

Draft Comparative Effectiveness Review

Number xx

Safety of Vaccines Used for Routine Immunization of Adults (Including Pregnant Women) and Children

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The **Office of the Assistant Secretary of Health, National Vaccine Program** requested and provided funding for this report.

The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

We welcome comments on this evidence report. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to epc@ahrq.hhs.gov.

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Safety of Vaccines Used for Routine Immunization of Adults (Including Pregnant Women) and Children

Structured Abstract

Objectives:

To conduct a systematic review of the literature on the safety of vaccines currently recommended for routine immunization of children, adolescents, and adults in the United States.

Data Sources:

We included placebo-controlled clinical trials and cohort studies comparing vaccinated and unvaccinated patients. We also included the following types of post-licensure studies: case-control studies, self-controlled case series, and multivariate risk factor analyses. We conducted an electronic search of PubMed® from inception through October 2012, and reviewed ACIP statements, vaccine package inserts, and previously published reviews to identify studies. Scientific Information Packets (SIPs) were requested from vaccine manufacturers by an AHRQ-funded Scientific Resource Center (SRC).

Review Methods:

In addition to data pertaining to the presence or absence of adverse health outcomes, we identified and abstracted characteristics of patients, study design, and vaccine description, including type, dosage, timing, and formulation, where available. We excluded studies of vaccines not on the current US recommended schedules, such as formulations never available in the US or no longer used. We used the McHarm instrument to evaluate the quality of included studies. We were unable to pool results; we rated the overall strength of evidence (SOE) as High, Moderate, Low, or Insufficient by using guidance suggested by AHRQ for its Effective Health Care Program. We used the findings of the 2011 Institute of Medicine (IOM) consensus report *Adverse Effects of Vaccines: Evidence and Causality* as a base and augmented with a search update until October 2012, and additional vaccines.

Results:

A total of 19,597 titles were identified; after title, abstract, and full text review, 145 studies were accepted for abstraction. The vast majority of studies either did not investigate or could not identify risk factors for adverse events (AEs) associated with vaccination. Similarly, the severity of AEs was inconsistently reported, as was information that would make independent severity determination possible.

Strength of evidence was high for the following associations in (non-pregnant) adults: influenza vaccine and arthralgia, myalgia, malaise, fever, pain at injection site, anaphylaxis, and Guillain-Barré Syndrome (GBS); Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis Vaccines and anaphylaxis; and a lack of association between influenza and pneumococcal vaccines and cardiovascular events in the elderly. Strength of evidence was high for the following associations in children and adolescents: Measles/Mumps/Rubella Vaccine and anaphylaxis, febrile seizures, and measles inclusion body encephalitis and a lack of association between Measles/Mumps/Rubella Vaccine and autism spectrum disorders; Varicella vaccine and

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, and vaccine strain viral reactivation with subsequent infection resulting in meningitis or encephalitis. Moderate strength evidence exists regarding Human Papilloma Virus Vaccine and a lack of association with onset of juvenile rheumatoid arthritis, type 1 diabetes, and GBS. Only studies of influenza vaccine exposure were found for pregnant women: moderate strength evidence shows no association with serious adverse events.

Conclusions:

In general, the findings of this review support those of earlier reviews. Evidence is insufficient to make conclusions regarding whether several routinely recommended vaccines are associated with serious conditions such as Multiple Sclerosis (MS), transverse myelitis, and Acute Disseminated Encephalomyelitis (ADEM). To assess associations between vaccines and adverse events of interest, studies are needed that can utilize large medical databases that enable linkage of vaccination history and health outcomes. Studies must be powered to assess patient risk factors potentially associated with adverse events.

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Executive Summary

Background

Vaccines are considered one of the greatest public health achievements of the last 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, substantial gaps in vaccine uptake persist. Vaccination rates for young children are high;² however, vaccination rates remain well below established Healthy People 2020 targets for many vaccines recommended for adolescents,³ adults,⁴ and pregnant women.⁵

In the United States (US), vaccine guidelines are set by the Centers for Disease Control and Prevention (CDC)' Advisory Committee for Immunization Practices (ACIP). The number of routine immunizations recommended for children and adolescents (Table A), adults (Table B), and pregnant women (Table C) has expanded considerably over the past 10 years. For example, since 2005, the routine adolescent vaccination schedule has grown to include the following vaccines at ages 11 or 12 years: meningococcal conjugate vaccine; tetanus, diphtheria, and acellular pertussis (Tdap); Human Papilloma Virus (HPV); and influenza (one dose annually). Pregnant women are now advised to receive Tdap during every pregnancy to protect their newborns from pertussis, regardless of prior Tdap vaccination history.⁶

Table A. Vaccines routinely recommended for children and adolescents

Vaccine	Age
DTaP (diphtheria, tetanus, and acellular pertussis)	2 months – 6 years
Hepatitis A	12 months and older
Hepatitis B	Birth and older
Hib (<i>Haemophilus influenzae</i> type b)	6 weeks – 59 months
HPV (human papillomavirus)	9 years – 26 years
Influenza (inactivated)	6 months and older
Influenza (live attenuated)	2 years and older
IPV (inactivated polio vaccine)	6 weeks and older
MCV (meningococcal conjugate vaccine)	2 years and older
MMR (measles, mumps, and rubella)	12 months and older
MPSV (meningococcal polysaccharide vaccine)	2 years and older, in specific circumstances
PCV13 (pneumococcal conjugate vaccine)	6 weeks – 18 years
Pneumococcal polysaccharide vaccine	2 years and older, in specific circumstances
Rotavirus	6 weeks – 8 months
Tdap (tetanus, diphtheria, and acellular pertussis)	7 years and older
Varicella	12 months and older

Table B. Vaccines routinely recommended for non-pregnant adults

Vaccine	Recommendation
Hepatitis A	All adults at increased risk of hepatitis A infection
Hepatitis B	All unvaccinated adults at risk for or requesting protection from Hepatitis B infection
HPV (human papillomavirus)	Adults 26 years and younger
Influenza (inactivated)	All adults
Influenza (live attenuated)	All adults 49 years and younger
Meningococcal conjugate vaccine (MCV4) and meningococcal polysaccharide vaccine (MPSV)	Adults at risk of meningococcal disease (MCV4 or MPS5 if younger than 55 years;

Vaccine	Recommendation
	MPS5 if older than 55 years)
MMR (measles, mumps, and rubella)	All adults
Pneumococcal polysaccharide vaccine	Adults 64 years and younger with certain conditions, and all adults 65 years and older
Td (tetanus, diphtheria)	All adults
Tdap (tetanus, diphtheria, and acellular pertussis)	All adults 19–64 years old; some adults 65 years and older
Varicella	All adults without evidence of varicella immunity
Zoster	All adults 60 years and older

Table C. Vaccines routinely recommended for pregnant women

Vaccine	Recommendation
Hepatitis B	Recommended in some circumstances
Influenza (inactivated)	All pregnant women
Td (tetanus, diphtheria)	Should be used if indicated
Tdap (tetanus, diphtheria, and acellular pertussis)	All pregnant women during each pregnancy, regardless of prior history of receiving Tdap

As the number of recommended immunizations has expanded across the population, so too have concerns about the safety of vaccines. Perhaps the most highly publicized safety concern of the last two decades has been the proposed link between autism and the Measles, Mumps, Rubella (MMR) vaccine, first reported in 1998 in *The Lancet* by Dr. Andrew Wakefield.⁷ In 2010, *The Lancet* fully retracted the 1998 report,⁸ noting that elements of the research had been deliberately falsified. Although multiple large studies have confirmed the lack of association between MMR and autism, parental worries about the safety of the vaccine persist. Other parental concerns about childhood vaccines include potential links to multiple sclerosis, sudden infant death syndrome, asthma, and diabetes.⁹ Thus, vaccine safety is high on the nation’s public health agenda.

Objectives

The Agency for Healthcare Research and Quality (AHRQ) requested an evidence report on the safety of vaccines used for routine immunization of adults (including pregnant women), children, and adolescents, based on a comprehensive and systematic review of the scientific literature. This report, which represents the results of that review, describes potential associations between vaccines and adverse events (AEs) and will be used by the Office of the Assistant Secretary of Health (OASH) to identify the gaps in evidence. The report was guided by the following key questions.

KQ 1 What is the evidence that vaccines included in the 2011 immunization schedule recommended for U.S. **adults**¹⁰ are safe in the short term (within 30–42 days following immunization) or long term (>42 days after immunization)?

- a. What adverse events (AEs) are collected in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?

- b. What AEs are reported in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?
- c. What AEs are associated with these vaccines?
 - 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 - 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 - 3. For each AE associated with a particular vaccine, what are the risk factors for the AE (including age, sex, race/ethnicity, genotype, underlying medical condition, whether a vaccine is administered individually or in a combination vaccine product, schedule of vaccine administration, adjuvants, and medications administered concomitantly)?

KQ 2 What is the evidence that vaccines included in the immunization schedules recommended for U.S. **children and adolescents** in 2011¹¹ are safe in the short term (within 30–42 days following immunization) or long term (>42 days after immunization)?

- a. What AEs are collected in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?
- b. What AEs are reported in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?
- c. What AEs are associated with these vaccines?
 - 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 - 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 - 3. For each AE associated with a particular vaccine, what are the risk factors for the AE (including age, sex, race/ethnicity, genotype, underlying medical condition, whether a vaccine is administered individually or in a combination vaccine product, schedule of vaccine administration, adjuvants, and medications administered concomitantly)?

KQ 3 What is the evidence that vaccines recommended for **pregnant women**¹² are safe both for the woman and for her fetus/infant?

- a. What AEs are collected in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?

- b. What AEs are reported in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?
- c. What AEs are associated with these vaccines in women?
 - 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 - 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 - 3. For each AE associated with a particular vaccine, what are the risk factors for the AE (including age, sex, race/ethnicity, genotype, underlying medical condition, whether the vaccine is administered individually or in a combination vaccine product, the schedule of vaccine administration, adjuvants, and medications administered concomitantly)?
- d. What AEs are associated with these vaccines in the fetus/infant?
 - 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 - 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 - 3. For each AE associated with a particular vaccine, what are risk factors for the AE (including age, gender, race/ethnicity, genotype, underlying medical condition, whether vaccine administered individually or in a combination vaccine product, vaccine schedule of administration, adjuvants, medications administered concomitantly)?

Methods

In 2011, the Institute of Medicine (IOM) published a consensus report entitled *Adverse Effects of Vaccines: Evidence and Causality*.¹³ That report evaluated the scientific evidence for event-vaccine relationships and covered many vaccines included in currently recommended immunization schedules (varicella, influenza, hepatitis A, Hepatitis B, HPV, MMR, meningococcal, tetanus, diphtheria, and pertussis). Our work builds upon the IOM report in a number of important ways. Using the existing IOM findings as a springboard, we updated their literature searches with more recent studies on the vaccines included in that report. We also conducted original searches for the vaccines recommended for adults, children, and pregnant women that were not included in the IOM report: pneumococcal, rotavirus, Haemophilus influenzae type b, inactivated poliovirus, and zoster vaccines.

After reviewing the IOM report, we searched electronic databases for additional relevant studies; complete search terms are provided in Appendix A. We searched through October, 2012. We also reviewed ACIP statements and Scientific Information Packets (SIPs) requested from vaccine manufacturers by an AHRQ-funded Scientific Resource Center (SRC). Finally we scanned review articles for additional references.

The following study designs were included in this review:

- Controlled clinical trial - A study where human subjects are assigned prospectively, usually through randomization, to receive an intervention (in this case a vaccine) or an alternate intervention (another vaccine) or placebo. Clinical trials are used to determine safety and efficacy.
- Cohort comparing two or more groups - Follows over time a group of similar individuals (for example, all children born in Denmark in 2001) who differ with respect to whether they received a vaccine, to determine how/whether the vaccination affects rates of one or more AEs.
- Case-control study - A study that compares persons who have a disease or adverse event (AE) (cases) with persons who do not have the disease or AE, and looks back retrospectively to compare exposure to vaccine in each group to determine the relationship between the vaccine and the disease / AE.
- Self-controlled case series (SCCS) – Only cases (individuals who experienced the AEs) are included in the analysis. With SCCS, each individual serves as his own control. The analysis inherently controls for time and other covariates that remain stable within a person during the study period. In other words, SCCS compares outcome event rates during times when a person is exposed with those during times when the same person is unexposed to calculate the relative incidence of AEs.
- Multivariate risk factor analyses – We included case series and cohort studies that used logistic regression to control for confounders and test multiple relationships simultaneously.

Studies using passive surveillance such as the US Vaccine Adverse Event Reporting System (VAERS),¹⁴ are crucial in identifying signals regarding AEs post-licensure. However, because by definition they do not consider the rate of such events in non-vaccinated populations, they are not designed to assess a statistical association between a vaccine and an adverse event, so they were excluded from this project. We also excluded studies of vaccines not on the current U.S. recommended schedules. These vaccines include brands/ and formulations never available in the U.S. and formulations no longer used. Examples include whole cell pertussis vaccine, oral polio vaccine, and PCV7 pneumococcal vaccine.

Two researchers independently reviewed the titles and abstracts identified. The union of their selections was retrieved. Two researchers also independently reviewed the full text of study reports and met to reach consensus regarding exclusion/inclusion. Disputes were settled by the principal investigators and team physician experts. Patient and study characteristics were abstracted by single researchers and confirmed by the principal investigator. The McHarm instrument¹⁵ was used to evaluate the quality of the included studies. The scores are presented in the body of the report and were taken into consideration in rating the strength of the evidence.

Studies that reported timing and severity, and defined AEs using standard, precise definitions were rated higher than those that did not. Epidemiological studies that used medical records to ascertain vaccination and health outcomes were rated higher than those that relied on patient or parent report.

We assess the overall strength of evidence by using guidance suggested by AHRQ for its Effective Health Care Program.¹⁶ This method is based on one developed by the GRADE Working Group¹⁷ and classifies the evidence according to the following criteria:

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.

The evidence grade is based on four primary (required) domains and four optional domains. The required domains are risk of bias, consistency, directness, and precision, as described in the full-text version of the Methods section of this report. The additional domains are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias.

Results

As presented in Figure A, a total of 19,597 titles were identified through electronic literature searches; review of product inserts; review of FDA, ACIP, and other web sites; reference mining; and requests for Scientific Information Packets (SIPs) from drug manufacturers. Of those, 16,536 were excluded upon review of abstract (where available) or title, mostly due to lack of data on safety of vaccines. Other reasons for exclusion included use of vaccines not within the scope of this project (i.e. not routinely recommended in the US, recommended only for travel, no longer used in the US), publication in languages other than English, and study not conducted on humans. Five articles could not be obtained.

