Safety of Vaccines Used for Routine Immunization of US Children: A Systematic Review

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KEY WORDS
evidence-based medicine, vaccine/immunization, infectious disease

ABBREVIATIONS
AEs—adverse events
AHRQ—Agency for Healthcare Research and Quality
CI—confidence interval
DTaP—diphtheria, tetanus, and acellular pertussis
H1N1—Swine Flu
Hib—*Haemophilus influenza* type b
ILI—influenza-like illness
IOM—Institute of Medicine
IPV—inactivated poliovirus
IRR—incidence rate ratio
LAIV—live attenuated vaccine
MMR—measles/mumps/rubella
Oka VZV—Oka strain varicella zoster virus
OR—odds ratio
PCV—pneumococcal conjugate vaccine
PRISM—Post-Licensure Rapid Immunization Safety Monitoring
Td—tetanus-diphtheria
TIV—trivalent inactivated vaccine
VSD—Vaccine Safety Datalink

Ms Maglione conceptualized and designed the study, oversaw the abstraction of data, interpreted the results, and drafted the manuscript; Ms Das abstracted data, interpreted results, and revised the manuscript; Ms Raaen abstracted data, interpreted results, and revised the manuscript; Ms Smith designed data collection instruments, analyzed data, and revised the manuscript; Dr Chari abstracted data, interpreted results, and revised the manuscript; Dr Newberry revised the manuscript for important content and approved the final manuscript as submitted; Ms Shanman developed the literature search strategy, conducted electronic literature searches, and acquired data; Ms Perry acquired data and designed screening and data abstraction forms; Dr Goetz contributed to the conceptualization and design of the study, interpreted results, and critically reviewed and revised the manuscript; Dr Gidengil participated in study design, interpreted the results, drafted part of the manuscript, and critically reviewed the manuscript, and all authors approved the final manuscript as submitted.

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abstract

FREE

BACKGROUND: Concerns about vaccine safety have led some parents to decline recommended vaccination of their children, leading to the resurgence of diseases. Reassurance of vaccine safety remains critical for population health. This study systematically reviewed the literature on the safety of routine vaccines recommended for children in the United States.

METHODS: Data sources included PubMed, Advisory Committee on Immunization Practices statements, package inserts, existing reviews, manufacturer information packets, and the 2011 Institute of Medicine consensus report on vaccine safety. We augmented the Institute of Medicine report with more recent studies and increased the scope to include more vaccines. Only studies that used active surveillance and had a control mechanism were included. Formulations not used in the United States were excluded. Adverse events and patient and vaccine characteristics were abstracted. Adverse event collection and reporting was evaluated by using the McHarm scale. We were unable to pool results. Strength of evidence was rated as high, moderate, low, or insufficient.

RESULTS: Of 20 478 titles identified, 67 were included. Strength of evidence was high for measles/mumps/rubella (MMR) vaccine and febrile seizures; the varicella vaccine was associated with complications in immunodeficient individuals. There is strong evidence that MMR vaccine is not associated with autism. There is moderate evidence that rotavirus vaccines are associated with intussusception. Limitations of the study include that the majority of studies did not investigate or identify risk factors for AEs; and the severity of AEs was inconsistently reported.

CONCLUSIONS: We found evidence that some vaccines are associated with serious AEs; however, these events are extremely rare and must be weighed against the protective benefits that vaccines provide. *Pediatrics* 2014;134:325–337

Vaccines are considered one of the greatest public health achievements of the 20th century for their role in eradicating smallpox and controlling polio, measles, rubella, and other infectious diseases in the United States.[1] Despite their effectiveness in preventing and eradicating disease, routine childhood vaccine uptake remains suboptimal. Parent refusal of vaccines has contributed to outbreaks of vaccine-preventable diseases such as measles[2] and pertussis.[3] In addition, although multiple large studies have confirmed the lack of association between measles/mumps/rubella (MMR) and autism, parental worries about the safety of vaccines persist.

The Agency for Healthcare Research and Quality (AHRQ) requested an evidence report on the safety of vaccines recommended for routine immunization of adults (including pregnant women), children, and adolescents to be used by the Office of the Assistant Secretary of Health to identify the gaps in evidence. This article addresses the safety of vaccines recommended for routine use in children aged 6 years and younger: DTaP (diphtheria, tetanus, and acellular pertussis), hepatitis A, hepatitis B, *Haemophilus influenza* type b (Hib), influenza (live attenuated and inactivated), meningococcal (conjugate or polysaccharide), MMR, pneumococcal (conjugate or polysaccharide), rotavirus, and varicella. It represents the results of a comprehensive and systematic review of scientific evidence, describes statistical associations between vaccines and adverse events (AEs), and reports on any risk factors identified.

