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# Safety of Vaccines Used for Routine Immunization of U.S. Children: A Systematic Review

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**Short title:** Vaccine safety for U.S. children

**Abbreviations:** ACIP - Advisory Committee on Immunization Practices; AEs - Adverse Events; AHRQ - Agency for Healthcare Research and Quality; CI - Confidence Interval; CINAHL - Cumulative Index to Nursing and Allied Health; CTCAE - Common Terminology Criteria for Adverse Events; DARE - Database of Abstracts of Reviews of Effects; DTaP - diphtheria, tetanus, and acellular pertussis; FDA - Food and Drug Administration; GERD - gastroesophageal reflux disease; GI – Gastrointestinal; GRADE - Grading of Recommendations Assessment, Development and Evaluation; H1N1 - Swine Flu; Hib - Haemophilus influenza type b; HMOs - health maintenance organizations; ILI - influenza-like illness; IOM - Institute of Medicine; IPV - Inactivated polio virus; IRR - Inter-rater Reliability; ITP - immune thrombocytopenic purpura; LAIV - live attenuated vaccine; MCOs - managed care organizations; MMR - Measles/Mumps/Rubella; MS - Multiple Sclerosis; OASH - Office of the Assistant Secretary of Health; Oka VZV - Oka strain varicella zoster virus; OR - Odds Ratio; PCV - Pneumococcal Conjugate Vaccine; PRISM - Post-Licensure Rapid Immunization Safety Monitoring ; SCCS - self-controlled case series; SIPs - Scientific Information Packets; SOE - Strength of Evidence; Td - tetanus-diphtheria; TEP - Technical Expert Panel; TIV - trivalent inactivated vaccine; TOXLINE - Toxicology Literature Online; VAERS - Vaccine Adverse Event Reporting System; VICP - Vaccine Injury Compensation Program; VSD - Vaccine Safety Datalink

**Key words:** Evidence-Based Medicine, Vaccine/Immunization, Infectious Disease

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**Contributors' Statements:**

Margaret A. Maglione: Conceptualized and designed the study, oversaw the abstraction of data, interpreted the results, drafted the manuscript, and approved the final manuscript as submitted.

Lopamudra Das: Abstracted data, interpreted results, revised the manuscript, and approved the final manuscript as submitted.

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Ramya Chari: Abstracted data, interpreted results, revised the manuscript, and approved the final manuscript as submitted.

Sydne Newberry: Revised the manuscript for important content and approved the final manuscript as submitted.

Roberta Shanman: Developed the literature search strategy, conducted electronic literature searches, acquired data, and approved the final manuscript as submitted.

Tanja Perry: Acquired data, designed screening and data abstraction forms, and approved the final manuscript as submitted.

Matthew Bidwell Goetz: Contributed to the conceptualization and design of the study, interpreted results, critically reviewed and revised the manuscript and approved the final manuscript as submitted.

Courtney Gidengil: Participated in study design, interpreted the results, drafted part of the manuscript, critically reviewed the manuscript, and approved the final manuscript as submitted.

## Structured Abstract

**Context:** Concerns about vaccine safety have led some parents to decline recommended vaccination of their children, leading the resurgence of diseases. Reassurance of vaccine safety remains critical for population health.

**Objective:** To systematically review the literature on the safety of routine vaccines recommended for children in the United States.

**Data Sources:** PubMed, ACIP statements, package inserts, existing reviews, manufacturer information packets, and the 2011 IOM consensus report on vaccine safety.

**Study Selection:** We augmented the 2011 IOM report with additional 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 US were excluded.

**Data Extraction:** Adverse events, patient-, and vaccine- characteristics were abstracted. AE collection and reporting was evaluated using the McHarm scale. We were unable to pool results. Strength of evidence was rated as high, moderate, low, or insufficient.

**Results:** 20,478 titles identified; 67 were included. Strength of evidence was high for 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:** The majority of studies did not investigate or identify vaccination related risk factors for AEs; 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.