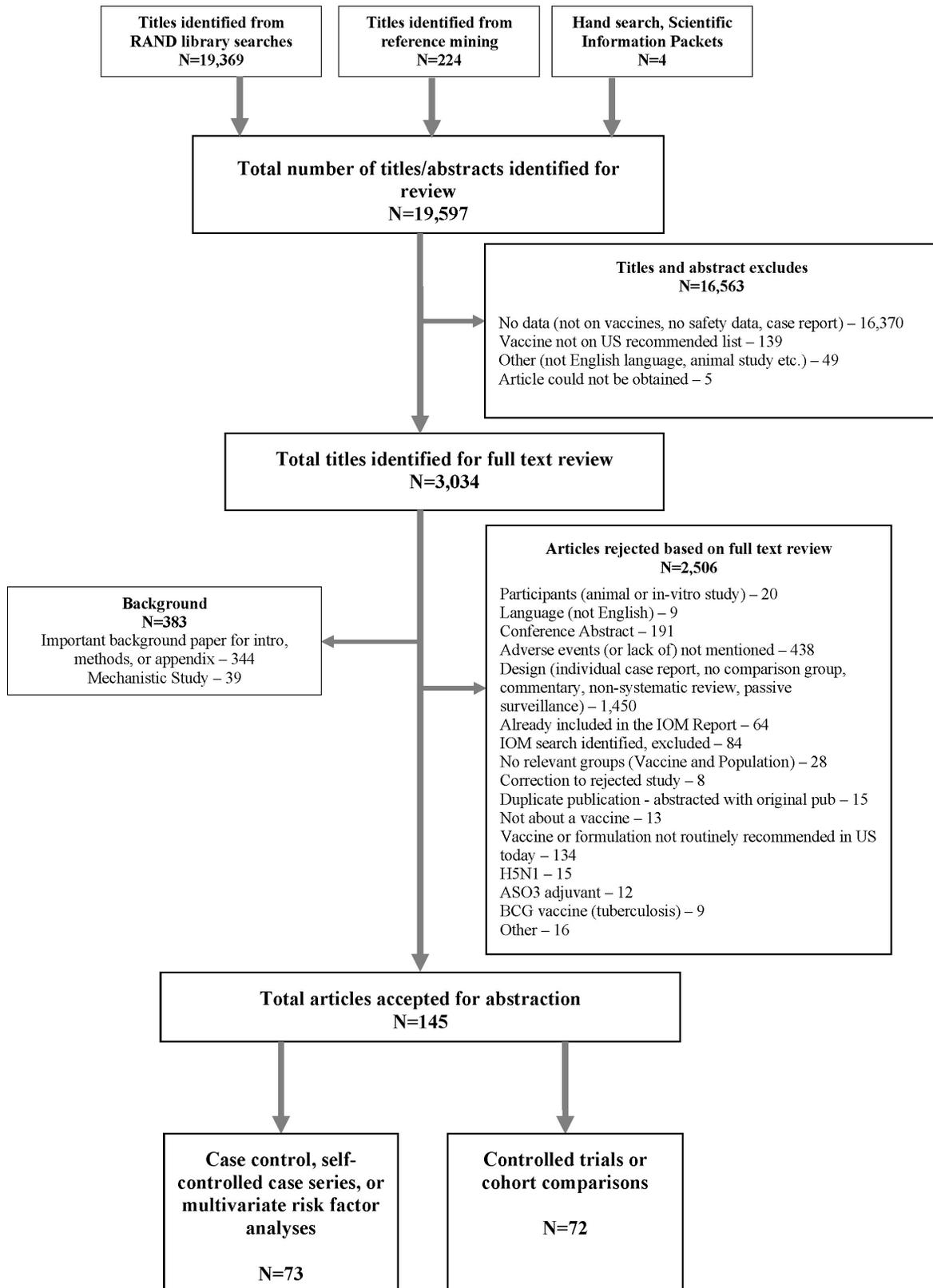
Based on title/abstract screenings, 3,034 articles were selected for full text review. Of those, 383 were identified as relevant background/theoretical materials and set aside as potential references. A total of 2,506 other articles were excluded. The most common reason for exclusion was lack of suitable study design (1,450): Individual case reports, non-systematic reviews, and studies using passive surveillance (for example, reports from VAERS) were not included. Many publications (438) discussed vaccines on the recommended schedule, but did not report AEs (or a lack thereof).

Studies using formulations not currently or routinely recommended in the US were excluded at full text review. For example, we identified 15 studies of H5N1 vaccine, twelve studies using the adjuvant ASO3, and nine studies of BCG vaccine. We excluded 134 additional studies that used vaccines beyond the scope of the project; for example, vaccines no longer used in the US

(i.e. oral polio vaccine), removed from the market due to safety concerns (i.e. RotaShield®), or in dosages never approved in the US. Determining whether a dosage or formulation was the one approved for clinical use was often difficult; the process involved comparing the dosage listed on product materials and in FDA filings with that reported in the study.

Based on full text screening, 145 studies were accepted for abstraction, including 72 controlled trials or cohort studies directly comparing a group who received a vaccine with an unvaccinated group. We also identified 73 case-control studies, self-controlled case series, or multivariate risk factor analyses that met our inclusion criteria. These studies are in addition to the studies included in the 2011 IOM consensus report *Adverse Effects of Vaccines: Evidence and Causality*.

Figure A. Study/Literature flow diagram



A summary of our results for each key population is displayed in Table D. The table displays the strength of evidence (SOE) regarding the positive statistical association of each vaccine type with key AE. The term “null” next to the SOE indicates evidence that a) the vaccine has no statistical association with the AE or b) the vaccine is associated with a protective effect against the AE.

Importantly, the vast majority of studies did not report potential risk factors for the AEs that were found to be associated with vaccination. Similarly, the severity of AEs was inconsistently reported, as was information that would make independent severity determination possible. We identified only one study that assessed vaccination schedule;¹⁸ it found that increasing exposure to antibody-stimulating proteins and polysaccharides in vaccines was not associated with autism. The recent IOM report, *The Childhood Immunization Schedule and Safety: Stakeholder Concerns, Scientific Evidence, and Future Studies*¹⁹ makes recommendations for future research on childhood vaccine schedules and cumulative effect.

Table D. Summary: Safety of Vaccines Used for Routine Immunization of Adults (Including Pregnant Women) and Children

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
Adults			
Influenza Vaccines	<p>High – arthralgia, myalgia, malaise, fever, pain at injection site, anaphylaxis</p> <p>High (null) - cardiovascular or cerebrovascular events in the elderly</p> <p>High – H1N1 with Guillain-Barré Syndrome (GBS)</p> <p>Moderate (null) - Serious Adverse Events in renal patients</p> <p>Insufficient - Multiple Sclerosis (MS)</p>	<p>Studied two forms of influenza vaccines: live attenuated form, administered intranasally (LAIV), and inactivated form (TIV), administered intramuscularly.</p> <p>Evidence “convincingly supports” a causal relationship between influenza vaccines and anaphylaxis</p>	<p>Many clinical trials reported that influenza vaccines are associated with arthralgia, myalgia, malaise, fever, and pain in the short-term in adults. These adverse events (AEs) were not considered serious; severity was graded mild to moderate. Odds of experiencing these events were 1.5 to 2 times higher in vaccinated patients than in unvaccinated. Risk factors were not discussed in the trials.</p> <p>Post-licensure studies report mixed results regarding association of seasonal influenza vaccines, including those containing H1N1 strains, with Guillain-Barré Syndrome (GBS) in adults. A high quality meta-analysis published as this report was finalized found an association with monovalent H1N1 vaccine in the 42 days post vaccination;²⁰ results translate to about 1.6 excess cases per million vaccinated.</p> <p>Post-licensure studies have found inconsistent evidence associating influenza vaccines with onset or exacerbation of MS in adults.</p> <p>Post-licensure studies have found influenza vaccines are NOT associated with increased risk of cardiovascular or cerebrovascular events in the elderly.</p> <p>Post-licensure studies have shown that influenza vaccines are NOT associated with increased risk of serious AEs (SAEs) in renal patients.</p>
Pneumococcal Polysaccharide Vaccine	High (null) - cardiovascular or cerebrovascular events in the elderly	Not covered	<p>We found no placebo-controlled trials of the current US version. (We did find studies of the current version vs older versions, but these did not include a placebo group).</p> <p>Post-licensure studies of pneumococcal polysaccharide vaccine found vaccination was NOT</p>

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
			associated with increased risk of cardiovascular events in older adults.
Zoster Vaccine	<p>Moderate – injection site reactions, cellulitis, allergic reactions</p> <p>Insufficient – Serious Adverse Events</p>	Recommended for US adults over age 60; AEs specific to this population were not covered.	<p>In clinical trials, adverse events were often reported only in broad categories such as “injection–related adverse events,” “systematic adverse events,” or “serious adverse events” rather than specifying type or severity. This made assessing specific serious adverse events impossible.</p> <p>Vaccination was associated with injection site reactions in clinical trials.</p> <p>In post-licensure studies, vaccination was associated with cellulitis and allergic reactions, such as redness and swelling; 1 to 7 days post vaccination. These mild AEs occurred in less than 1% of patients, and were more likely in the younger (aged 50-59) vaccines.²¹</p>
Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis Vaccines	High - anaphylaxis	Evidence “convincingly supports” a causal relationship in the adult population between the tetanus toxoid vaccine and anaphylaxis.	We identified one additional trial of adults. No association with AEs was reported. We identified no additional post-licensure studies of vaccines against diphtheria, tetanus, or pertussis in adults.
MMR Vaccine	<p>Moderate (null) – Type 1 diabetes</p> <p>Low - transient arthralgia in women</p>	<p>Evidence “favors acceptance” of a causal relationship with transient arthralgia in women.</p> <p>Evidence is “inadequate to accept or reject” a causal relationship with MS onset, Guillain-Barré Syndrome, chronic arthralgia in women, and chronic arthritis and arthropathy in men.</p>	MMR was NOT associated with onset of type 1 diabetes in adults in a very large recent high quality epidemiological study. ²² RR=0.71 (95% CI 0.61, 0.83)
Hepatitis A Vaccine	Insufficient - Serious Adverse Events	Evidence “neither convincingly supports convincingly supports nor favors acceptance favors acceptance” of any causal relationships with AEs the committee was tasked with investigating: acute disseminated encephalomyelitis, transverse myelitis, MS, Guillain-Barre Syndrome, chronic inflammatory disseminated polyneuropathy, Bells’ Palsy, anaphylaxis, and autoimmune hepatitis.	We identified one additional post-licensure study; there was no evidence regarding association of this vaccine with any adverse events or onset of medical conditions.

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
Hepatitis B Vaccine	Insufficient Serious Adverse Events	<p>Although no epidemiological studies were identified on anaphylaxis, mechanistic evidence “favours acceptance” of a causal relationship between the vaccine and anaphylaxis in yeast-sensitive individuals.</p> <p>Epidemiological studies of the following AEs in adults had evidence “inadequate to accept or reject” a causal relationship: optic neuritis, MS onset or relapse, first demyelinating event, Guillain-Barré Syndrome, SLE, onset or exacerbation of vasculitis, polyarteritis nodosa, and onset or exacerbation of rheumatoid arthritis. No epidemiological studies of the following AEs in adults were found, evidence is also “inadequate to accept or reject” a causal relationship: encephalitis, encephalopathy, acute disseminated encephalomyelitis ADEM, transverse myelitis, neuromyelitis optica, chronic inflammatory disseminated polyneuropathy, brachial neuritis, erythema nodosum, onset or exacerbation of psoriatic arthritis, onset or exacerbation of reactive arthritis, and fibromyalgia.</p>	We found no additional studies that met our inclusion criteria.
Children and Adolescents			
Influenza Vaccines	<p>Moderate - mild gastrointestinal disorders</p> <p>Low (null) – Serious Adverse Events in the short term in children with cancer or who have received organ transplants</p> <p>Low - influenza-like symptoms</p> <p>Insufficient – asthma exacerbation, seizures, ADEM, transverse myelitis</p>	<p>The IOM committee studied seasonal influenza vaccines. The influenza vaccine is administered in two forms: a live attenuated form, administered intranasally, and an inactivated form, administered intramuscularly.</p> <p>Evidence was “inadequate to accept or reject” a causal relationship in the pediatric population between seasonal influenza vaccines and the following: seizures, (ADEM), and transverse myelitis.</p> <p>Evidence was “inadequate to accept or reject” a causal relationship between live attenuated influenza vaccine (LAIV) and asthma exacerbation or reactive airway disease (RAD) episodes.</p>	<p>Seasonal influenza vaccines were NOT associated with any serious adverse events in the short term in immunocompromised children (one study each of children with malignancy and children who had received organ transplants).</p> <p>Both seasonal influenza vaccines and H1N1 vaccines were associated with mild gastrointestinal disorders, such as vomiting and diarrhea in children in the short-term in several large post-licensure studies. One large study²³ 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).</p> <p>Both live and inactivated seasonal influenza vaccines were associated with influenza-like symptoms in children in the short term in multiple studies, while not associated in others.</p>

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
Hib	Low (null) – serious adverse events	Not covered	No serious adverse events associated in two clinical trials.
Measles-Mumps-Rubella	<p>High (null) – Autism Spectrum Disorders</p> <p>High - anaphylaxis in children who may be allergic to ingredients, febrile seizures, measles inclusion body encephalitis</p> <p>Moderate – Transient arthralgia</p> <p>Low - thrombocytopenic purpura</p>	<p>Evidence “convincingly supports” causal relationships with measles inclusion body encephalitis, febrile seizures, and anaphylaxis.</p> <p>Evidence “favours acceptance” of a causal relationship between MMR and transient arthralgia</p> <p>Evidence “favours rejection” of a causal relationship between MMR and autism.</p> <p>Evidence is “inadequate to accept or reject” a causal relationship with encephalitis, encephalopathy, afebrile seizures, meningitis, cerebellar ataxia, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, neuromyelitis optica, MS onset, and chronic arthropathy.</p>	Four additional post-marketing studies were identified. Vaccination was associated with thrombocytopenic purpura in the short term. ²⁴⁻²⁶ MMR vaccination was associated with increased emergency department visits within two weeks; ²⁷ this is consistent with the IOM’s findings that MMR vaccine is associated with febrile seizures.
Rotavirus Vaccines: RotaTeq and Rotarix	<p>Moderate – mild adverse events (e.g. cough, runny nose, irritability)</p> <p>Low – intussusception for RotaTeq, Rotarix</p>	Not covered.	<p>In clinical trials, both RotaTeq and Rotarix were associated with cough, runny nose and irritability in children in the short-term. In clinical trials, there was no association between either of the two currently available vaccines (RotaTeq and Rotarix) and any serious adverse events, including intussusception, in the long or short-term.</p> <p>A high quality epidemiological study in Australia found RotaTeq was associated with intussusception 1 to 21 days following the first of three required doses in infants 1 to 3 months of age. However, a post-licensure study in the US²⁸ found no association. Two case-control studies^{29, 30} conducted in Latin America found an association of Rotarix with intussusception in children following the first of three required doses. One of these studies estimated a risk of 3.7 (95% CI 1.2, 7.3) additional cases per 100,000 person/year in Mexico. The other estimated a risk of about 1 per</p>

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
			51,000 vaccines in Mexico and 1 per 68,000 vaccines in Brazil.
Hepatitis B Vaccine	Insufficient – Serious adverse events Insufficient – food allergy	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 IOM found insufficient evidence to accept or reject a causal relationship with any other AEs.	Hepatitis 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.
HPV Vaccine	Moderate – (null) juvenile rheumatoid arthritis, Type 1 diabetes, appendicitis, Guillain Barré Syndrome, seizures, stroke, syncope, venous thromboembolism Moderate – anaphylaxis Insufficient - ADEM, transverse myelitis, neuromyelitis optica, MS, onset of Hashimoto’s disease, chronic inflammatory disseminated polyneuropathy, brachial neuritis, amyotrophic lateral sclerosis, transient arthralgia, pancreatitis, thromboembolic events, and hypercoagulable states	Evidence “ favours acceptance ” of a causal relationship between the HPV vaccine and anaphylaxis. Evidence is “ inadequate to accept or reject ” causal relationships between HPV vaccines and the following: ADEM, transverse myelitis, neuromyelitis optica, MS, Guillain-Barré syndrome, chronic inflammatory disseminated polyneuropathy, brachial neuritis, amyotrophic lateral sclerosis, transient arthralgia, pancreatitis, thromboembolic events, and hypercoagulable states.	A large post-licensure study found HPV vaccine was NOT associated with onset of juvenile rheumatoid arthritis or Type 1 diabetes. ³¹ This study reported an IRR of 1.29 (95% CI 1.08, 1.56) of onset of Hashimoto’s disease. However, investigation of a temporal relationship and biological plausibility revealed no consistent evidence of a safety signal. A large post-licensure study found HPV vaccine was NOT associated with Guillain Barré Syndrome, seizures, stroke, syncope, or venous thromboembolism. ³²

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
Varicella Vaccine	<p>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</p> <p>Insufficient – seizures, ADEM, transverse myelitis, Guillain-Barré syndrome, small fiber neuropathy, onset or exacerbation of arthropathy, thrombocytopenia.</p>	<p>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.</p> <p>The evidence is “inadequate to accept or reject” a causal relationship between the vaccine and seizures, ADEM, transverse myelitis, Guillain-Barré syndrome, small fiber neuropathy, onset or exacerbation of arthropathy, and thrombocytopenia.</p>	We found no additional studies that met our inclusion criteria.
Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis-	<p>Moderate (null) – type 1 diabetes</p> <p>Insufficient - infantile spasms, seizures, cerebellar</p>	<p>Evidence “favours rejection” of a causal relationship between vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens and type 1 diabetes.</p> <p>Evidence is “inadequate to accept or reject” causal relationships between vaccination and the following: infantile</p>	We found no additional studies that met our inclusion criteria.