METHODS

In 2011, the Institute of Medicine (IOM) published a consensus report titled *Adverse Effects of Vaccines: Evidence and Causality*.[4] That report evaluated the scientific evidence for AEs potentially associated with varicella, influenza, hepatitis A, hepatitis B, human papillomavirus, MMR, meningococcal, tetanus, diphtheria, and pertussis vaccines. We report the IOM findings regarding children and update those findings by identifying and evaluating studies published after the IOM searches. We also identify studies and evaluate evidence on pneumococcal, rotavirus, Hib, and inactivated poliovirus (IPV) vaccines because these are recommended for children aged 6 years and younger.

The following databases were searched: DARE (Database of Abstracts of Reviews of Effects), the Cochrane Database of Systematic Reviews, CENTRAL, PubMed, Embase, CINAHL (Cumulative Index to Nursing and Allied Health), TOXLINE (Toxicology Literature Online), and TOXFILE. The IOM report, Advisory Committee on Immunization Practices statements, vaccine package inserts, and review articles were mined for studies. Using the IOM keyword search strategy, we updated their searches to identify more recently published studies. The following structure was used: "vaccine term" AND "health term," where vaccine terms include the technical vaccine name, general descriptions of the vaccine of interest (eg, rotavirus AND vaccine), or manufacturer names; health terms include a list of AEs potentially associated with the vaccine. We also added more general AE keywords to the list of health terms such as "safe" or "safety," "side effect" or "harm." We searched from a year before the publication of the IOM report through August 2013. Using this approach, we developed new search strategies for the vaccines not originally included in the IOM report and searched each database from its inception through August 2013. AE terms were based on AEs reported in systems such as the Vaccine Injury Compensation Program, Vaccine Adverse Event Reporting System, and the Food and Drug Administration's Mini-Sentinel Program. A Technical Expert Panel reviewed the draft list of AEs and suggested additional AEs of interest.

We included studies that used active surveillance and had a control mechanism; eligible designs were controlled trials, cohorts comparing a vaccinated with nonvaccinated group, case–control studies, self-controlled case series, and observational studies that used regression to control for confounders and test multiple relationships simultaneously (multivariate risk factor analyses). Common sources of data included medical records, health insurance claims, and government registries.

To maintain applicability to the current US context, we excluded studies of vaccine formulations never used or no longer available in the United States; examples include whole cell pertussis vaccine, oral polio vaccine, and pneumococcal conjugate vaccine (PCV)7 vaccine. The recent IOM report, *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies*,[5] makes recommendations for future research on childhood vaccine schedules and cumulative effect, so the current project focused on specific vaccines, rather than any cumulative effect.

Two researchers experienced in systematic review methodology independently reviewed the titles and abstracts identified. The union of their selections was retrieved. These researchers independently reviewed the full text of study reports and met to reach consensus regarding exclusion/inclusion. Disputes were settled by the lead investigators and team physician experts. Patient and study characteristics were abstracted by single researchers and confirmed by the project leader. If a study reported severity or if adequate information was

provided for our investigators to categorize severity, we used the Common Terminology Criteria for Adverse Events classification system[6] to characterize AEs. The definition of "serious" differs by AE type; each category of AE (ie fever, headache) is rated on a 5-point scale, with 1 being very mild and 5 being death due to the event.

The McHarm instrument[7] was used to evaluate the quality of the studies with regard to their assessment of AEs. Studies that reported timing and severity and defined AEs using standard, precise definitions were rated higher than those that did not. We assessed the overall strength of evidence by using guidance suggested by AHRQ for its Effective Health Care Program[8] as of 2013. (The guidance has since been modified slightly.) The method is based on one developed by the Grading of Recommendations Assessment Working Group[9] and classifies the evidence based on risk of bias, consistency, directness, precision, dose–response, plausible confounders that would decrease the observed effect, strength of association, and publication bias. Possible ratings are as follows:

High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

Insufficient = Evidence either is unavailable or does not permit a conclusion.

It is important to note that the 2011 IOM report used different terminology to classify the strength of evidence; evidence was classified as either "convincingly supports," "favors acceptance," "inadequate to accept or reject," or "favors rejection" of a causal association. They also included mechanistic studies and individual case reports to assess the biological plausibility of AE and considered this in addition to any statistical association. For each vaccine discussed in the IOM report, we started with the IOM findings and modified them, if needed, on the basis of any additional evidence we identified.

RESULTS

As presented in Fig 1, 20 478 titles were identified through electronic literature searches; review of product inserts; review of Food and Drug Administration, Advisory Committee on Immunization Practices, and other Web sites; reference mining; and requests for Scientific Information Packets from drug manufacturers. Of those, 17 270 were excluded on review of abstract or title for reasons such as "not about a vaccine," "vaccine not within the scope of this project" (formulations never available in the United States, recommended only for travel), or because they were animal studies. Upon full text review of the remaining 3208 articles, 392 were identified as relevant background/theoretical materials and set aside as potential references for the Introduction; 2749 other articles were excluded. The most common reason for exclusion was lack of suitable study design (1549): individual case reports, nonsystematic reviews, and studies using passive surveillance were excluded. Many publications (458) discussed vaccines on the recommended schedule but did not report or assess AEs. Eighty-eight studies on adults or adolescents were excluded for this article, as were 11 studies of children with preexisting conditions such as HIV, juvenile arthritis, or cancer, which left 67 studies. These studies are in addition to those included in the 2011 IOM consensus report *Adverse Effects of Vaccines: Evidence and Causality*, which were not abstracted.