Abstract word count: 250

## Introduction

Vaccines are considered one of the greatest public health achievements of the twentieth 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 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 (OASH) to identify the gaps in evidence. This manuscript addresses the safety of vaccines recommended for routine use in children age six and under: DTaP (diphtheria, tetanus, and acellular pertussis), hepatitis A, hepatitis B, Hib (*Haemophilus influenza* type b), influenza (live attenuated and inactivated), meningococcal (conjugate or polysaccharide), MMR (measles, mumps, and rubella), 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 entitled *Adverse Effects of Vaccines: Evidence and Causality.*[4] That report evaluated the scientific evidence for adverse

events potentially associated with varicella, influenza, hepatitis A, hepatitis B, HPV, 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, *Haemophilus influenzae* type b, and inactivated poliovirus vaccines, as these are recommended for children age six and under.

The following databases were searched: DARE, the Cochrane Database of Systematic Reviews, CENTRAL, PubMed, EMBASE, CINAHL, TOXLINE, and TOXFILE. The IOM report, ACIP 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 (e.g., 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 (VICP), Vaccine Adverse Event Reporting System (VAERS), and the FDA's Mini-Sentinel Program. A Technical Expert Panel (TEP) reviewed the draft list of AEs and suggested additional AEs of interest.

We included studies that utilized active surveillance and had a control mechanism; eligible designs were controlled trials, cohorts comparing a vaccinated with non-vaccinated group, case-control studies, self-controlled case series (SCCS), 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 US; examples include whole cell pertussis vaccine, oral polio vaccine, and PCV7 pneumococcal 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 (CTCAE) classification system[6] to characterize AEs. The definition of “serious” differs

by AE type; each category of AE (i.e. fever, headache) is rated on a five-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 adverse events. 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 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 GRADE 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 listed below.

**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, based on any additional evidence that we identified.

**Results**

As presented in Figure 1, a total of 20,478 titles were identified through electronic literature searches; review of product inserts; review of Food and Drug Administration, ACIP, and other Web sites; reference mining; and requests for Scientific Information Packets from drug manufacturers. Of those, 17,270 were excluded upon 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 US, recommended only for travel), or because they were animal studies. Upon full text review of the remaining 3,208 articles, 392 were identified as relevant background/theoretical materials and set aside as potential references for the Introduction. A total of 2,749 other articles were excluded. The most common reason for exclusion was lack of suitable study design (1,549): 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 manuscript, as were 11 studies of children with pre-existing 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, alphabetical order. Results are summarized in Table 1.

Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis (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 1diabetes 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.

*Haemophilus Influenza* Type B (Hib) Vaccine

The IOM did not study the safety of *Haemophilus influenza* type B (Hib) vaccine. We identified three controlled trials of the Hib vaccine in children;[15-17] one was set in the US, the other two in Asia. Results of the US trial (N = 5,190) indicated that Hib vaccination was associated with redness (OR 2.71, 95% CI 1.57, 4.67) and swelling (OR 9.44, 95% CI 4.90, 18.19), but not associated 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 adverse events, including convulsion, diarrhea, fungal infection, or GERD. No other AEs were associated with the Hib vaccination.

Hepatitis A

Hepatatis 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 adverse events. However, we did identify a recent analysis that investigated possible relationships between Hib, PCV, MMR, DTaP, TIV, Hepatitis A, varicella, and meningococcal vaccines and immune thrombocytopenic purpura (ITP) in children enrolled in five US health maintenance

organizations (HMOs).[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 (IRR 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 epidemiological 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 long term adverse events in children. A 2002 IOM review on Hepatitis B vaccine and demyelinating neurological disorders concluded that the evidence "favors rejection" of a causal relationship with incident MS or MS relapse.[19] We identified one study published after the IOM 2011 search: Gallagher and Goodman (2010)[20] conducted a secondary analysis of National Health Interview Survey data on 7,074 boys born prior to 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 two 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." Due to high risk of bias and low quality, this study presents insufficient evidence that Hepatitis B vaccine is associated with autism.