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
Containing Vaccines	ataxia, autism, ADEM, transverse myelitis, MS relapse, serum sickness, immune thrombocytopenic purpura, and SIDS.	spasms, seizures, cerebellar ataxia, autism, ADEM, transverse myelitis, MS relapse in children, serum sickness, immune thrombocytopenic purpura, and SIDS.	
Meningococcal Vaccines	Moderate – anaphylaxis Insufficient - encephalitis, encephalopathy, ADEM, transverse myelitis, MS, Guillain-Barre syndrome, CIDP, chronic headache.	Evidence “ convincingly supports ” a causal relationship with anaphylaxis in children who may be allergic to ingredients. Evidence is “ inadequate to accept or reject ” causal relationships between meningococcal vaccine and the following: encephalitis, encephalopathy, ADEM, transverse myelitis, MS, Guillain-Barre syndrome, CIDP, and chronic headache.	We found no additional studies that met our inclusion criteria.
Inactivated polio vaccine	Insufficient – food allergy	Not covered	One post-licensure study reported association between polio vaccine in newborns and sensitivity to food allergens.
Studies of combination vaccines or multiple vaccines	Moderate - DTaP-IPV-Hib vaccination with febrile seizures High – (null) association of childhood leukemia with MMR, DTaP, Td, Hib, Hep B, and polio vaccines Moderate – Hepatitis A, MMR, and varicella vaccine with purpura	Not covered	Association of DTaP-IPV-Hib vaccination with febrile seizures in children was found in a very large, high quality post-licensure study. ³³ Rate for first dose was estimated as 5.5 cases per 100,000 person/days. Rate for second dose was estimated as 5.7 cases per 100,000 person/days. Multiple large epidemiological studies ³⁴⁻³⁷ have assessed MMR, DTaP, Td, Hib, Hep B, and polio vaccine and have found no association with childhood leukemia. In a large post-licensure study of over 1.8 million vaccines, ²⁵ purpura were associated with vaccination against Hepatitis A in children aged 7 to 17 years, vaccination against varicella in children aged 11 to 17, and MMR in children from 12 to 19 months of age. These results were based on one or two cases per

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
			vaccine type/age group. According to the authors most cases were mild and acute.
Pregnant Women			
Influenza Vaccines	Moderate (Null) – Serious adverse events	Results not specific to pregnant women	In comparison studies, H1N1 vaccine and seasonal influenza vaccine (inactivated) were not associated with serious adverse events in pregnant women or their offspring. No other vaccines were studied in pregnant women.

IOM = Institute of Medicine; GBS = Guillain-Barré Syndrome; TIV = Trivalent Influenza Vaccine; LAIV = Live Attenuated Influenza Vaccine; MMR = Measles, Mumps, Rubella Vaccine; MS = Multiple Sclerosis; SLE = Systemic Lupus Erythematosus; AEs – Adverse Events; ADEM = Acute Disseminated Encephalomyelitis; RAD = Reactive Airway Disease; HPV = Human Papillomavirus; VZV = Varicella-Zoster Virus; SIDS = Sudden Infant Death Syndrome; CIDP = Chronic Inflammatory Demyelinating Polyneuropathy; DTaP = Diphtheria, Tetanus, and Pertussis Vaccine; Td = Tetanus-Diphtheria; Hib = Haemophilus Influenzae Type B; Hep B = Hepatitis B

Discussion

At the request of AHRQ and OASH we assessed the evidence on the safety of vaccines recommended for routine use among adults, children, and pregnant women in the US. We conducted an extensive literature search for clinical trials and observational studies meeting our inclusion criteria: cohort studies comparing vaccinated and unvaccinated groups, case-control studies, self-controlled case series, and designs utilizing multivariate risk factor analyses. Our results support most findings of the IOM report, add conclusions on some adverse events where new evidence was identified, and include findings on several additional vaccines.

The findings of this project may allay some patient, caregiver, and healthcare provider concerns. Strength of evidence is high that vaccines against pneumonia and influenza are not associated with cardiovascular or cerebrovascular events in the elderly. 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 moderate strength evidence that HPV vaccine is not associated with appendicitis, stroke, seizures, syncope, venous thromboembolism, onset of juvenile arthritis, or onset of Type 1 diabetes and high strength evidence that childhood vaccines such as MMR, DTaP, Td, Hib, and Hep B vaccine are not associated with childhood leukemia.

Evidence of association with vaccines was found for several serious adverse events; however, these events were relatively rare. For example, strength of evidence is high that H1N1 influenza vaccine is associated with Guillian-Barre Syndrome (GBS) but results translate to about 1.6 additional cases per million persons vaccinated. Strength of evidence is low for association of intussusception with rotavirus vaccines; case-control studies of Rotarix in Mexico estimated the risk as 1 per 51,000 vaccinees or 3.7 additional cases per person-year.

Importantly, evidence is insufficient to make conclusions regarding whether several routinely recommended vaccines are associated with serious conditions such as Multiple Sclerosis (MS), transverse myelitis, and Acute Disseminated Encephalomyelitis (ADEM). This and other research gaps are described later in this Executive Summary.

Conclusions must be viewed in light of the important caveats below.

Literature search procedures were extensive; however, some unpublished trial results may not have been identified. An independent Scientific Resource Center (SRC) under contract with AHRQ requested Scientific Information Packets (SIPs) from the manufacturers of all vaccines routinely recommended in the US. (The research team was prohibited from contacting manufacturers directly.) Only two companies responded.

We included trials of the formulations currently on the market in the US. We tried to exclude Phase II studies that used dosages that were never licensed and/ or formulations available only in foreign countries. Some studies reported the potency or formulation of the vaccines in a different manner or unit than reported in the product materials. We assessed these formulations to the best of our abilities; we point out discrepancies in dosage where applicable. In addition, several large epidemiological studies included any available formulation of vaccines against a particular disease and did not stratify results by dosage or formulation. For example, the relationship between the “seasonal influenza vaccine” and an adverse event might be studied over several years of data, without addressing the changes in formulation over the seasons.

Our findings are based on only the most rigorous study designs to assess potential statistical associations; however, these designs have limitations which must be considered. Controlled trials often have insufficient sample size to identify very rare adverse events, or do not have extended follow-up to identify long term sequelae. In addition, trials may purposely exclude subjects such

as the elderly, pregnant women, and persons with medical conditions who could be more susceptible to adverse events. For this reason, any comprehensive review of vaccine safety also includes post-licensure studies, but these are not without limitations. Persons who avoid vaccinations (whether purposely or not) may differ from those who receive vaccinations in terms of race, gender, age, SES, and pre-existing medical conditions; observational studies should control for such potential confounders. Observational studies often use matched cohorts or multivariate regression analysis to calculate an adjusted odds ratio. More recently, the self-controlled case series (SCCS) was developed specifically to assess the safety of vaccines. To summarize in simple terms, SCCS eliminates confounding by all time-independent variables by using cases as their own controls and pre-defined “time windows” before and after vaccination. This design has been used to study purpura, febrile seizures, intussusception and autism in children. However, SCCS is sometimes problematic for assessing vaccines administered to very young children; age is likely to be a major confounder.

There may be important adverse event signals not identified in this report that warrant future research. Passive surveillance systems such as the US Vaccine Adverse Event Reporting System (VAERS),¹⁴ are crucial in identifying signals regarding adverse events post-licensure but they are not designed to assess a statistical association so were excluded from this project. The suggestions for future research discussed below are based only on the studies that met inclusion criteria for this report.

Research Gaps

While this report undergoes peer review and public comment, we will conduct a search update and incorporate new studies into our final report. During our current literature search, we identified the following research gaps.

Adults. We found insufficient evidence regarding the association of influenza vaccines with both onset or exacerbation of MS. The field could benefit from future research, using studies powered adequately to determine risk factors such as demographic and health characteristics of patients, and formulations of vaccine. There is particular concern regarding monovalent H1N1 vaccine and trivalent influenza vaccines that include H1N1 strains.

A late-breaking meta-analysis on H1N1 vaccine published as this report was written provided high strength evidence that H1N1 vaccine is associated with Guillain Barré Syndrome in adults. As the vaccine is associated with only 1.6 excess cases per million vaccinated, it will be very difficult to assess risk factors.

Published trials of zoster vaccine were not always transparent in reporting AEs. They often reported only broad categories such as “injection-related adverse events,” “systemic adverse events,” “one or more adverse events” or “serious adverse events” rather than specifying type or severity. Vaccinated groups often had significantly higher risk of these “categorical” events. Unfortunately, it is impossible to determine the rate of any particular serious adverse event from the information reported in the peer-reviewed publications. In the future, data from these trials could be re-analyzed and presented in a standard and transparent format. Two large, high quality post-licensure studies of zoster vaccine met our inclusion criteria; both used the Vaccine Safety Datalink (VSD). One investigated post-vaccination herpes zoster incidence in patients with pre-existing conditions; another investigated serious adverse events (such as acute myocardial infarction, stroke, and Bell’s Palsy) in the weeks following vaccination in healthy patients. Both found no association between vaccination and the adverse events studied. Additional studies might be conducted using the VSD if signals arise from passive surveillance systems.

Both MS and GBS are concerns regarding vaccines for MMR and hepatitis A and B. Further post-licensure studies are suggested.

Children. There is insufficient evidence regarding the associations between influenza vaccines and asthma exacerbation, seizures, acute disseminated encephalomyelitis (ADEM), and transverse myelitis. The field would benefit from additional post-licensure studies.

Febrile seizures, transient arthralgia, and importantly, measles inclusion body encephalitis were associated with MMR vaccine. Large scale studies are needed to determine patient risk factors. Purpura were also associated with MMR as well as with vaccination against varicella and hepatitis A; however, most cases were considered mild and acute.

Post-licensure studies in foreign countries have associated both Rotarix and RotaTeq with intussusception 21 days following vaccination. However, a large U.S. study of RotaTeq found no association. The risk with Rotarix could be investigated further in US populations, unless there are known underlying factors that would make children in Latin American more vulnerable to this medical condition or the dosage / formulation differs from that used in the US. One study estimated the risk as 1 case per 51,000 vaccinations; the morbidity and mortality prevented through vaccination may be valued by policy makers more than the risk of this rare event.

Strong evidence for a lack of association of HPV vaccines with several serious medical conditions (juvenile rheumatoid arthritis, type 1 diabetes, GBS) has been found in large post-licensure studies. However, there is insufficient evidence regarding other serious conditions such as MS, chronic inflammatory disseminated polyneuropathy, amyotrophic lateral sclerosis, and pancreatitis. These issues warrant further study.

There is insufficient evidence to determine the possible association, if any, between vaccines such as DTaP, meningococcal vaccine, and varicella vaccine and the onset of nervous system conditions such as ADEM, transverse myelitis, MS, and GBS. Large scale epidemiological studies are needed to investigate further.

Pregnant women. Only vaccines against influenza were studied in pregnant women. Given the relatively recent introduction of the recommendation to administer the Tdap vaccine during pregnancy, passive surveillance systems might be regularly monitored for AEs in this population. This is a particular concern for women with multiple pregnancies over a period of a few years. Preliminary analyses of VSD could also identify adverse events associated with the vaccine and possible related risk factors.

Advanced health information technology (HIT) systems that contain both vaccination and health outcome records can be used to conduct high quality epidemiological studies. In the US, the VSD uses data obtained through such systems at nine very large MCOs. Nations with single payer healthcare systems often have electronic registries, which allow even larger epidemiological studies of entire populations. Future studies would benefit from such databases rather than relying on surveys that use patient / parent recall for ascertainment of vaccination or health outcome. Not only are such surveys subject to recall bias, but there may be no way of determining the formulation or brand of vaccination.

Independent abstraction and systematic reassessment of the studies included in the Institute of Medicine consensus report *Adverse Effects of Vaccines: Evidence and Causality* may be a useful future endeavor. Odds ratios could be calculated for each event reported in each study, and, where appropriate, meta-analysis conducted to calculate overall odds ratios for each AE and each vaccine type. If these additional studies were abstracted, the totality of data abstracted could be used for secondary analyses to explore additional hypotheses and issues beyond the scope of the current report.