We present the results for each vaccine in alphabetical order. Results are summarized in Table 1.

DTaP

The IOM studied diphtheria toxoid, tetanus toxoid, and acellular pertussis-containing vaccines alone and in combination in both children and adults. The IOM committee did not find evidence that "favors acceptance" of causal relationships for any conditions. They found the evidence "favors rejection" of a causal relationship between type 1 diabetes and vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens.[10–14] We found no additional studies in children published after the IOM search date; our review of their assessment supports their conclusions.

Hib Vaccine

The IOM did not study the safety of Hib vaccine. We identified 3 controlled trials of the Hib vaccine in children[15–17]; 1 was set in the United States, the other 2 in Asia. Results of the US trial (N = 5190) indicated that Hib vaccination was associated with redness (odds ratio [OR] 2.71, 95% confidence interval [CI] 1.57–4.67) and swelling (OR 9.44, 95% CI 4.90–18.19) but not with hospitalizations. Vaccination was not associated with high fever in either the US trial or a trial in the Philippines. A trial in Vietnam[15] found the vaccine was not associated with any serious AEs, including convulsion, diarrhea, fungal infection, or gastroesophageal reflux disease. No other AEs were associated with the Hib vaccination.

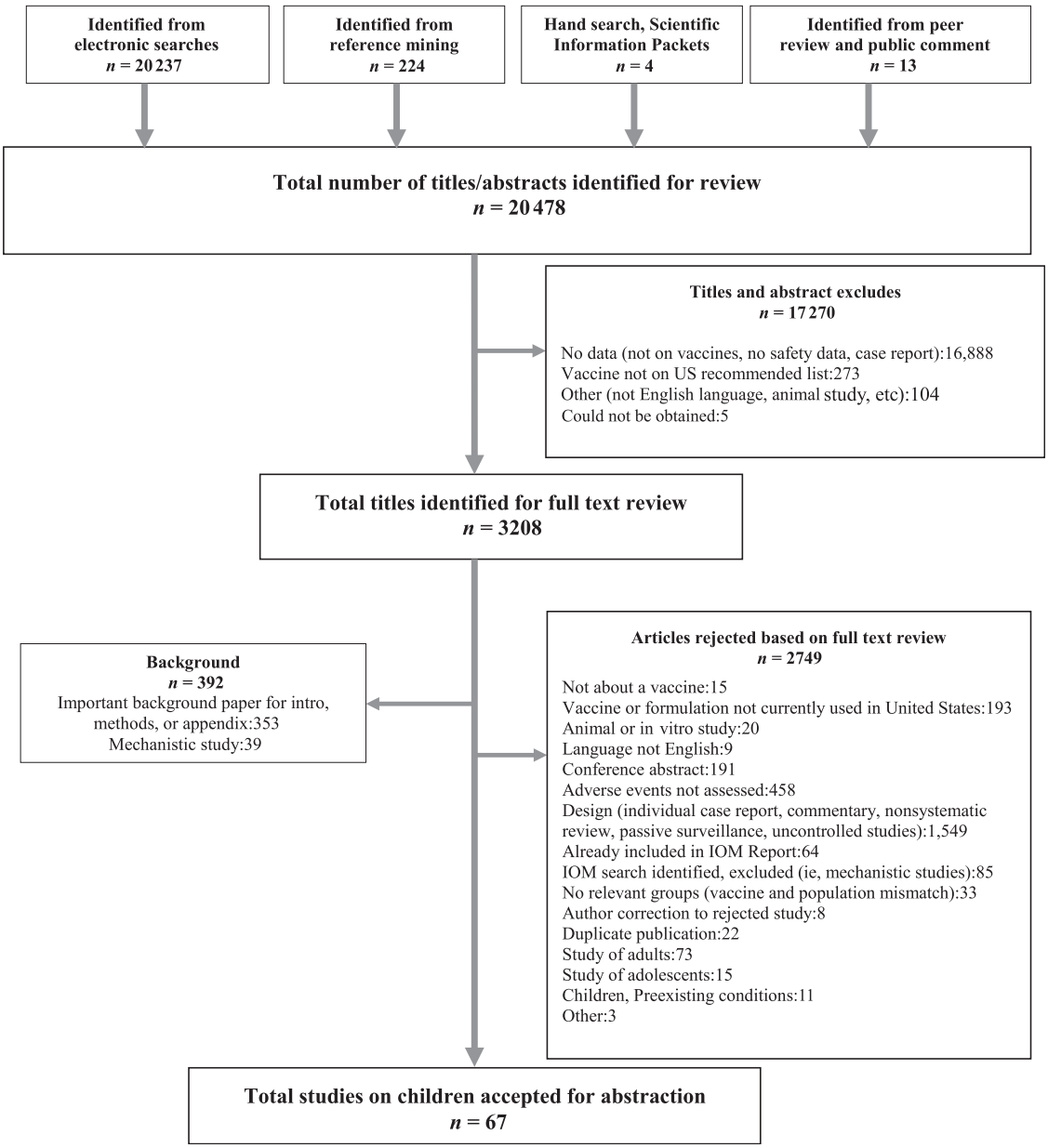

FIGURE 1
Literature diagram.