Inactivated Polio Virus (IPV)

The IOM did not study IPV vaccine. Our search identified a case-control study of over 2,000 children with atopic dermatitis and a family history of allergy in twelve 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 US[22] found no increased risk of wheezing and lower respiratory syndrome associated with DTaP, inactivated polio virus (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 two forms: live attenuated vaccine (LAIV), administered intranasally, and trivalent inactivated vaccine (TIV), administered intramuscularly. The IOM found no evidence that "convincingly supports" causal relationships in the pediatric population for any adverse events. We identified one trial of seasonal influenza vaccine (which included a strain of H1N1)[23] and one 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 2,336 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 post-licensure studies, both LAIV and TIV were associated with mild gastrointestinal disorders 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 to 8 years) were more likely to experience these symptoms than older vaccinated children (aged 9 to 17 years). (Children under 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 GI events and febrile seizures and low for ILI.

Measles-Mumps-Rubella (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 epidemiological 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 US, to this adverse event.

We identified five post-licensure 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. 2012[51] found that childhood receipt of mumps-measles-rubella (MMR) vaccine was not associated with an increased rate of new onset autism (OR 1.10, 95% CI 0.64, 1.90). In three studies, MMR vaccination was associated with thrombocytopenic purpura in children in the short term after vaccination. Strength of evidence is moderate, as findings were consistent and odds ratios similar in three European countries, Canada, and the US. Finally, one Canadian study found MMR vaccination was associated with increased emergency department visits within two 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 two studies of quadrivalent meningococcal conjugate vaccine in children 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 US 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 following 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.

Pneumococcal conjugate vaccine (PCV13)

The IOM did not study the safety of PCV13. As noted above, the VSD[26] analyzed data on over 200,000 US children under age five 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 co-administered 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 two or three 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 five post-licensure 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 epidemiological study (N = 296,023) conducted in Australia[86] found RotaTeq associated with intussusception in children 1 to 21 days following the first of three required doses but found no association with Rotarix. Two post-licensure studies were recently conducted in the US. Shui, 2012[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, as 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, two case-control studies conducted in Latin America found an association with intussusception in children following the first of two 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 one case per 51,000 vaccinations in Mexico and one 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 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 one study that investigated possible relationships between Hib, PCV, MMR, DTaP, TIV, Hepatitis A, varicella, and meningococcal vaccines and immune thrombocytopenic purpura (ITP) in children enrolled in five US HMOs.[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 (IRR 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 epidemiological 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 SES 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, sex, 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 like 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 7-17 years; PCV13 and febrile seizures with an escalation of risk when co-administered 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 GI 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 11-17 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 two 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 very rare AEs and do not have extended followup 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 epidemiological 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, sex, 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, as 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 (VAERS)[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.

## Conclusion

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 (diphtheria, tetanus, and pertussis), Td (tetanus-diphtheria), Hib (*Haemophilus influenzae* type B), 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 very low. For example, strength of evidence is moderate for association of vaccines against rotavirus with intussusception. Although one large US epidemiological study found no association, a recent analysis of the US Post-Licensure Rapid Immunization Safety Monitoring (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 Vaccine Safety Datalink (VSD) contains data from such systems at nine very large managed care organizations (MCOs). In addition, the PRISM program also conducts active surveillance using electronic health care databases from MCOs. Nations with single-payer health care systems often have electronic registries that allow very large epidemiological studies of entire populations. Future analyses should be stratified by formulation and brand of vaccine whenever possible.

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## References

Table 1. Results: Safety of vaccines used for routine immunization of children

| Vaccine | EPC Conclusions and Strength of Evidence | Institute of Medicine (IOM) Findings | New findings |
|---|---|---|---|
| **Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis-Vaccine (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 post licensure study of over 1.8 million vaccine recipients, purpura was associated with vaccination against hepatitis A in children aged 7 to 17 years. 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** | I**nsufficien**t: Food allergy<br>**Moderate:** No association with MS | Although no epidemiological studies were identified by the IOM, mechanistic evidence "**favored acceptance"** of a causal relationship between the vaccine and anaphylaxis in yeast-sensitive individuals.<br><br>A 2002 IOM report **"favors rejection"** of a causal relationship with MS onset or exacerbation. | Hep B vaccine in the first 6 months of life was associated with elevated total IgE in a post licensure study of children with a family history of food allergy, but not with clinical allergy. |
| **Hib Vaccine** | **Moderate:** No association with serious AEs in short term | Not covered. | No serious AEs were associated in 3 high-quality clinical trials. |
| **Inactivated Polio Vaccine** | **Insufficient:** Food allergy | Not covered. | One post-licensure 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<br><br>**Low:** Influenza-like symptoms | Evidence was **"inadequate to accept or reject"** a causal relationship with any AEs investigated. | We identified one trial of seasonal influenza vaccine (including a strain of H1N1) and one 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.<br><br>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 |