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Introduction

Background

Vaccines are considered one of the greatest public health achievements of the last 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, substantial gaps in vaccine uptake exist. Vaccination rates for young children are high;² however, vaccination rates remain well below established Healthy People 2020 targets for many vaccines recommended for adolescents,³ adults,⁴ and pregnant women.⁵

Increasing vaccination rates remains critically important, as vaccine-preventable diseases such as influenza, pertussis, and human papilloma virus (HPV)-associated cervical cancer continue to take a heavy toll despite the widespread availability of effective vaccines. The health and productivity costs of influenza infection alone in adults have been estimated to be as high as \$87 billion per year.⁶ The recent pertussis outbreaks in California, Washington, Minnesota, and Wisconsin highlight the importance of protecting vulnerable infants by vaccinating their pregnant mothers, caregivers, and other contacts. HPV is the most common sexually transmitted infection, affecting approximately 27 percent of U.S. women aged 14–59. HPV-16 and HPV-18—the two strains covered by the HPV vaccine—are thought to be responsible for approximately 70 percent of incident cervical cancer. Nationally, in 2005, there were nearly 12,000 new cases of cervical cancer reported, with 4,000 cervical cancer-related deaths.⁷ Despite the availability of an HPV vaccine that could prevent a substantial proportion of these cases of cervical cancer, completion of the three-dose series was only 34.8 percent among adolescent females in 2011.³

The shortfall in vaccination coverage rates occurs in the context of a rapidly changing immunization schedule. The number of routine immunizations recommended for children (Table 1), adolescents (Table 1), adults (Table 2), and pregnant women (Table 3) has expanded considerably over the past 10 years. Since 2005, the routine adolescent vaccination schedule has grown to include these vaccines at ages 11 or 12 years: meningococcal conjugate vaccine; tetanus, diphtheria, and acellular pertussis (Tdap); HPV; and influenza (one dose annually). Pregnant women are now advised to receive Tdap during every pregnancy to protect their newborns from pertussis regardless of prior history of receiving Tdap.⁸

Table 1. Vaccines routinely recommended for children and adolescents

Vaccine	Age
DTaP (diphtheria, tetanus, and acellular pertussis)	2 months – 6 years
Hepatitis A	12 months and older
Hepatitis B	Birth and older
Hib (<i>Haemophilus influenzae</i> type b)	6 weeks – 59 months
HPV (human papillomavirus)	9 years – 26 years
Influenza (inactivated)	6 months and older
Influenza (live attenuated)	2 years and older
IPV (inactivated polio vaccine)	6 weeks and older
MCV (meningococcal conjugate vaccine)	2 years and older
MMR (measles, mumps, and rubella)	12 months and older
MPSV (meningococcal polysaccharide vaccine)	2 years and older, in specific circumstances
PCV13 (pneumococcal conjugate vaccine)	6 weeks – 18 years
Pneumococcal polysaccharide vaccine	2 years and older, in specific circumstances

Vaccine	Age
Rotavirus	6 weeks – 8 months
Tdap (tetanus, diphtheria, and acellular pertussis)	7 years and older
Varicella	12 months and older

Table 2. Vaccines routinely recommended for nonpregnant adults

Vaccine	Recommendation
Hepatitis A	All adults at increased risk of hepatitis A infection
Hepatitis B	All unvaccinated adults at risk for or requesting protection from Hepatitis B infection
HPV (human papillomavirus)	Adults 26 years and younger
Influenza (inactivated)	All adults
Influenza (live attenuated)	All adults 49 years and younger
Meningococcal conjugate vaccine (MCV4) and meningococcal polysaccharide vaccine (MPSV)	Adults at risk of meningococcal disease (MCV4 or MPS5 if younger than 55 years; MPS5 if older than 55 years)
MMR (measles, mumps, and rubella)	All adults
Pneumococcal polysaccharide vaccine	Adults 64 years and younger with certain conditions, and all adults 65 years and older
Td (tetanus, diphtheria)	All adults
Tdap (tetanus, diphtheria, and acellular pertussis)	All adults 19–64 years old; some adults 65 years and older
Varicella	All adults without evidence of varicella immunity
Zoster	All adults 60 years and older

Table 3. Vaccines routinely recommended for pregnant women

Vaccine	Recommendation
Hepatitis B	Recommended in some circumstances
Influenza (inactivated)	All pregnant women
Td (tetanus, diphtheria)	Should be used if indicated
Tdap (tetanus, diphtheria, and acellular pertussis)	All pregnant women during each pregnancy, regardless of prior history of receiving Tdap

As the number of recommended immunizations have expanded across the population, so too have concerns about the safety of vaccines, despite the rigorous processes new vaccines must undergo before receiving approval from the U.S. Food and Drug Administration (FDA). Vaccine development and commercialization are complex processes, and the regulatory review process is overseen by the Center for Biologics Evaluation and Research of the FDA.⁹ Vaccines are unique when compared with many other medications because they are administered to a large population of mostly young healthy people to prevent rather than treat disease. Vaccines must meet stringent criteria for safety, efficacy, and potency. Preclinical studies are conducted in the early stages of vaccine development and are meant to be sufficient to rule out overt toxicity and identify potential toxic effects that might occur during the clinical trial. Once a vaccine is ready for clinical evaluation, an Investigational New Drug application must be submitted so the FDA can monitor the safety of clinical trial subjects and ensure that the study design is appropriate to assess the vaccine’s effectiveness and safety.

The clinical evaluation of a vaccine typically consists of three phases.⁹ Phase I studies—which typically enroll 20 to 80 subjects—are designed to evaluate vaccine safety and tolerability and to generate preliminary immunogenicity data. Phase II studies evaluate the immunogenicity

of the vaccine and provide preliminary estimates on the rates of common adverse events, typically enrolling several hundred subjects. Phase III trials provide the information on a vaccine's safety and effectiveness that is required to support licensure. After a vaccine is licensed and in use, multiple systems are in place to ensure ongoing assessments of safety,¹⁰ including post licensure safety surveillance conducted by sponsors as postmarketing commitments or requirements to the FDA,¹¹ the FDA's Post-Licensure Rapid Immunization Monitoring (PRISM) system,¹²⁻¹⁴ FDA surveillance using databases of Federal Partners such as the Centers for Medicare and Medicaid Services (CMS),¹⁵ the Vaccine Adverse Event Reporting System (VAERS),¹⁶ the Vaccine Safety Datalink,¹⁷ and the Clinical Immunization Safety Assessment Network.¹⁸

Despite the stringent regulation and evaluation of vaccines, public concerns about vaccine safety continue to persist. Perhaps the most highly publicized safety concern of the last two decades has been the link between autism and the MMR vaccine, first reported in *The Lancet* by Dr. Andrew Wakefield.¹⁹ Vaccination rates for measles, mumps, and rubella plummeted in the United Kingdom leading to measles outbreaks²⁰ and concern about vaccines and autism spread globally. In 2010, *The Lancet* fully retracted the 1998 publication,²¹ noting that elements of the manuscript had been deliberately falsified. Subsequently, Dr. Wakefield was barred from practicing medicine in the United Kingdom. Although multiple large studies have confirmed the lack of association between MMR and autism, parental worries about the safety of the vaccine persist. In addition to autism, other parental concerns about childhood vaccines include links to multiple sclerosis, sudden infant death syndrome, asthma, and diabetes.²² Though no systematic data exist on the safety concerns of pregnant women, this is likely to be an active focus given the relatively recent introduction of the recommendation to administer the Tdap vaccine during pregnancy.

The Agency for Healthcare Research and Quality (AHRQ) has requested an evidence report on the safety of vaccines used for routine immunization of adults (including pregnant women), children, and adolescents that will, based on a comprehensive and systematic review of the scientific literature, describe associations between vaccines and adverse events (AEs) and help to outline the gaps in evidence. This report focuses on the adverse events (AEs) potentially associated with vaccines as opposed to the benefits, as all of these vaccines are already recommended.

Our work expands upon the consensus report *Adverse Effects of Vaccines: Evidence and Causality*, which was published by the Institute of Medicine (IOM) in late 2011. This report evaluated the scientific evidence for event-vaccine relationships and covered many vaccines included in current recommended immunization schedules (varicella, influenza, hepatitis A, Hepatitis B, HPV, MMR, meningococcal, tetanus, diphtheria, and pertussis) in the United States. Our work builds upon the IOM report in a number of important ways. In addition to those vaccines covered by the IOM report, our systematic review also covers pneumococcal, rotavirus, *Haemophilus influenzae* type b, inactivated poliovirus, and zoster vaccines. We use the existing IOM findings as a springboard, update the literature search with more recent studies, and conduct original searches for the vaccines recommended for adults, children, and pregnant women that were not included. We provide an assessment of AEs for all recommended vaccines.

Methods

Original Proposed Key Questions (KQs)

AHRQ provided following original key questions. Not all questions were answerable through a systematic review of the published research; we discuss important research gaps later in this report.

KQ 1 What is the evidence that vaccines included in the 2011 immunization schedule recommended for U.S. **adults**²³ are safe in the short term (within 30–42 days following immunization) or long term (>42 days after immunization)?

- a. What adverse events (AEs) are collected in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?
- b. What AEs are reported in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?
- c. What AEs are associated with these vaccines?
 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 3. For each AE associated with a particular vaccine, what are the risk factors for the AE (including age, sex, race/ethnicity, genotype, underlying medical condition, whether a vaccine is administered individually or in a combination vaccine product, schedule of vaccine administration, adjuvants, and medications administered concomitantly)?

KQ 2 What is the evidence that vaccines included in the immunization schedules recommended for U.S. **children and adolescents** in 2011²⁴ are safe in the short term (within 30–42 days following immunization) or long term (>42 days after immunization)?

- a. What AEs are collected in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?
- b. What AEs are reported in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?
- c. What AEs are associated with these vaccines?
 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?

2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
3. For each AE associated with a particular vaccine, what are the risk factors for the AE (including age, sex, race/ethnicity, genotype, underlying medical condition, whether a vaccine is administered individually or in a combination vaccine product, schedule of vaccine administration, adjuvants, and medications administered concomitantly)?

KQ 3 What is the evidence that vaccines recommended for **pregnant women**²⁵ are safe both for the woman and for her fetus/infant?

- a. What AEs are collected in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?
- b. What AEs are reported in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?
- c. What AEs are associated with these vaccines in women?
 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 3. For each AE associated with a particular vaccine, what are the risk factors for the AE (including age, sex, race/ethnicity, genotype, underlying medical condition, whether the vaccine is administered individually or in a combination vaccine product, the schedule of vaccine administration, adjuvants, and medications administered concomitantly)?
- d. What AEs are associated with these vaccines in the fetus/infant?
 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 3. For each AE associated with a particular vaccine, what are risk factors for the AE (including age, gender, race/ethnicity, genotype, underlying medical condition, whether vaccine administered individually or in a combination vaccine product, vaccine schedule of administration, adjuvants, medications administered concomitantly)?

Technical Expert Panel

For each Agency for Healthcare Research and Quality (AHRQ) systematic review, a Technical Expert Panel (TEP) is assembled to provide clinical expertise and context. A distinguished group of scientists and clinicians were invited to participate in the TEP for this report. Potential members submitted conflict of interest disclosure forms; any current or prior relationship with a vaccine manufacturer was grounds for disqualification per AHRQ. A list of members is included in the front matter.

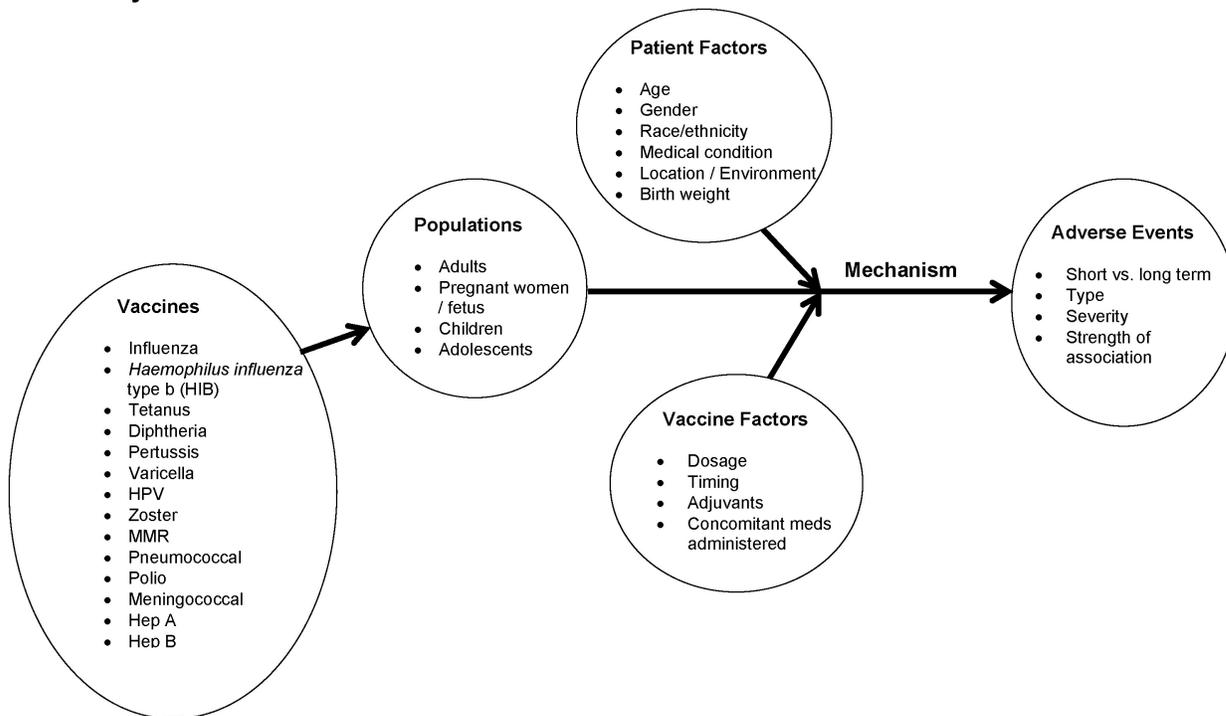
TEP conference calls were held on June 18, June 19, and July 19, 2012. The calls were attended by project staff and Task Order Officers (TOO) from AHRQ and OASH. The TEP informed staff of recent developments in the field, gave input on which AEs and issues were most important, and emphasized we should focus on studies which use the same dosage and formulation as vaccines currently used in the U.S. Vaccines with adjuvants not currently used in the U.S. (for example, ASO3) or strengths that were never licensed in the U.S. (for example, those used in Phase II studies that did not advance to Phase III) should be excluded. They also advised that, given resource limitations, minor AEs such as crying and injection site redness should not be included.

Panel members were invited to review the current draft version of this report and provide feedback.

Analytic Framework

The analytic framework for the project is displayed in the figure below. Vaccinations recommended by the Centers for Disease Control and Prevention (CDC) are listed in the large oval. Various subsets are administered annually to children, adolescents, and adults, including pregnant women (next circle), according to a schedule developed by the Advisory Committee on Immunization Practices (ACIP). Both patient factors (i.e., age, pre-existing conditions) and vaccine factors (i.e., formulation, dosage, and timing) may be risk factors for potential AEs associated with vaccination.

Figure 1. Analytic framework



Literature Search

The following databases were searched to identify relevant studies: DARE, the Cochrane Database of Systematic Reviews, CENTRAL, PubMed®, EMBASE®, CINAHL®, TOXLINE®, and TOXFILE®. The IOM report, ACIP statements, and vaccine package inserts were reviewed. Review articles were mined for references.

Our search strategy built upon the recent IOM report for the eight vaccines contained therein. Using the IOM keyword search strategy, we updated their searches on varicella, influenza, hepatitis A, Hepatitis B, HPV, MMR, meningococcal, diphtheria, pertussis, and tetanus vaccines to identify more recently published studies. The following structure was used in the IOM keyword search strategy: “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 database inception through October, 2012.

Using this approach, we developed new search strategies for the vaccines not originally included in the IOM report: pneumococcal, rotavirus, *H. influenzae* type b, inactivated poliovirus, and zoster.

Searches were based on AEs reported in systems such as the Vaccine Injury Compensation Program (VICP), Vaccine Adverse Event Reporting System, and the FDA’s Mini-Sentinel Program. The Technical Expert Panel (TEP) reviewed the draft list of AEs and suggested additional AEs of interest. Appendix A contains the detailed search strategy and a list of AEs included in the searches.

Article Review

Two researchers independently reviewed the titles and abstracts identified. The union of their selections was retrieved. Two researchers also independently reviewed the full text of study reports and met to reach consensus regarding exclusion/inclusion. Disputes were settled by the principal investigators and team physician experts.

Data were entered directly by researchers into DistillerSR software (Evidence Partners Inc., Ottawa, Ontario, Canada),²⁶ which is designed specifically for systematic reviews and meta-analyses, and exported to SAS (SAS Institute Inc., Cary, NC) for analysis.