Hepatitis A

Hepatitis A vaccine was not covered by the IOM report on vaccine safety. We did not identify any studies of children that assessed the association of hepatitis A alone with AEs. However, we did identify a recent analysis that investigated possible relationships among Hib, PCV, MMR, DTaP, trivalent inactivated vaccine (TIV), hepatitis A, varicella, and meningococcal vaccines and immune thrombocytopenic purpura in children enrolled in 5 US health maintenance organizations.[18] Purpura was not associated with any of the vaccines in children aged 2 to 6 years but was associated with vaccination against hepatitis A in children aged 7 to 17 years (incidence rate ratio 23.14, 95% CI 3.59–149.30; findings related to other vaccines are reported in their respective sections). This study provides evidence for a moderate association between hepatitis A vaccine and purpura in children aged 7 to 17 years.

Hepatitis B

Although no epidemiologic studies were identified by the IOM, mechanistic evidence "favored acceptance" of a causal relationship between the vaccine and anaphylaxis in yeast-sensitive individuals. The 2011 IOM study found "insufficient" evidence of an association of hepatitis B vaccine with any short- or

TABLE 1 Results: Safety of Vaccines Used for Routine Immunization of Children

Vaccine	Conclusions and Strength of Evidence	2011 IOM Findings	New Findings
DTaP	Moderate: no association with type 1 diabetes	Evidence "favors rejection" of a causal relationship between vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens and type 1 diabetes.	No additional studies met inclusion criteria.
Hepatitis A vaccine	Moderate: purpura	Not covered.	In a large postlicensure study of >1.8 million vaccine recipients, purpura was associated with vaccination against hepatitis A in children aged 7–17 y. These results were based on 1 or 2 cases per vaccine type/age group. According to the authors, most cases were mild and acute.
Hepatitis B vaccine	Insufficient: food allergy	Although no epidemiologic studies were identified by the IOM, mechanistic evidence "favored acceptance" of a causal relationship between the vaccine and anaphylaxis in yeast-sensitive individuals.	Hepatitis B vaccine in the first 6 mo of life was associated with elevated total immunoglobulin E in a postlicensure study of children with a family history of food allergy but not with clinical allergy.
	Moderate: no association with MS	A 2002 IOM report "favors rejection" of a causal relationship with MS onset or exacerbation.	
Hib vaccine	Moderate: no association with serious AEs in short term	Not covered.	No serious AEs were associated in 3 high-quality clinical trials.
IPV	Insufficient: food allergy	Not covered.	One postlicensure study reported association between polio vaccine in newborns and sensitivity to food allergens.
Influenza vaccines (live attenuated and inactivated)	Moderate: mild gastrointestinal disorders, febrile seizures	Evidence was "inadequate to accept or reject" a causal relationship with any AEs investigated.	We identified 1 trial of seasonal influenza vaccine (including a strain of H1N1) and 1 cohort comparison study of 2009 monovalent H1N1 vaccine published after the IOM search dates; the studies found no evidence of an association of the vaccines with any AEs.
	Low: Influenza-like symptoms		Both seasonal influenza vaccines and monovalent H1N1 vaccine (administered only in 2009 season) were associated with mild gastrointestinal disorders, such as vomiting and diarrhea, in children in the short term in 2 large postlicensure studies. One of these studies found that younger vaccinated children (aged 5–8 y) were more likely to experience these symptoms than older vaccinated children (aged 9–17 y). (Children aged <5 y were not included in that study). Both live and inactivated seasonal influenza vaccines were associated with influenza-like symptoms in children in the short term in 1 new study. A large US postlicensure study of children aged <5 y found TIV associated with febrile seizures. Risk was increased if PCV13 was administered concomitantly.
MMR	High: no association with autism spectrum disorders	Evidence "convincingly supports" causal relationships anaphylaxis in allergic children and febrile seizures.	Five new postmarketing studies were identified. Vaccination was associated with thrombocytopenic purpura in the short term in 3; it was not studied in the other 2. In 1 study, MMR vaccination was associated with increased emergency department visits within 2 wk; this is indirect support of the IOM's findings that MMR vaccine is associated with febrile seizures.