| Vaccine | EPC Conclusions and Strength of Evidence | Institute of Medicine (IOM) Findings | New findings |
|---|---|---|---|
| | | | children in the short term in two large post licensure studies. One of these studies found that younger vaccinated children (aged 5 to 8 years) were more likely to experience these symptoms than older vaccinated children (aged 9 to 17 years). (Children under 5 years of age were not included in that study).<br><br>Both live and inactivated seasonal influenza vaccines were associated with influenza-like symptoms in children in the short term in one new study.<br><br>A large U.S. post licensure study of children under age 5 years found TIV associated with febrile seizures. Risk was increased if PCV13 was administered concomitantly. |
| **MMR Vaccine** | **High:** No association with autism spectrum disorders<br><br>**High:** Anaphylaxis in children with allergies, febrile seizures<br><br>**Moderate:** Transient arthralgia<br><br>**Moderate:** Thrombocytopenic purpura | Evidence **"convincingly supports"** causal relationships anaphylaxis in allergic children and febrile seizures.<br><br>Evidence **"favors acceptance"** of a causal relationship between MMR and transient arthralgia<br><br>Evidence **"favors rejection"** of a causal relationship between MMR and autism. | Five new post marketing studies were identified. Vaccination was associated with thrombocytopenic purpura in the short term in the three; it was not studied in the other two. In one study, MMR vaccination was associated with increased emergency department visits within 2 weeks; this is indirect support of the IOM's findings that MMR vaccine is associated with febrile seizures.<br>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. |
| **Pneumococcal Conjugate Vaccine (PCV13)** | **Moderate:** Febrile seizures | Not covered. | The U.S. Vaccine Safety Datalink (VSD) found an association with febrile seizures. Estimated rate for 16-month-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** | **Moderate:** | Not covered. | In 31 clinical trials, there was |

| Vaccine | EPC Conclusions and Strength of Evidence | Institute of Medicine (IOM) Findings | New findings |
|---|---|---|---|
| **Vaccines: RotaTeq and Rotarix** | Intussusception | | no association between either of the current vaccines (RotaTeq and Rotarix) and any serious AEs, including intussusception, in the long or short term.<br><br>A high-quality Australian epidemiological study found RotaTeq associated with intussusception 1 to 21 days following the first of 3 required doses in infants 1 to 3 months of age. Two case-control studies conducted in Latin America found an association of Rotarix with intussusception in children following the first of 2 required doses. Although one U.S. epidemiological study found no association, a recent analysis of the U.S. Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program found both RotaTeq and Rotarix associated with intussusception in the short term. Estimated rate was 1.1 to 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.<br><br>**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 post licensure study of over 1.8 million vaccine recipients, purpura was associated with vaccination against varicella in children aged 11 to 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, Hep B, and polio vaccines | Not applicable. | Four large epidemiological studies conducted analyses to assess which, if any, of the following vaccines might be associated with childhood |

| Vaccine | EPC Conclusions and Strength of Evidence | Institute of Medicine (IOM) Findings | New findings |
|---|---|---|---|
| | | | leukemia: MMR, DTaP, Td, Hib, Hep B, and polio vaccine. No association was found for any vaccine. |

**Note:** AE = adverse event; CI = confidence interval; DTaP = diphtheria, tetanus, and pertussis vaccine; EPC = Evidence-based Practice Center; Hep B = hepatitis B; Hib = *Haemophilus influenzae* type B; HPV = human papillomavirus; IgE = immunoglobulin E; IOM = Institute of Medicine; MMR = measles, mumps, rubella vaccine; MS = multiple sclerosis; TIV = trivalent influenza vaccine; IPV = inactivated polio vaccine; MCV = meningococcal conjugate vaccine; MPSV = meningococcal polysaccharide vaccine; PCV = pneumococcal conjugate vaccine; RR = relative risk; VZV = varicella-zoster virus