Study Inclusion

We **include** the following study designs:

Controlled clinical trial - A study where human subjects are assigned prospectively, usually through randomization, to receive an intervention (in this case a vaccine) or an alternate intervention (another vaccine) or placebo. Clinical trials are used to determine safety and efficacy.

Cohort comparing two or more groups - Follows over time a group of similar individuals (for example, all children born in Denmark in 2001) who differ with respect to whether they received a vaccine, to determine how/whether the vaccination affects rates of one or more AEs.

Case-control study - A study that compares persons who have a disease or adverse event (AE) (cases) with persons who do not have the disease or AE, and looks back retrospectively to compare exposure to vaccine in each group to determine the relationship between the vaccine and the disease / AE.

Self-controlled case series (SCCS) – Only cases (individuals who experienced the AEs) are included in the analysis. With SCCS, each individual serves as their own control. The analysis controls for time and other covariates that don't vary within a person during the study period. In other words, SCCS compares outcome event rates during times when a person is exposed versus outcome event rates during times when the same person is unexposed to calculate the relative incidence of AEs.

Multivariate risk factor analyses – We included case series, and cohort studies that used logistic regression to control for confounders and test multiple relationships simultaneously.

Studies using passive surveillance such as the US Vaccine Adverse Event Reporting System (VAERS),¹⁶ are crucial in identifying signals regarding adverse events post-licensure. However, because by definition they do not consider the rate of such events in non-vaccinated populations, they are not designed to assess a statistical association between a vaccine and an adverse event, so they were excluded from this project. We also excluded studies of vaccines not on the current US recommended schedules. These include brands/ and formulations never available in the US and formulations no longer used. Examples include whole cell pertussis vaccine, oral polio vaccine, and PCV7 pneumococcal vaccine.

The following publication types / studies were **excluded**:

- Letters
- Editorials
- Individual case reports
- Animal studies
- Mechanistic/in vitro studies
- Conference abstracts
- Vaccine efficacy studies which do not mention AEs or lack of AEs
- Observational studies which use passive surveillance for AEs
- Non–English-language studies. Given the focus of this review and the corresponding literature base, we concluded the risk of language bias to be low and that it was thereby acceptable to limit the inclusion criteria to English studies only.
- Studies of vaccines not on the US recommended schedules, including brands/formulations never available in the US, or no longer used. Examples include whole cell pertussis vaccine, oral polio vaccine, PCV7 pneumococcal vaccine, etc.

Data Abstraction and Synthesis of Results

Based on our experience conducting systematic reviews of the evidence on other health care interventions, we developed a structured approach to assessing AEs instead of relying on a random post-hoc grouping. We used a tested and standardized form to extract AEs; when possible, researchers characterized the severity using the Common Terminology Criteria for Adverse Events (CTCAE) classification system as part of the data extraction process. Serious adverse events (SAE) were defined and coded.

Clinical trials and cohort comparisons were abstracted using an electronic form which contained items for sample size, population description (age, gender, race/ethnicity, country, any co-morbidities), items on study quality (described below), vaccine description (name, manufacturer, dosage, formulation, adjuvants, preservatives, timing, mode of administration), and AEs (exact description, severity, timing, number) for each group. Odds ratios of AEs for vaccination and comparison arms were computed for each study, along with the 95% confidence interval. The risk of SAEs and “any adverse event” was also computed. Studies were included for analysis if the total number of people in each group and the number of people with events in each group were reported. Occasionally, this information was missing, or the number of AEs and number of doses (rather than number of persons) was provided. Since AEs are generally rare, conditional pooling using exact methods provided a fixed effects estimate of the odds ratio. Analyses were conducted with Stat Xact® Procs for SAS.²⁷ Subgroup analyses are narrative in order to be able to make comparisons between study designs and other variables in the heterogeneous dataset.

The case-control, self-controlled case series, and multivariate risk factor analyses were abstracted onto another electronic form containing similar items; however, the statistical findings were abstracted directly. These types of studies generally do not include enough information for researchers to re-calculate the statistics independently, as they are not simple comparisons of a vaccinated group with an unvaccinated group. To assess the reliability and validity of the findings, we abstracted how vaccination status and health outcomes were ascertained (self-

report, national registry, parent interview, medical record, etc); potential sources of bias due to selection, participation, attrition, and non-response of subjects; amount of missing data; funding source; and how potential confounders were handled. The abstraction forms are presented in Appendix B.

We created detailed evidence tables displaying critical data for each included study. Multiple publications of the same study are noted and counted (extracted, assessed for quality, and analyzed) as one study to ensure that the same participants do not enter the analyses multiple times. Multiple publications were defined by the investigated patients.

Assessment of Methodological Quality

For controlled trials and cohort comparisons, we used a quality-rating instrument Santaguida and colleagues (2008)²⁸ developed for evaluating studies reporting harms. Called McHarm, the tool was developed from quality rating items generated by a review of the literature on harms and from previous quality assessment instruments. McHarm was tested for reliability and face, construct, and criterion validity and includes important factors such as:

- Were harms predefined using standard, precise definitions?
- Was the mode of harms collection active (participants are asked about the occurrence of specific AEs) or passive (participants are not specifically asked about or tested for the occurrence of AEs; patient reports of AEs are made on their own initiative)?
- Did the study specify who collected the harms data?
- Did the study specify the timing of harms?
- Was the number of participants who withdrew or were lost to followup reported?

Grading the Evidence for Each Key Question

We assess the overall strength of evidence by using guidance suggested by AHRQ for its Effective Health Care Program.²⁹ This method is based on one developed by the GRADE Working Group³⁰ and classifies the grade of evidence according to the following criteria:

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.

The evidence grade is based on four primary (required) domains and four optional domains. The required domains are risk of bias, consistency, directness, and precision, as described in Table 4 below. The additional domains are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias.

Table 4. Grading the strength of a body of evidence: Required domains and their definitions

Domain	Definition and Elements	Score and Application
Risk of Bias	<p>Risk of bias is the degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements:</p> <ul style="list-style-type: none"> • Study design (e.g., RCTs or observational studies) • Aggregate quality of the studies under consideration. <p>Information for this determination comes from the rating of quality (good/fair/poor) done for individual studies</p>	<p>Use one of three levels of aggregate risk of bias:</p> <ul style="list-style-type: none"> • Low risk of bias • Medium risk of bias • High risk of bias
Consistency	<p>The principal definition of consistency is the degree to which reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements:</p> <ul style="list-style-type: none"> • Effect sizes have the same sign (that is, are on the same side of “no effect”) • The range of effect sizes is narrow. 	<p>Use one of three levels of consistency:</p> <ul style="list-style-type: none"> • Consistent (i.e., no inconsistency) • Inconsistent • Unknown or not applicable (e.g., single study) <p>As noted in the text, single-study evidence bases (even mega-trials) cannot be judged with respect to consistency. In that instance, use “Consistency unknown (single study).”</p>
Directness	<p>The rating of directness relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies that head-to-head trials measure the most important health or ultimate outcomes.</p> <p>Two types of directness, which can coexist, may be of concern: Evidence is indirect if:</p> <ul style="list-style-type: none"> • It uses intermediate or surrogate outcomes instead of health outcomes. In this case, one body of evidence links the intervention to intermediate outcomes and another body of evidence links the intermediate to most important (health or ultimate) outcomes. • It uses two or more bodies of evidence to compare interventions A and B -- e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not A vs. B. <p>Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcomes.</p> <p>Directness may be contingent on the outcomes of interest. EPC authors are expected to make clear the outcomes involved when assessing this domain.</p>	<p>Score dichotomously as one of two levels directness</p> <ul style="list-style-type: none"> • Direct • Indirect <p>If indirect, specify which of the two types of indirectness account for the rating (or both, if that is the case) -- namely, use of intermediate/ surrogate outcomes rather than health outcomes, and use of indirect comparisons. Comment on the potential weaknesses caused by, or inherent in, the indirect analysis. The EPC should note if both direct and indirect evidence was available, particularly when indirect evidence supports a small body of direct evidence.</p>

Domain	Definition and Elements	Score and Application
Precision	<p>Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome (i.e., for each outcome separately)</p> <p>If a meta-analysis was performed, this will be the confidence interval around the summary effect size.</p>	<p>Score dichotomously as one of two levels of precision:</p> <ul style="list-style-type: none"> • Precise • Imprecise <p>A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For example, results may be statistically compatible with both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a valid conclusion.</p>

Peer Review and Public Commentary

A draft of this report was submitted in May, 2013. The AHRQ Effective Healthcare Program Scientific Resource Center (SRC) located at Oregon Health Sciences University (OHSU) coordinated peer review by experts and stakeholders. The report will be posted on AHRQ’s web site for a month for public comment. Resulting comments will be considered by the EPC in preparation of the final report. **Synthesis of the scientific literature presented here does not necessarily represent the views of individual reviewers, and service as a peer reviewer or member of the TEP cannot be construed as endorsement of the report’s findings.**

Results

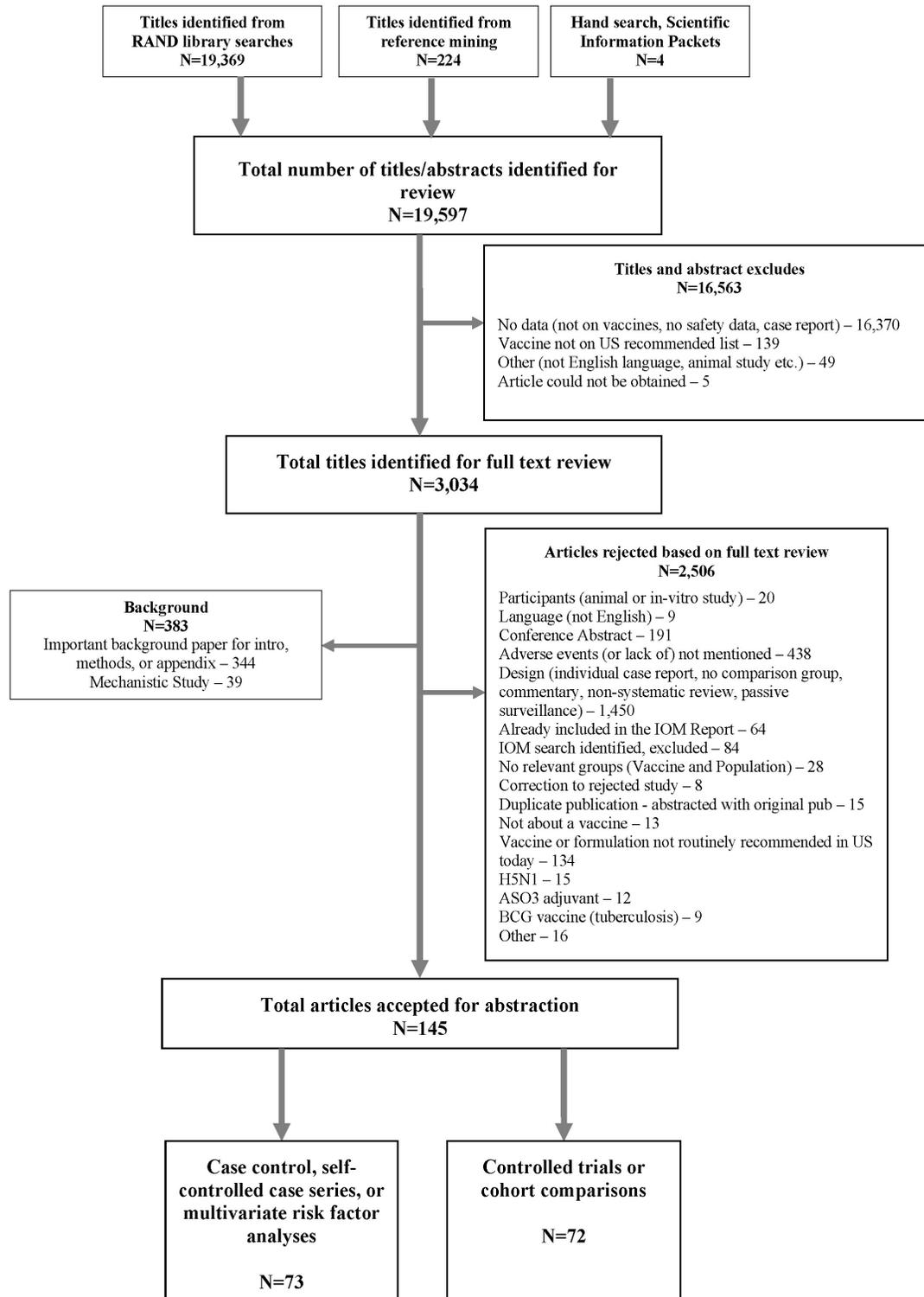
A total of 19,597 titles were identified through electronic literature searches; suggestions from TEP members; review of product inserts; review of FDA, ACIP, and other web sites; reference mining; and finally, Scientific Information Packets (SIPs) requested from vaccine manufacturers by the AHRQ-funded Scientific Resource Center (SRC). Of those, 16,536 were excluded upon review of abstract (where available) or title, mostly due to lack of data on safety of vaccines (see Figure 2). Other reasons for exclusion included use of vaccines not within the scope of this project (i.e. not routinely recommended in the US, recommended only for travel, no longer used in the US), publication in languages other than English, and study not conducted on humans. Five articles could not be obtained.

Based on title/abstract screenings, 3,034 articles were selected for full text review. Of those, 383 were identified as relevant background/theoretical materials and set aside as potential references. A total of 2,506 other articles were excluded. The most common reason for exclusion was lack of suitable study design (1,450): Individual case reports, non-systematic reviews, and studies using passive surveillance (for example, reports from VAERS) were not included. Many publications (438) discussed vaccines on the recommended schedule, but did not report adverse events (or a lack thereof).

Studies using formulations not currently or routinely recommended in the US were excluded at full text review. For example, we identified 15 studies of H5N1 vaccine, twelve studies using the adjuvant ASO3, and nine studies of BCG vaccine. We excluded 134 additional studies using vaccines beyond the scope of the project; for example, vaccines no longer used in the US (i.e. oral polio vaccine), removed from the market due to safety concerns (i.e. RotaShield®), or of strengths never approved in the US. Identifying strength / formulation was often difficult; this process involved comparing dosage listed on product materials and in FDA filings with that reported in the studies.

Based on full text screening, 145 studies were accepted for abstraction, including 72 controlled trials or cohort studies directly comparing a group who received a vaccine with an unvaccinated group. We also identified 73 case-control studies, self-controlled case series, or multivariate risk factor analyses that met our inclusion criteria. These studies are in addition to the studies included in the 2011 IOM consensus report *Adverse Effects of Vaccines: Evidence and Causality*; we summarize their findings for each population and vaccine, as resources did not permit abstracting those studies. The results are presented by population (adults, children and adolescents, pregnant women) for each of the key questions provided by the project sponsor.

Figure 2. Study/Literature flow diagram



Key Question (KQ) 1: What is the evidence that vaccines included in the 2011 immunization schedule recommended for U.S. **adults**²³ are safe in the short term (within 30–42 days following immunization) or long term (>42 days after immunization)?

- a. What adverse events (AEs) are collected in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?
- b. What AEs are reported in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?

Table 5 lists all AEs reported in placebo-controlled trials and vaccinated/ unvaccinated cohort comparisons of adults, abstracted verbatim. We are uncertain if additional AEs were collected; we can rely only on what was reported in the literature. The list does not imply an association with vaccination; it displays reported AEs, regardless of whether they were reported in vaccinated or unvaccinated study participants. Later in this report, we further describe the studies and assess association.