TABLE 1 Continued

Vaccine	Conclusions and Strength of Evidence	2011 IOM Findings	New Findings
	High: anaphylaxis in children with allergies, febrile seizures Moderate: transient arthralgia Moderate: thrombocytopenic purpura	Evidence "favors acceptance" of a causal relationship between MMR and transient arthralgia Evidence "favors rejection" of a causal relationship between MMR and autism.	A new case-control study found MMR vaccine was unrelated to autism.
Meningococcal vaccines (MCV4, MPSV)	Moderate: anaphylaxis in children with allergies	Evidence "convincingly supports" a causal relationship with anaphylaxis allergic children.	Two new trials of quadrivalent meningococcal conjugate vaccines found no association with any AEs assessed.
PCV13	Moderate: febrile seizures	Not covered.	The US VSD found an association with febrile seizures. Estimated rate for 16-mo-old patients is 13.7 cases per 100 000 doses for PCV13 without concomitant TIV and 44.9 per 100 000 doses for concomitant TIV and PCV13.
Rotavirus vaccines: RotaTeq and Rotarix	Moderate: Intussusception	Not covered.	In 31 clinical trials, there was no association between either of the current vaccines (RotaTeq and Rotarix) and any serious AEs, including intussusception, in the long or short term. A high-quality Australian epidemiologic study found RotaTeq associated with intussusception 1–21 d after the first of 3 required doses in infants 1–3 mo of age. Two case–control studies conducted in Latin America found an association of Rotarix with intussusception in children after the first of 2 required doses. Although 1 US epidemiologic study found no association, a recent analysis of the US PRISM program found both RotaTeq and Rotarix associated with intussusception in the short term. Estimated rate was 1.1–1.5 cases per 100 000 doses of RotaTeq and 5.1 cases per 100 000 doses of Rotarix.
Varicella vaccine	High: anaphylaxis; disseminated Oka VZV without other organ involvement; disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis in individuals with demonstrated immunodeficiencies; vaccine strain viral reactivation without other organ involvement; vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis. Moderate: purpura	Evidence "convincingly supports" causal relationships between varicella virus vaccine and the following: disseminated Oka VZV without other organ involvement; disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis in individuals with demonstrated immunodeficiencies; vaccine strain viral reactivation without other organ involvement; vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis; and anaphylaxis.	In a large postlicensure study of >1.8 million vaccine recipients, purpura was associated with vaccination against varicella in children aged 11–17. These results were based on 1 or 2 cases per vaccine type/age group. According to the authors most cases were mild and acute.
Miscellaneous	High: no association of childhood leukemia with MMR, DTaP, Td, Hib, hepatitis B, and polio vaccines	Not applicable.	Four large epidemiologic studies conducted analyses to assess which, if any, of the following vaccines might be associated with childhood leukemia: MMR, DTaP, Td, Hib, hepatitis B, and polio vaccine. No association was found for any vaccine.

EPC, Evidence-based Practice Center; MS, multiple sclerosis; MCV, meningococcal conjugate vaccine; MPSV, meningococcal polysaccharide vaccine; PCV, pneumococcal conjugate vaccine; VZV, varicella-zoster virus.

long-term AEs in children. A 2002 IOM review on hepatitis B vaccine and demyelinating neurologic disorders concluded that the evidence "favors rejection" of a causal relationship with incident multiple sclerosis or multiple sclerosis relapse.[19] We identified 1 study published after the IOM 2011 search: Gallagher and Goodman (2010)[20] conducted a secondary analysis of National Health Interview Survey data on 7074 boys born before 1999. Vaccination status and health outcomes were reported by parents. Results were significant for the risk of autism in children who received their first dose of hepatitis B vaccine during the first month of life (OR 3.00, 95% CI 1.11–8.13), compared with those who received the vaccination after the first month of life or not at all. Significant protective factors included non-Hispanic white ethnicity (OR 0.36, 95% CI 0.15–0.88) and belonging to a household with 2 parents (OR 0.30, 95% CI 0.12–0.75). It is unclear why the authors selected "first month of life" as the only vaccination time period studied, without presenting analyses for other time periods or comparing "ever vaccinated" with "never vaccinated." Because of high risk of bias and low quality, this study presents insufficient evidence that hepatitis B vaccine is associated with autism.

IPV: Inactivated Polio Virus

The IOM did not study IPV vaccine. Our search identified a case–control study of >2000 children with atopic dermatitis and a family history of allergy in 12 Western countries,[21] which found that newborns immunized against polio had higher odds (OR 2.60, 95% CI 1.08–6.25) of sensitivity to food allergens. This relationship did not hold for those immunized against polio later in life. A self-controlled case series of premature infants born in the United States[22] found no increased risk of wheezing and lower respiratory syndrome associated with DTaP, IPV, Hib, varicella, PCV7, MMR, or TIV vaccination. In sum, the strength of evidence is insufficient to determine an association between polio vaccine in newborns and sensitivity to food allergens.

