, I am counsel in *Thomas v. Monarez* (D.D.C., Case No. 1:25-cv-02685), a lawsuit challenging the CDC's childhood vaccine schedule and seeking reclassification of all childhood vaccines to shared clinical decision-making. So yes, I have a stake in this debate.

December 25, 2025 at 2:33 pm (https://rickjaffeesq.com/2025/12/23/the-denmark-schedule-hysteria-misses-the-point-its-about-shared-clinical-decision-making/#comment-42003)

I can, and do so, appreciate your perspective and attitude. Thank-you for this article. My best regards to you.