Table 5. Adverse events reported in trials of adults

HPV*	Influenza - monovalent H1N1
Acute appendicitis	Any systemic AE
Arthralgia	Chills
Fatigue	Fever
Fever	Headache
GI symptoms	Malaise
Headache	Myalgia
Lymph node tuberculosis	Nausea
Myalgia	Vomiting
Pain (Grade 3)	Td
Rash	Hypoesthesia
Redness (>50 mm)	"Serious adverse events"
Swelling (>50 mm)	Varicella / Zoster
Urticaria	Oka VZV with or without other organ involvement
* For HPV, Table 5 includes trials in young adults (age 18 and over); adverse events in trials of younger patients appear in the children & adolescents section.	Adenopathy
Influenza (inactivated)	Anaphylaxis
Arthralgia	Chest pain
Bruising	Influenza-like illness
Burning/stinging nose (Grade2/3)	Liver enzyme elevation
Burning/stinging throat (Grade 2/3)	Nose bleed
Chills	Systemic rash (non-zosteriform)
Conjunctival hemorrhage	"Serious adverse events"
Cough	Blood/Lymphatic disorders
Death	Cardiac disorders
Fatigue	Death
Fever	Discontinued due to a vaccine-related AE
Fits (seizures)	Fever
Gingival bleeding	GI disorders
Headache	Hospitalization related to herpes zoster
Hyperhidrosis	Injection-site reaction
Itching nose/throat/eyes (Grade 2/3)	Neoplasms
Joint pain	Nervous system
Lightheadedness/Dizziness (Grade2/3)	"Systemic adverse events"
Lump formation	"Vaccine-related systemic adverse events"
Malaise	"Overall - Vaccine related AEs"
Muscle pain	Pruritus
Myalgia	Psychiatric
Nausea	Rash
Nosebleeds	Respiratory/Thoracic
Oropharyngeal pain	
Pain	
Posttraumatic elbow hematoma	
Pyrexia	
Redness	
Rigors (muscle cramp)	
Seizures	
Shivering or chills	
Shortness of breath (Grade 2/3)	
Sweating (mild-moderate)	
Swelling	
Withdrawal after AE	

HPV = Human Papillomavirus; AE = Adverse Events; GI = Gastrointestinal; VZV = Varicella-Zoster Virus;

Table 6 lists all AEs and medical conditions investigated in the case-control studies, self-controlled case series, and multivariate risk factor analyses in adults. The majority of these studies were designed to assess the association of a specific AE with vaccination. Again, appearance on the list does not imply an association.

Table 6. Adverse events investigated in post-marketing studies of adults

Influenza vaccines	MMR
H1N1	Arthropathy in men
Allograft loss in kidney patients	Autism
Chronic obstructive pulmonary disease - exacerbation	Multiple sclerosis
Guillain-Barré Syndrome (GBS)	Transient Arthralgia
Hematologic diseases	Type 1 diabetes
Immune thrombocytopenia	Meningococcal Vaccines
Mortality	Encephalitis
Multiple Sclerosis	Encephalopathy
Myocardial infarction	Guillain-Barre Syndrome
Sickle cell disease – exacerbation	Zoster
Spasmodic dysphonia	Acute myocardial infarction
Stroke	Acute myocarditis
LAIV or TIV	Acute pericarditis
Anaphylaxis	Allergic reactions
Asthma exacerbation	Bell's palsy
Death	Cardiomyopathy
Hospitalization	Cellulitis
Oculorespiratory syndrome	Encephalopathy
Influenza with 23-valent pneumococcal vaccine	Hospitalization for meningitis or encephalitis
Cardiac failure	Inflammatory bowel disease
COPD	Meningitis encephalitis
Hospitalization for influenza	Pain
Hospitalization for pneumococcal diseases	Psoriasis
Mortality due to pneumonia	Psoriatic arthritis
Myocardial infarction	Ramsay-Hunt syndrome
Stroke	Rheumatoid arthritis
Pneumococcal vaccines	Studies of multiple vaccines, including Hepatitis A, Hepatitis B, MMR, IPV
Acute coronary syndrome	Graves' disease
Death	Hashimoto's thyroiditis
Major vascular events	Psoriatic arthritis
Myocardial infarction	Type 1 diabetes
Stroke	
Hep B	
Anaphylaxis	
Demyelinating Event, First	
Guillain-Barré Syndrome	
Multiple Sclerosis - Onset	
Multiple Sclerosis - Relapse	
Optic Neuritis	
Rheumatoid Arthritis	
Systemic Lupus Erythematosus	
Vasculitis	

GBS = Guillain-Barré Syndrome; LAIV = Live Attenuated Influenza Vaccine; TIV = Trivalent Influenza Vaccine; COPD = Chronic Obstructive Pulmonary Disease; MMR = Measles, Mumps, Rubella; IPV = Polio Vaccine

Key Question (KQ) 1 - Adults

- c. What AEs are associated with these vaccines?
 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 3. For each AE associated with a particular vaccine, what are the risk factors for the AE (including age, sex, race/ethnicity, genotype, underlying medical condition, whether a vaccine is administered individually or in a combination vaccine product, schedule of vaccine administration, adjuvants, and medications administered concomitantly)?

Our primary focus is the association of AEs with vaccination. The average severity of AEs was infrequently reported in peer-reviewed publications. Where it was reported, or where it was possible for our researchers to categorize, it is displayed in the Evidence Tables (Appendix C) for each study. Some clinical trials reported severity; most simply provided a list of AEs along with the number of patients in each group reporting them. Post-marketing studies using case-control, self-controlled case series, and multivariate risk factor analyses tended to combine all cases of a particular AE, as severity details were often unavailable or inadequate.

Results are organized by vaccine type. We first describe the findings of the 2011 Institute of Medicine (IOM) report *Adverse Events of Vaccine: Evidence and Causality*, where applicable. (Not all recommended vaccines are covered in that report.) We then describe the findings from studies published after the IOM report that met our inclusion criteria: clinical trials and cohort studies that included an unvaccinated group, followed by the results of post-marketing studies. The results of every analysis conducted in each study, including results for AEs without statistically significant association with vaccination, are displayed in the right-hand column of tables in this section. The 95% confidence intervals reflect the level of certainty.

Finally, we summarize and critique the evidence, taking into consideration the number and size of studies, study design and quality, and applicability.

Influenza vaccines

The seasonal influenza vaccine is administered in two forms: a live attenuated form, administered intranasally (LAIV), and an inactivated form (TIV), administered intramuscularly. The H1N1 or “swine flu” vaccine was administered widely during the winter of 2009-2010; we were encouraged by our expert panel to include it as well.

The IOM committee studied the two seasonal influenza vaccines. They found that evidence³¹ “convincingly supports” a causal relationship between influenza vaccine and anaphylaxis. The committee found that evidence³²⁻³⁵ “favors acceptance” of a causal relationship between two particular influenza vaccines used in Canada and oculorespiratory syndrome. The IOM committee found the evidence³⁶⁻⁴¹ “favors rejection” of a causal relationship between TIV and asthma exacerbation or reactive airway disease episodes in adults. Finally, despite finding

some studies of influenza vaccine and the following AEs, the IOM found evidence was “inadequate to accept or reject” a causal relationship: encephalitis, encephalopathy, optic neuritis, multiple sclerosis (MS) onset or relapse, Guillain-Barre Syndrome (GBS), chronic inflammatory disseminated polyneuropathy, Bell’s Palsy, onset of exacerbation of systemic lupus erythematosus (SLE), onset or exacerbation of vasculitis, polyarteritis nodosa, onset or exacerbation of arthropathy, ischemic stroke, myocardial infarction, and all-cause mortality.

We identified eight trials of influenza vaccine published after the IOM search dates. All administered some formulation of inactivated influenza vaccine; two of these studied monovalent H1N1 vaccine. The results are summarized in Table 7.

A trial in Canada⁴² included 1,348 adults (54.2% female) who received inactivated trivalent influenza vaccine at study start and then 14 days later. Odds ratios were not calculated because the study reported AEs per dose rather than per patient.

A controlled clinical trial in the US⁴³ included 7,250 adults aged 18 to 49 who received one dose of inactivated influenza vaccine. Compared to the control group, vaccinated individuals were more likely to experience arthralgia (OR 2.10, 95% CI 1.67-2.66), chills (OR 2.24, 95% CI 1.77-2.84), fatigue (OR 1.58, 95% CI 1.38-1.80), headache (OR 1.40, 95% CI 1.23-1.59), hyperhidrosis (OR 1.68, 95% CI 1.31-2.16), malaise (OR 2.02, 95% CI 1.74-2.36), myalgia (OR 3.28, 95% CI 2.80-3.85), oropharyngeal pain (OR 1.63, 95% CI 1.06-2.50), and pyrexia (OR 2.27, 95% CI 1.54-3.36).

A controlled clinical trial in the US, Finland, and Poland⁴⁴ included 11,404 adults (55% female) separated into two vaccine groups that receive one dose inactivated influenza vaccine and one placebo group. Group 1 received Agrippal and Group 2 received Optaflu. Compared to the control group, Group 1 was more likely to experience mild to moderate fever (OR 2.01, 95% CI 1.16-3.49), mild to moderate malaise (OR 1.27, 95% CI 1.06-1.52), and mild to moderate myalgia (OR 1.31, 95% CI 1.11-1.55). A trial in Italy⁴⁵ included 104 adults (45.1% female) who received inactivated influenza vaccine (Fluad) at study start and then 42 days later. No statistically significant differences in AEs between vaccinated and unvaccinated groups were reported. A trial in the US⁴⁶ included 7,611 adults (60% female, 0.7% pregnant) who received one dose of inactivated influenza vaccine (Flulaval). Compared to the unvaccinated group, vaccinated individuals were more likely to experience fever (OR 1.79, 95% CI 1.28-2.50) and myalgia/arthralgia (OR 1.98, 95% CI 1.73-2.26).

A controlled clinical trial in the US⁴⁷ included 4,648 adults (59% female, 0.8% pregnant) who received one dose of inactivated trivalent influenza vaccine (FluBlok). Compared to the unvaccinated group, vaccinated individuals were more likely to experience any pain (OR 6.69, 95% CI 5.62-7.95) and muscle pain (OR 1.59, 95% CI 1.28-1.96).

Regarding H1N1, a trial in the US⁴⁸ included 1,313 adults (57.1% female) who were divided into two groups receiving different doses (7.5 mg [Group 1] or 15 mg [Group 2]) of monovalent H1N1 vaccine at study baseline and then 21 days later. Compared to the control group, the only statistically significant finding was a protective effect against systemic AEs in Group 2 (OR 0.56, 95% CI 0.32-0.99).

Finally, a controlled clinical trial in South Africa⁴⁹ included 189 HIV+ adults (84% female) who received inactivated influenza vaccine (Mutagrip). No statistically significant differences in AEs between vaccinated and unvaccinated groups were reported.

Table 7. Vaccinated vs unvaccinated adults. Influenza vaccines

Author-Year-Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Barrett P. N. et al.,2011 ⁴³ US	Controlled Clinical Trial	4	Sample size : 7,250, Mean age: NR, Age range: 18 - 49	Influenza (inactivated), Baxter, Austria, contain 15 µg of hemagglutinin antigen from each of the three virus strains - A/Brisbane/59/2007 (A/H1N1), A/Uruguay/716/2007(A/Brisbane/10/2007-like) (A/H3N2), and B/Florida/4/2006 (B). The three virus strains were egg-derived wild-type strains provided by the National Institute for Biological Standards and Control (Potters Bar, UK)., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Intramuscular	Dose1: 0 Days	Arthralgia: OR 2.103 (1.666-2.655)** Chills: OR 2.239 (1.766-2.838) ** Cough: OR 1.427 (0.862-2.361) ** Fatigue: OR 1.577 (1.382-1.8) ** Headache: OR 1.396 (1.229-1.587) ** Hyperhidrosis: OR 1.678 (1.306-2.155) ** Malaise: OR 2.024 (1.736-2.36) ** Myalgia: OR 3.281 (2.799-3.846) ** Oropharyngeal pain: OR 1.626 (1.058-2.5) ** Pyrexia: OR 2.271 (1.537-3.355) **
Frey S. et al.,2010 ⁴⁴ US, Finland, Poland	Controlled Clinical Trial	4	Sample size : 11,404, Mean age: 33, Age range: 18 - 49, Percent female: 55%	Influenza (inactivated), Agrippal, Novartis, 15 mg of hemagglutinin per 0.5-mL dose of each virus strain recommended for the 2007–2008 Northern Hemisphere influenza season: A/Solomon Islands/3/2006 (H1N1)–like, A/Wisconsin/67/2005 (H3N2)–like, and B/Malaysia/2506/2004–like, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Intramuscular	Dose1: 0 Days	Headache (mild-moderate): OR 1 (0.881-1.134) Arthralgia (mild-moderate): OR 0.961 (0.722-1.279) Chills (mild-moderate): OR 1 (0.813-1.23) Death: OR 1.061 (0.066-16.969) Fatigue (mild-moderate): OR 1.112 (0.96-1.289) Fever (mild-moderate): OR 2.01 (1.159-3.487) ** Malaise (mild-moderate): OR 1.27 (1.061-1.521) ** Myalgia (mild-moderate): OR 1.314 (1.112-1.553) ** Sweating (mild-moderate): OR 1 (0.749-1.335) Withdrawal after AE: OR 1.061 (0.066-16.969)
Iorio A. et al.,2010 ⁴⁵ Italy	Controlled Clinical Trial	4	Sample size : 104, Mean age: 71, Age range: 18 - NR, Percent female: 45.1%	Influenza (inactivated), Fluad, Novartis, Fujian/411/02 (influenza A[H3N2]),NewCaledonia/20/99 (influenza A[H1N1]), and Shanghai/361/02 (influenzaB), Adjuvant: Other adjuvant, Preservative: Not reported, Delivery: Intramuscular	Dose1: 0 Days Dose2: 42 Days	Nosebleeds: OR 0.743 (0.162-3.403)

Author-Year-Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Jackson L. A. et al., 2010 ⁴⁶ US	Controlled Clinical Trial	7	Sample size : 7,611, Mean age: 32.7, Age range: 18 - 49, Percent female: 60%, Percent pregnant: Percent Pregnant: 0.7%	Influenza (inactivated), Flulaval, ID Biomedical Corporation of Quebec (trademarked, 15 ig of hemagglutinin (HA) antigen of each recommended influenza strain.) Antigens for Season 1 (2005-2006) were A/New Caledonia/20/1999 (H1N1), A/New York/55/2004 (H3N2, A/California/7/2004-like), and B/Jiangsu/10/2003 (B/Shanghai/361/2002-like). Antigens for Season 2 (2006-2007) were A/New Caledonia/20/1999 (H1N1) virus, A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Not reported	Dose1: 0 Days	Chest tightness or difficulty breathing: OR 1.218 (0.938-1.581) Cough: OR 1.17 (0.982-1.396) Fever: OR 1.786 (1.278-2.496)** Myalgia/arthralgia: OR 1.979 (1.732-2.262)** Sore throat, hoarseness, or pain swallowing: OR 0.949 (0.809-1.112) Swelling of the face: OR 1.4 (0.915-2.143)
Langley J. M. et al., 2011 ⁴² Canada	Controlled Clinical Trial	4	Sample size : 1,348, Mean age: 37.1, Age range: 18 - 64, Percent female: 54.2%	Influenza (inactivated), NR, Contains equal parts of three monovalent egg-grown, formalin-inactivated influenza antigens formulated with OMPs of N. meningitidis serogroup B strain 8047 at an initial ratio of OMP to hemagglutinin (HA) of 4:1. After diafiltration to removed detergents necessary to keep the OMPs in stable solution in the absence of antigen, the overall total protein to HA ratio in the final vaccine product is 2.5 to 5:1. The trivalent vaccine stock contained HA from each of A/New Caledonia/20/99 [H1N1], A/Panama/2007/99 [H3N2] and B/Shangdong/7/97 [H1N1, Adjuvant: Not Reported, Preservative: Thimerosal, Delivery: Intranasal	Dose1: 0 Days Dose2: 14 Days	Not calculable