Influenza Vaccines

Influenza vaccine is administered in 2 forms: live attenuated vaccine (LAIV), administered intranasally, and TIV, administered intramuscularly. The IOM found no evidence that "convincingly supports" causal relationships in the pediatric population for any AEs. We identified 1 trial of seasonal influenza vaccine (which included a strain of H1N1 [swine flu])[23] and 1 cohort comparison study of 2009 monovalent H1N1 vaccine[24] published after the IOM search dates; the studies found no evidence of an association of the vaccines with AEs.

Six observational studies also met our inclusion criteria.[25–30] A 2011 UK study of 2336 children[25] found no association between flu vaccines and febrile seizures; however, a recent study using the US Vaccine Safety Datalink (VSD)[26] found an association of flu vaccine with febrile seizures, which increased with concomitant administration of pneumococcal vaccine (PCV13). In the highest risk age group (16 months), estimated rate was 12.5 per 100 000 doses for TIV without concomitant PCV13, 13.7 per 100 000 doses for PCV13 without concomitant TIV, and 44.9 per 100 000 doses for concomitant TIV and PCV13. In large, high-quality postlicensure studies, both LAIV and TIV were associated with mild gastrointestinal disorders,[27,28] such as short-term vomiting and diarrhea in children. Strength of evidence is moderate for these AEs. One of these studies found that younger vaccinated children (aged 5–8 years) were more likely to experience these symptoms than older vaccinated children (aged 9–17 years). (Children <5 years of age were not included in that study). Finally, an Italian study[31] of children hospitalized for influenza-like illness (ILI) found those vaccinated with seasonal vaccine (OR 2.1, 95% CI 1.1–4.1) were significantly more likely to show symptoms of ILI than unvaccinated children, whereas those vaccinated for H1N1 were not at higher risk (OR 1.3, 95% CI 0.6–3.1). Strength of evidence is moderate for mild gastrointestinal events and febrile seizures and low for ILI.

MMR

The IOM committee found that mechanistic evidence "convincingly supports" causal relationships between MMR and measles inclusion body encephalitis in immunocompromised children and anaphylaxis in allergic patients. They also found epidemiologic evidence that "convincingly supports" a causal relationship between MMR vaccine and febrile seizures.[32–38] The IOM committee found the evidence "favors acceptance" of a causal relationship between MMR and transient arthralgia in the pediatric population.[39–45] They found the evidence "favors rejection" of a causal relationship between MMR and autism.[46–50] In addition, a causal relationship between the Urabe strain of mumps and aseptic meningitis has been shown; there is no evidence to link Jeryl Lynn strain, commonly used in the United States, to this AE.

We identified 5 postlicensure studies of childhood MMR vaccination published after the IOM searches. In a case–control study of 189 young adults with autism spectrum disorder and 224 controls, Uno et al[51] found that childhood receipt of MMR vaccine was not associated with an increased rate of new-onset autism (OR 1.10, 95% CI 0.64–1.90). In 3 studies,[18,52,53] MMR vaccination was associated with thrombocytopenic purpura in children in the

short term after vaccination. Strength of evidence is moderate because findings were consistent and ORs similar in 3 European countries, Canada, and the United States. Finally, 1 Canadian study found MMR vaccination was associated with increased emergency department visits within 2 weeks. This finding is consistent with the IOM's findings that MMR vaccine is associated with febrile seizures.

Meningococcal

The IOM found the evidence "convincingly supports" a causal relationship with anaphylaxis in children who may be allergic to ingredients. The IOM conclusion does not differentiate between meningococcal conjugate or meningococcal polysaccharide vaccines. We found 2 studies of quadrivalent meningococcal conjugate vaccine in children[54,55] published after the IOM report. A trial in Saudi Arabia found no statistical association with grade 2 or 3 fever, malaise, myalgia, or headache in the short term.[54] A trial in the United States and South America[55] found vaccination was not associated with severe change in eating habits, severe irritability, severe persistent crying, severe sleepiness, or urticaria in the year after vaccination.

Thus, the strength of evidence is moderate that meningococcal vaccine may cause anaphylaxis in children who are allergic to ingredients. Strength of evidence is insufficient to determine an association with less serious events such as headache, irritability, and urticaria.

PCV13

The IOM did not study the safety of PCV13. As noted earlier, the VSD[26] analyzed data on >200 000 US children aged <5 years and found that vaccine against pneumonia (PCV13) was associated with febrile seizures; importantly, administration of influenza vaccine at the same visit was associated with increased risk. For example, in the highest risk group, which was 16-month-old children, the estimated rate was 13.7 per 100 000 doses for PCV13 without concomitant TIV and 44.9 per 100 000 doses for concomitant TIV and PCV13. Risk difference estimates varied by age due to the varying baseline risk for seizures in young children. Thus the strength of evidence for an association between PCV13 and febrile seizures is moderate, and the risk is particularly high when coadministered with influenza vaccine.

Rotavirus Vaccines: RotaTeq and Rotarix

The IOM report did not address vaccines against rotavirus. Thirty-one trials of rotavirus vaccine[56–85] met our inclusion criteria. Participants in the accepted studies received 2 or 3 oral-administered doses of Rotarix (18 studies) or RotaTeq (13 studies). Neither Rotarix nor RotaTeq was associated with increased risk of AEs other than cough, runny nose, or irritability.

We identified 5 postlicensure studies on intussusception risk[86–90]; an earlier brand of rotavirus vaccine (Rotashield) was withdrawn from the market in 1999 due to concerns about risk for this condition. A high-quality epidemiologic study ($N = 296\,023$) conducted in Australia[86] found RotaTeq associated with intussusception in children 1 to 21 days after the first of 3 required doses but found no association with Rotarix. Two postlicensure studies were recently conducted in the United States. Shui et al[89] analyzed VSD data on 786 725 doses of RotaTeq and found no association with intussusception at any time after vaccination. However, a recent analysis of data from the US Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program[90] found that intussusception risk was increased after Dose 1 of RotaTeq and Dose 2 of Rotarix. The RotaTeq analysis had higher statistical power because that vaccine was administered to orders of magnitude more children than Rotarix. Estimated rate of intussusception was 1.1 to 1.5 cases per 100 000 doses of RotaTeq and 5.1 cases per 100 000 doses of Rotarix.

In addition, 2 case–control studies conducted in Latin America found an association with intussusception in children after the first of 2 required doses of Rotarix. One study estimated Rotarix increased risk by 3.7 additional cases per 100 000 person years in Mexico.[87] The other Latin American study estimated risk as 1 case per 51 000 vaccinations in Mexico and 1 case per 68 000 vaccinations in Brazil.[88] In sum, there is moderate strength evidence that vaccination against rotavirus is associated with intussusception, but the occurrence is extremely rare, and risk factors have not been investigated.

Varicella

The IOM committee found evidence "convincingly supports" causal relationships in children between varicella virus vaccine and the following: disseminated Oka strain varicella zoster virus (Oka VZV) without other organ involvement; disseminated Oka VZV with subsequent infection resulting in pneumonia,[91] meningitis, or hepatitis in individuals with demonstrated immunodeficiencies; vaccine strain viral reactivation without other organ involvement; vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis[92]; and anaphylaxis.[91]

We identified 1 study that investigated possible relationships among Hib, PCV, MMR, DTaP, TIV, hepatitis A, varicella, and meningococcal vaccines and immune thrombocytopenic purpura in children enrolled in 5 US health maintenance organizations.[18] Purpura was not

associated with any of the vaccines in children aged 2 to 6 years but was associated with vaccination against varicella in children aged 11 to 17 years (incidence rate ratio *R* 12.14, 95% CI 1.10–133.96; findings related to other vaccines are reported in their respective sections). This study provides evidence for a moderate association between varicella vaccine and purpura in children aged 11 to 17 years.

Studies Controlling for Multiple Vaccinations During Childhood

Four high-quality epidemiologic studies investigated the potential relationship between vaccinations and onset of childhood leukemia. Groves and colleagues[93] included 439 US children with lymphoblastic leukemia in a case–control analysis to investigate any possible relationship with oral or injected polio vaccine, diphtheria-tetanus pertussis vaccine, MMR, Hib, or hepatitis B vaccine. Controls were selected using random-digit dialing, which resulted in controls of higher socioeconomic status then the 439 cases. None of the vaccines were associated with leukemia. The relationship between vaccination and leukemia was also assessed in a case–control study of children in Northern California.[94] Cases were matched on date of birth, gender, and race/ethnicity. Analysis also controlled for maternal education and family income. None of the vaccines investigated (DPT, polio vaccine, MMR, Hib, hepatitis B vaccine) were associated with increased risk of leukemia. Similarly, the Cross-Canada Childhood Leukemia Study[95] found no association between vaccines against mumps, measles, rubella, diphtheria, tetanus, pertussis, polio, or hepatitis B and leukemia. Finally, a large case–control study of children born in Texas[96] found that several vaccines may have a protective effect against acute lymphoblastic leukemia.

DISCUSSION

This study updated the evidence presented in the 2011 IOM report and expanded the scope of that study by including additional vaccines such as those against Hib, hepatitis A, PCV13, rotavirus, and IPV. Findings related to these vaccines indicate that the Hib vaccine is associated with local discomfort such as redness and swelling but is not associated with serious AEs or hospitalization. Strength of evidence is moderate for the following associations: Hepatitis A vaccine and purpura in children aged 7 to 17 years, PCV13 and febrile seizures with an escalation of risk when coadministered with TIV, and rotavirus vaccine and intussusception. None of the vaccines studied here were associated with childhood-onset leukemia.

Our findings support the following IOM results: vaccine against hepatitis B is not associated with any long- or short-term AEs; the MMR vaccine is associated with febrile seizures; MMR vaccine is not associated with autism. In addition, our study found moderate evidence linking both LAIV and TIV forms of the influenza vaccines with mild gastrointestinal events; TIV was associated with febrile seizures. We also found moderate (but consistent) strength evidence of an association between the MMR vaccine and thrombocytopenic purpura in children; there was a similar association between the varicella vaccine and thrombocytopenic purpura in children aged 11 to 17 years.