Author-Year-Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Talaat K. R. et al.,2010 ⁴⁸ United States	Controlled Clinical Trial	5	Sample size : 1,313, Mean age: 56.5, Age range: 18 – 93, Percent female: 57.1%	Influenza – monovalent H1N1, CSL Limited, The 7.5-mg doses were supplied in prefilled syringes that contained 7.5 mg of HA in 0.25 mL of thimerosal-free diluent., Adjuvant: Adjuvant Free, Preservative: Other, Delivery: Intramuscular	Dose1: NR Dose2: 21 Days	Any systemic AE (Dose 1): OR 1.176 (0.701-1.974) Any systemic AE (Dose 2): OR 0.562 (0.32-0.987) Chills(Dose 1): OR 1 (0.208-4.801) Fever (Dose 1): OR 0.99 (0.11-8.922) Headache (Dose 1): OR 1.428 (0.719-2.835) Headache (Dose 2): OR 1 (0.464-2.154) Malaise (Dose 1): OR 1 (0.445-2.247) Malaise (Dose 2): OR 0.704 (0.341-1.452) Myalgia (Dose 1): OR 2.136 (0.885-5.159) Myalgia (Dose 2): OR 0.645 (0.29-1.437) Nausea (Dose 1): OR 1 (0.326-3.067) Nausea(Dose 2): OR 3.062 (0.39-24.025) Vomiting(Dose 1): OR 0.495 (0.089-2.744) Vomiting(Dose 2): OR 0.497 (0.045-5.549)
Treanor J. et al.,2011 ⁴⁷ USA	Controlled Clinical Trial	3	Sample size : 4,648, Mean age: 32.5, Age range: 18 – 55, Percent female: 59%, Percent Pregnant: 0.8%	Influenza (inactivated), FluBlok, NR, The trivalent vaccine contained 45 mcg of each purified rHA0 derived from the A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 influenza viruses recommended for the 2007–2008 influenza season formulated with 0.005% Tween®-20 in 10mM sodium phosphate buffer pH 7.0 ± 0.4 without a preservative, Adjuvant: Not Reported, Preservative: Preservative Free, Delivery: Intramuscular	Dose1: 0 Days	Bruising: OR 1.258 (0.89-1.778) Fatigue or lack of energy: OR 1.004 (0.853-1.182) Fever (=100.4): OR 1.395 (0.665-2.928) Headache: OR 0.964 (0.821-1.131) Joint pain: OR 1.056 (0.779-1.432) Muscle pain: OR 1.585 (1.283-1.958) ** Nausea: OR 1.173 (0.903-1.524) Pain: OR 6.686 (5.62-7.953) ** Shivering or chills: OR 0.968 (0.692-1.354)
Madhi S. A. et al.,2011 ⁴⁹ South Africa	Controlled Clinical Trial	3	Sample size : 189, Mean age: 36.3, Percent female: 84%, Condition: HIV	Influenza (inactivated), Mutagrip, Sanofi, 15ugm each (per 0.5 ml) A/Solomon Islands/3/2006 (IVR-145), A/Brisbane/10/2007(IVR-147),B/Florida/4/2006, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Intramuscular	Dose1: NR Dose2: NR Dose3: NR	Arthralgia: OR 0.694 (0.151-3.19) Fatigue: OR 0.179 (0.021-1.564) Headache: OR 0.936 (0.184-4.762) Itching: OR 2.872 (0.293-28.127) Lump formation: OR 0.464 (0.041-5.201) Myalgia: OR 1.42 (0.232-8.7) Pain: OR 1.955 (0.568-6.73) Redness: OR 1.895 (0.169-21.26)

NR = Not reported; OR = Odds Ratio; CI = Confidence Interval; AE = Adverse Event; HA = Hemagglutinin; OMPs = Outer Membrane Proteins;

We identified 15 post-marketing studies of influenza vaccines in adults published after the IOM report; they are displayed in Table 8. The vast majority investigated the relationship between vaccination and one adverse event / condition of particular interest. A few assessed whether vaccination had a protective effect against cardiovascular events in the elderly. Finally, some studied the effect of vaccine in adults with pre-existing conditions such as MS, renal disease or COPD.

Guillain–Barré Syndrome (GBS). Three studies evaluated whether the 2009 pandemic H1N1 vaccine was associated with an increased risk of developing Guillain-Barre Syndrome. Greene et al. 2012⁵⁰ performed separate self-controlled risk interval and case-centered analyses among members of eight managed care organizations (MCOs) in the US who received 1.48 million doses of monovalent inactivated pandemic H1N1 vaccine (MIV) and 1.72 million doses of TIV. Altogether 13 confirmed cases of Guillain-Barre Syndrome were identified after receipt of MIV and 16 after receipt of TIV. Statistically significant increases in GBS risk following receipt of MIV were suggested by the self-controlled risk interval analysis (RR = 4.4 [95% CI: 1.3, 14.2]; risk difference = 5.0 per million MIV doses [95% CI: 0.5 per million, 9.5 per million]). The case-centered analysis found that the OR for having illness onset inside of the 42-day risk period versus outside of that period was 2.0 (95% CI: 0.5, 8.1). The risk difference was 3.4 per million MIV doses (95% CI: -6.4 per million, 7.6 per million). No increased risk for developing GBS was associated with receipt of seasonal trivalent inactivated influenza vaccine (RR 1.3, 95% CI: 0.5, 3.8), so case-centered analysis was not conducted. In contrast, in a case-control study of 104 cases of GBS and 1,198 matched controls, Dieleman et al. 2011⁵¹ failed to find any relationship between receipt of influenza A Pandemic (H1N1) 2009 vaccines and development of GBS in the UK, Netherlands, and Sweden (OR 1.0, 95% CI: 0.3, 2.7). Similarly, in a prospective case-control study of 1,225 subjects in France, Grimaldi-Bensouda et al. 2011⁵² were unable to demonstrate any statistically significant association between receipt of pandemic and/or seasonal influenza vaccine and the development of GBS in eight separate analyses (see Table 7 for statistics).

Other neurological conditions. Other neurological sequelae following MIV vaccination were evaluated in two studies. Using a self-controlled case series method, Farez et al. 2012⁵³ assessed whether receipt of MIV was associated with relapses of MS. No significant relationship was found in this study of 137 patients (98% of whom were receiving interferon-beta and 25% glatiramer acetate) with previously diagnosed MS (for 30-day risk period, OR 0.86, 95% CI: 0.20, 3.62). Tanner et al. 2012⁵⁴ performed a case-control study of 150 patients with spasmodic dysphonia (cases) and 136 patients with other structural, neurological, and functional voice disorders (controls). There was no difference in post-vaccine incidence of spasmodic dysphonia among persons who did or did not self-report receipt of swine influenza vaccine (OR 2.1, 95% CI 0.9, 5.0), whereas persons who did not know whether they had received swine influenza vaccine were more likely to have spasmodic dysphonia than were persons who reported not receiving the vaccine.

Cardiovascular. The relationship between receipt of influenza vaccination and cardiovascular and cerebrovascular complications was assessed in four studies. In a self-controlled case series of 20,486 adults who had had their first myocardial infarction and 19,063 adults with their first stroke, Smeeth et al. 2004⁵⁵ found that receipt of influenza vaccine was associated with a decreased rate of first episode of both myocardial infarction and stroke in the first 28 days after vaccination. Similarly, there was a decreased incidence of recurrent myocardial infarction in the first 3 days after vaccination and of recurrent stroke at all times periods up to 91 days after vaccination, although this difference did not reach statistical significance 4 – 7 days after vaccination. Administration of tetanus or polysaccharide pneumococcal vaccination was not associated with any subsequent change in the age-adjusted rates of first and recurrent myocardial infarction or stroke. The study assessed the

protective effect of the vaccine; no other AEs were evaluated. Similarly, in a matched case-control study of 16,012 persons with myocardial infarction and 62,964 controls, Siriwardena et al. 2010⁵⁶ found that receipt of influenza vaccine within the previous year was significantly associated with lower odds of acute myocardial infarction (OR 0.83, 95% CI 0.80, 0.88). A multi-center study including 40 countries⁵⁷ following 31,546 subjects, aged 55 and above, with a history of vascular disease or diabetes with documented end-organ damage between 2004 and 2007 concluded that although initial analyses suggested that influenza vaccination was associated with reduced risk of major adverse vascular events during influenza seasons when the influenza vaccine matched the circulating virus, sensitivity analyses revealed that risk of bias remained. The primary outcome was a composite of death resulting from cardiovascular causes, myocardial infarction, or stroke during these four influenza seasons and the data were modeled using logistic regression and adjusted using propensity scores for influenza vaccination (demographics, body mass index, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination, and use of a variety of medications). Finally, in a self-controlled case series analysis, Gwini et al. 2011⁵⁸ found that the incidence of post vaccination myocardial infarction was reduced at time intervals extending up to 59 days after receipt of vaccine.

Hematological. Two studies addressed the relationship between receipt of influenza vaccine and the development of hematologic diseases. In a self-controlled case series conducted by Garbe et al. 2012,⁵⁹ two different statistical models revealed a significant association between prior influenza vaccination and new onset immune thrombocytopenia (OR 4.0, 95% CI 1.5, 9.6) in a model adjusted for age, sex, and multiple medications). In a self-controlled case series, Ambridge et al. 2011⁶⁰ found no relationship between receipt of influenza vaccine by adults with sickle cell disease and subsequent hospitalization for complications of sickle cell disease (OR 0.92, 95% CI 0.66, 1.28).

Regarding vaccination of dialysis patients, Gilbertson et al. (2011)⁶¹ studied 118,533 adult US Medicare patients who initiated hemodialysis before August 1, 2003 and were alive through October 31, 2005. Subjects were followed between 2005 and 2006 for data on health outcomes. The analysis adjusted for patient demographics, primary cause of end stage renal disease, duration of dialysis, existing comorbidities, and influenza vaccination. Results indicate that vaccination with influenza (RR 0.77, 95% CI 0.73, 0.81) or pneumococcal (RR 0.94, 95% CI 0.90, 0.98) vaccines was associated with lower mortality. In a retrospective cohort analysis of 51,730 adult Medicare patients with renal transplants, Hurst et al. 2011⁶² found that influenza vaccination in the first year after transplant was associated with lower risk of both subsequent allograft loss (adjusted hazard ratio, 0.77, 95% CI 0.69, 0.85) and death (adjusted hazard ratio, 0.82, 95% CI 0.76, 0.89).

Other. In a single retrospective matched cohort study of patients with chronic obstructive pulmonary diseases (COPD), Ting; 2011⁶³ found no change in the frequency of COPD exacerbations during the 14 days following vaccination.

General. A single study of the safety of live attenuated influenza vaccine (LAIV) was identified (Baxter et al. 2012).⁶⁴ In this retrospective cohort study of 21,340, 18,316, and 21,340 adults 18 to 49 years of age, who received LAIV, TIV, or no vaccine, respectively, the rate of hospitalization or death due to any condition within 180 days of vaccination with LAIV was significantly lower than with TIV or no vaccine. The incidence rate for any serious adverse event within 21 days and 42 days of vaccination with LAIV was lower than for no vaccination. The pattern of medically attended events did not suggest any safety signal associated with LAIV.

Summary

Based on the entire body of available evidence, including the IOM report, clinical trials, and post-licensure studies that met our inclusion criteria, we make the following conclusions regarding key adverse events.

We concur with the IOM's conclusion of a causal relationship between influenza vaccines and anaphylaxis in persons who may be allergic to ingredients. Anaphylactic reactions can be severe if not treated immediately.

The IOM conclusion favoring acceptance of a causal relationship between influenza vaccines and oculorespiratory syndrome was based on a specific vaccine used in Canada from 2001 to 2003; there is no basis for current concern in the US.

Based on many clinical trials, there is high strength of evidence that influenza vaccines currently used in the US are associated with arthralgia, myalgia, malaise, fever, and pain in the short-term in adults. These AEs are not considered serious; risk factors are not discussed in the trials. Clinical trials have found no association between influenza vaccines currently used in the US and serious adverse events (SAEs). (Data for AEs without significant association are displayed in the tables.)

Post-licensure studies with strong study designs reported inconsistent findings regarding seasonal influenza vaccines, including those containing H1N1 strains, and Guillain-Barré Syndrome (GBS) in adults. However, as this report was being finalized, a meta-analysis of data from six US surveillance systems was published;⁶⁵ it found a small risk of GBS (IRR 2.35, 95% CI 1.42,4.01) equivalent to about 1.6 excess cases per million vaccines, with monovalent H1N1 vaccine. Thus, strength of evidence is high for H1N1 vaccine.

Post-licensure studies with strong study designs have found inconsistent evidence associating influenza vaccines with onset or exacerbation of MS in adults. Strength of evidence is insufficient to determine an association.

Post-licensure studies with strong study designs have shown that influenza vaccines are not associated with increased risk of cardiovascular or cerebrovascular events in the elderly. Many studies report a protective effect. Strength of evidence is high, for lack of risk for these AEs.

Two large post-licensure studies with strong study designs have shown that influenza vaccines are not associated with increased risk of SAEs in renal patients. Strength of evidence is moderate.