Literature search procedures for this review were extensive; however, some unpublished trial results may not have been identified. An independent Scientific Resource Center under contract with AHRQ requested Scientific Information Packets from the vaccine manufacturers. (The research team was prohibited from contacting manufacturers directly.) Only 2 companies responded.

Our findings are based on only the most rigorous study designs to assess potential statistical associations; however, these designs have limitations that must be considered. Controlled trials often have insufficient sample size to identify rare AEs and do not have extended follow-up to identify long-term sequelae. In addition, trials may purposely exclude subjects who could be more susceptible to AEs. For this reason, any comprehensive review of vaccine safety must include post-licensure studies, but these also have limitations. Large epidemiologic studies sometimes include any available formulation of vaccines against a particular disease and may not stratify results by dosage or formulation. For example, the relationship between the "seasonal influenza vaccine" and an AE could be studied over several years of data without considering the changes in formulation over the seasons or differentiating between live or inactive vaccine. In addition, people who avoid vaccinations (whether purposely or not) may differ from those who receive vaccinations in terms of race, gender, age, socioeconomic status, and preexisting medical conditions, and these differences may be associated with health outcomes. Observational studies may attempt to control for such potential confounders by using matched cohorts or multivariate regression analysis; still, some factors such as environmental exposures may be unmeasured or challenging to adequately control for.

The self-controlled case series was developed specifically to assess the safety of vaccines; this method eliminates confounding by all time-independent variables by using cases as their own controls and predefined "time windows" before and after vaccination. This design has been used to study purpura, febrile seizures, intussusception, and autism

in children. However, the assumption of no temporal shifts in this model is difficult to justify in very young children because any patient characteristics that change with time will not be adequately controlled for.

Importantly, some AE signals that warrant future research may not have been identified by this project. Passive surveillance systems such as the US Vaccine Adverse Event Reporting System[97] are crucial in identifying signals regarding AEs post licensure, but they are not designed to assess a statistical association, so they were excluded as sources of data.

CONCLUSIONS

Our findings may allay some patient, caregiver, and health care provider concerns. Strength of evidence is high that MMR vaccine is not associated with the onset of autism in children; this conclusion supports findings of all previous reviews on the topic. There is also high-strength evidence that MMR, DTaP, Td, Hib, and hepatitis B vaccines are not associated with childhood leukemia.

Evidence was found for an association of several serious AEs with vaccines; however, these events were extremely rare: absolute risk is low. For example, strength of evidence is moderate for association of vaccines against rotavirus with intussusception. Although 1 large US epidemiologic study found no association, a recent analysis of the US PRISM program[90] found both RotaTeq and Rotarix associated with intussusception in the short term. Estimated rates were 1.1 to 1.5 cases per 100 000 doses of RotaTeq and 5.1 cases per 100 000 doses of Rotarix.

Few studies were powered to detect patient characteristics associated with increased risk of rare AEs. Advanced health information technology systems that contain both vaccination and health outcome records may be used to conduct such investigations. In the United States, the VSD contains data from such systems at 9 large managed care organizations. In addition, the PRISM program also conducts active surveillance using electronic health care databases from managed care organizations. Nations with single-payer health care systems often have electronic registries that allow large epidemiologic studies of entire populations. Future analyses should be stratified by formulation and brand of vaccine whenever possible.

ACKNOWLEDGMENTS

The authors thank Aneesa Motala, BA, for compiling the many peer review comments and formatting the final report. We thank Susanne Hempel, PhD, for her advice on study design, Paul Shekelle, MD, PhD, for his advice and review of the draft and final versions of the evidence report, Kim Wittenberg, MA, for serving as the AHRQ Task Order Officer and Steve Bende, PhD, for representing the Office of the Assistant Secretary for Health. We thank the following individuals for serving on the Technical Expert Panel for the project: Meghan Baker, MD ScD; Richard Beigi, MD, MSc; Kathryn Edwards, MD; Kristen Feemster, MD, MSPH; Bruce Fireman, MA; David Martin, MD; and Claudia Vellozzi, MD, MPH. Finally, we would like to thank the following Peer Reviewers: Janet D. Cragan, MD, MPH; Francesca Cunningham, Pharm D; Frank Destefano, MD, MPH; and Laura Elizabeth Riley, MD. Please note that service as a Peer Reviewer or Expert Panel member does not imply endorsement of the study findings.

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(Continued from first page)

www.pediatrics.org/cgi/doi/10.1542/peds.2014-1079

doi:10.1542/peds.2014-1079

Accepted for publication May 7, 2014

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported under Contract No. HHSA290200710062I from the Agency for Healthcare Research and Quality, US Department of Health and Human Services.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found on page 377, and online at www.pediatrics.org/cgi/doi/10.1542/peds.2014-1494.