Table 8. Post-marketing studies of influenza vaccines in adults

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Greene et al. 2012 ⁵⁰	N=1.48 million doses Monovalent inactivated H1N1 and 1.72 million doses TIV; 8 US MCOs	Monovalent inactivated influenza vaccine (MIV) and seasonal trivalent inactivated influenza vaccine (TIV) during the 2009-2010 season	Case-centered analyses by stratum of onset date, age, sex, VSD site)	Relative Risk (self-controlled risk analysis) of Guillain-Barré Syndrome (GBS), RR, 95% CI MIV Confirmed GBS 4.4 (1.3, 14.2) TIV Confirmed GBS: 1.3 (0.5, 3.8) Case-centered: The odds ratio for having illness onset inside of the 42-day risk period versus outside of that period was 2.0 (95% CI: 0.5, 8.1).	Not reported
Dieleman et al. 2011 ⁵¹	N=1,302 (104 cases, 1198 matched controls); Location=Denmark, France, the Netherlands, Sweden, and the UK; Age=50 (22) (mean (SD)); Setting=VAESCO (Vaccine Adverse Events Surveillance and Communication) consortium (network of organizations - public health institutes, regulatory agencies, and academic research centers) in Europe dedicated to improving monitoring of safety of vaccines after licensing	Pandemic influenza A (H1N1) 2009 vaccines	Influenza-like illness (ILI) or upper respiratory tract infection, and other vaccinations (especially seasonal influenza vaccination). Cases/controls matched on age (plus or minus one year), sex, index date, and GP practice in Netherlands and UK	Netherlands, UK, Sweden: Pooled OR (95% CI) Guillain-Barre syndrome H1N1: 1.0 (0.3 to 2.7) Netherlands, UK Pooled OR (95% CI) Guillain-Barre syndrome H1N1: 0.7 (0.2 to 2.5) Restricted to people without ILI/Upper respiratory tract infection Netherlands, UK, Sweden Pooled OR (95% CI) Guillain-Barre syndrome H1N1: 1.2 (0.4 to 4.0) Netherlands, UK Pooled OR (95% CI) Guillain-Barre syndrome H1N1: 1.2 (0.3 to 5.8)	Not reported
Grimaldi-Bensoud	N=1,225; Location=France;	Influenza vaccines (seasonal and	Cases/controls matched by age, gender, index date	OR, Guillain-Barré Syndrome All influenza vaccines (A/H1N1 +	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
a et al. 2011 ⁵²	Age=Cases/Controls, Mean (SD): 48.6 (18.0)/50.7 (18.1); Setting=Guillain-Barré cases drawn from all university and major regional hospital centers in metropolitan France known to have a large neurology clinic and centers treating neurological disease in children; Controls from registry of general practice patients across France	A/H1N1)	(calendar month), and region Receipt of other vaccines during the same time window, receipt of influenza vaccine in the past (before the time window considered), family history of autoimmune diseases, number of physician consultations in the previous year (0–2, 3–6, 7–12, or >=13), antibiotic or antiviral treatment in the previous 2 months, use of antipyretic agents in the previous 2 months.	seasonal) First 6 weeks: 1.22 (0.45-3.32) 7 weeks to 3 months: 0.66 (0.27-1.65) 4 months to 6 months: 0.80 (0.34-1.88) Seasonal influenza vaccine only First 6 weeks: 1.30 (0.41-4.12) 7 weeks to 3 months: 0.60 (0.23-1.60) 4 months to 6 months: 0.69 (0.29-1.66) Influenza A/H1N1 vaccine only First 6 weeks: 0.92 (0.11-7.55) 7 weeks to 3 months: 1.08 (0.09-13.15)	
Farez et al. 2012 ⁵³	N=137 Multiple Sclerosis patients; Location=Argentina; Age=37 +/-8 years (mean)	Monovalent H1N1 or trivalent vaccine containing both H1N1 and seasonal influenza strains	None reported	OR for MS relapse 30-day risk period: 0.86 (95% CI 0.20–3.62) 60-day risk period: 0.61 (95% CI 0.18–2.02) 90-day risk period: 0.51 (95% CI 0.18–1.47)	Not reported
Tanner et al. 2012 ⁵⁴	N=286; Location=Utah; Age=20.4 to 92.5; Setting=The University of Utah Voice Disorders Center	Swine flu of any type from any year	Age, sex, race/ethnicity	OR (95%) CI for Spasmodic Dysphonia Vaccinated v. Non-vaccinated: 2.1 (0.9-5.0) Don't Know v. Non-vaccinated: 2.3 (1.3-4.1)	Not reported
Johnston et al. 2012 ⁵⁷	N=31,546; Location=40 countries; Setting=Participants in the ONTARGET TRANSCEND trials: at least 55 years old and a history of vascular disease or diabetes with document end-organ	Influenza, pneumococcal	Adjusted by propensity score for influenza vaccination (body mass index, age, sex, ethnicity, education, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination), history of coronary artery disease, diabetes mellitus,	Association Between Influenza Vaccination and Risk of Major Adverse Vascular Events During the Influenza Season Cohort OR, 95% CI 2003-2004: 0.96 (0.73–1.27) 2004-2005: 0.62 (0.50–0.77) 2005-2006: 0.69 (0.53–0.91) 2006-2007: 0.52 (0.42–0.65)	Not given

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
	damage		hypertension, stroke, admission to a nursing home, or use of aspirin, beta-blocker, lipid-lowering drug, angiotensin-converting enzyme inhibitor, or angiotensin II inhibitor	<p>Association Between Influenza Vaccination and Risk of the Major Adverse Vascular Events During the Non-influenza Season</p> <p>Cohort 2003-2004: 0.81 (0.61–1.09) 2004-2005: 0.64 (0.50–0.83) 2005-2006: 0.74 (0.56–0.98) 2006-2007: 0.50 (0.38–0.67)</p> <p>Association Between Influenza Vaccination and Risk of Non-cardiovascular Death During the Influenza Season</p> <p>Cohort 2004-2005 Non-cardiovascular deaths: 0.26 (0.16–0.40) Cancer deaths: 0.20 (0.10–0.39) Deaths resulting from other causes: 0.33 (0.18–0.60)</p> <p>2005–2006 Non-cardiovascular deaths: 0.21 (0.10–0.46) Cancer deaths: 0.27 (0.10–0.69) Deaths resulting from other causes: 0.14 (0.03–0.58)</p> <p>2006-2007 Non-cardiovascular deaths: 0.27 (0.18–0.41) Cancer deaths: 0.17 (0.10–0.31) Deaths resulting from other causes: 0.47 (0.25–0.86)</p>	
Smeeth et al. 2004 ⁵⁵	N=20,486 adults with first MI and 19,063 with first stroke who received influenza immunization in UK	Influenza, pneumococcal	Age	<p>Incidence ratios of first disease</p> <p>Influenza vaccine Myocardial Infarction 1-3 days: 0.75 (0.60–0.94) 4-7 days: 0.68 (0.56–0.84) 8-14 days: 0.73 (0.63–0.85) 15-28 days: 0.87 (0.79–0.96) 29-91 days: 1.03 (0.98–1.08)</p>	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
				Stroke 1-3 days: 0.77 (0.61–0.96) 4-7 days: 0.72 (0.59–0.88) 8-14 days: 0.84 (0.73–0.96) 15-28 days: 0.88 (0.80–0.97) 29-91 days: 1.01 (0.96–1.06) Incidence ratios recurrent disease event Influenza vaccine Myocardial Infarction 1-3 days: 0.34 (0.19–0.61) 4-7 days: 0.77 (0.55–1.09) 8-14 days: 0.93 (0.73–1.18) 15-28 days: 0.97 (0.82–1.16) 29-91 days: 0.97 (0.88–1.06) Stroke 1-3 days: 0.56 (0.35–0.89) 4-7 days: 0.74 (0.52–1.05) 8-14 days: 0.72 (0.55–0.94) 15-28 days: 0.69 (0.57–0.85) 29-91 days: 0.79 (0.71–0.87)	
Siriwardena et al. 2010 ⁵⁶	N=78,706 (16,012 cases of myocardial infarction (MI), 62,964 controls); Location=UK; Age=40 to >=65; Setting=United Kingdom General Practice Research Database (GPRD), an extensively validated computerized database, representative of and comprising 5% of the population of England and Wales.	Influenza; pneumococcal (study didn't specify types)	Model 1 adjusted for asthma or chronic obstructive pulmonary disease, chronic heart disease, stroke or transient ischemic attack, diabetes, splenectomy, chronic liver disease, chronic renal failure, immunosuppression and HIV, hyperlipidemia, family history of acute myocardial infarction, peripheral vascular disease, hypertension, smoking status, treatment with acetylsalicylic acid, treatment with statins, treatment with antihypertensives, and general practice consultations. Each type of vaccination was adjusted for the other type. Second set of models	OR (95% CI) of acute MI Influenza vaccination within previous year: Model 1: 0.81 (0.77–0.85) Model 2: 0.83 (0.80–0.88)	None given, but subgroup results shows for the following categories: Influenza Vaccination in preceding yr: < 65 yr: Model 1: 0.81 (0.73–0.90) Model 2: 0.83 (0.75–0.92) ≥ 65 yr: Model 1: 0.79 (0.75–0.83) Model 2: 0.82 (0.78–0.86) Time since last vaccination at index date, months: 0–3 months: Model 1: 0.80 (0.74–0.86) Model 2: 0.84 (0.80–0.94) 3–6 months: Model 1: 0.82 (0.76–0.89) Model 2: 0.86 (0.85–0.99) 6–12 months: Model 1: 0.87 (0.81–0.94)

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
			(Model 2) adjusted for all of the above		<p>Model 2: 0.91 (1.06–1.24) 12–60 months: Model 1: 1.12 (1.03–1.21) Model 2: 1.15 (0.88–1.20) ≥ 60 months: Model 1: 0.96 (0.82–1.13) Model 2: 1.03</p> <p>Within-season vaccination Yes: Model 1: 0.80 (0.76–0.84) Model 2: 0.83 (0.79–0.87) Early within-season (Sept. to mid-Nov.): Model 1: 0.79 (0.75–0.83) Model 2: 0.82 (0.78–0.86) Late within-season (mid-Nov. to Feb.): Model 1: 0.88 (0.79–0.97) Model 2: 0.90 (0.82–1.00) Vaccination in previous yr, by month of index date: Sept. to Nov.: Model 1: 0.75 (0.68–0.83) Model 2: 0.77 (0.70–0.85) Dec. to Mar.: Model 1: 0.86 (0.79–0.93) Model 2: 0.88 (0.82–0.95) Apr. to Aug.: Model 1: 0.80 (0.73–0.86) Model 2: 0.84 (0.77–0.90)</p>
Gwini et al. 2011 ⁵⁸	N=8,180 cases of first acute myocardial infarction; Location=UK; Age=>=40 years;	Influenza	Seasonality	Incidence Rate Ratio, Acute MI Post-vaccination intervals 1-14 days: 0.68 (0.6–0.78) 15-28 days: 0.75 (0.66–0.86) 29-59 days: 0.82 (0.75–0.90) 60-90 days: 0.96 (0.87–1.07) 91-120 days: 0.98 (0.89–1.09) 121-180 days: 1.02 (0.95–1.10)	Not reported
Garbe et al. 2012 ⁵⁹	N=1,200 (outpatient + inpatient). Influenza results presented just for outpatients where N=861;	Influenza vaccine (Pneumococcal and poliomyelitis vaccine also assessed as	Model 1: age and sex (“single drug assessment”) Model 2: age, sex and all drugs that were significant	OR (95% CI) idiopathic thrombocytopenic purpura (ITP) Influenza, outpatient cases and controls: Model 1: 3.8 (1.5–9.1)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
	Location=Berlin, Germany; Age=18-92; Setting=Berlin hospitals, hematological practices, and laboratories	causing 1 case each but ORs were not given.)	in the single drug assessment ("joint drug assessment")	Model 2: 4.0 (1.5–9.6)	
Ambridge et al. 2011 ⁶⁰	N=348 adults with sickle cell disease in 8 MCOs in the US; (Vaccine Safety Datalink (VSD) cohort)	Influenza	Stratification by sex and age, adjustment for month within season	Incidence rate ratios for sickle cell hospitalization All: 0.92 (0.66, 1.28)	Males: 1.00 (0.59, 1.72), Females 0.87 (0.57, 1.31), 18-49 yrs.: 0.84 (0.57, 1.22), 50-64 yrs.: 1.51 (0.72, 3.18), >=65 yrs.: 0.94 (0.10, 8.55),
Gilbertson et al. (2011) ⁶¹	N=118,533 Medicare patients who initiated hemodialysis before August 1, 2003 and were alive through October 31, 2005; Location= US Age=>=18 years;	Influenza	Patient demographics, doesn't specify but variables assessed include age, sex, race, primary cause of end-stage renal disease, dialysis duration, comorbid conditions.	Relative risk of mortality Influenza vaccine (both seasons): 0.77 (0.73–0.81)	Vaccine associated with lower mortality. Higher risk of mortality if older, longer on dialysis, have comorbid conditions.
Hurst et al. 2011 ⁶²	N=51,730 adult Medicare patients with renal transplant; Location=US; Age=>=65 years; 9,678 had claims for influenza vaccine in the first year post transplant	Influenza	Factors known to be independently associated with allograft loss (recipient age, black race, PRA 20%, dialysis vintage, diabetes mellitus, congestive heart failure, ischemic heart disease, tobacco use, HLA matching, donor age of 50 years, donor black race, deceased-donor transplant, expanded criteria donor, delayed graft function, cold ischemic time of 24 hours, year of transplant, and induction/discharge immunosuppression). Others not specified for the relevant model but could include: older age, diabetes, later year of transplant, and tacrolimus	Vaccination in the first year after transplant was associated with lower risk of subsequent allograft loss and death Adjusted hazard ratio Allograft loss: 0.77 (0.69-0.85) Death: 0.82 (0.76-0.89) Acute rejection in the first year was not associated with vaccination in the first 6 or 12 months after transplant Adjusted odds ratio Rejection in first 6 mo: 1.00 (0.88-1.14), Rejection in first 12 mo: 0.97 (0.89-1.07)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
			or mycophenolate at discharge		
Ting et al. 2011 ⁶³	586 patients with moderate to severe COPD identified in COPD Registers of 6 general practices in North Derbyshire UK. Age range 37-89 (median 68)	Influenza	Environmental factors (weather, prevalence of respiratory viral pathogens)	In the 14 days following vaccination, the control group had 21 COPD exacerbations cf. 11 in the vaccinated group OR 0.52 (95% CI 0.29, 1.14)	Not reported
Baxter et al. 2012 ⁶⁴	Sample size: 60,996; Location: US; Age: 18-49; Setting: Kaiser Permanente Managed Care Health Plans	Ann Arbor Strain LAIV	Adjusted for: Matching factors, seasonal changes in background rates	The rate of hospitalization or death due to any condition within 180 days of vaccination with LAIV was lower than with TIV (1.46 vs. 9.10) or no vaccine (1.46 vs. 3.36). The incidence rate for any serious adverse event (SAE) within 21 days and 42 days of vaccination with LAIV was lower compared to no vaccination.	Not reported

MCOs = Managed Care Organizations; MIV = Monovalent Inactivated Influenza Vaccine; TIV = Trivalent Inactivated Influenza Vaccine; GBS = Guillain-Barré Syndrome; OR = Odds Ratio; CI = Confidence Interval; AE = Adverse Event; SAE = Serious Adverse Events; SD = Standard Deviation; VAESCO = Vaccine Adverse Events Surveillance and Communication; MS = Multiple Sclerosis; MMR = Measles, Mumps, Rubella Vaccine; GPRD = General Practice Research Database; Yr(s) = Year(s); MI = Myocardial Infarction; ITP = Thrombocytopenic Purpura; VSD = Vaccine Safety Datalink; Mo = Month; PRA = Plasma Renin Activity; HLA = Human Leukocyte Antigens; COPD = Chronic Obstructive Pulmonary Disease; LAIV = Live attenuated influenza vaccine

Pneumococcal vaccines

Pneumococcal vaccines were not covered by the IOM report.

We found no placebo controlled trials of currently available pneumococcal polysaccharide vaccine. We did find trials of current versions versus old versions (i.e. PCV13, PCV7), however those studies were excluded because they had no unvaccinated comparison group.

Six post-marketing studies in adults were identified; all studied the relationship between pneumococcal polysaccharide vaccine and occurrence of cardiovascular or cerebrovascular disease. Results are displayed in Table 9. No other case-control study, self-controlled case series, or multivariate analysis focused on pneumococcal vaccine alone.

Cardiovascular and cerebrovascular. In a prospective cohort study of 84,170 men aged 45 to 69 years, Tseng et al. 2010⁶⁶ found that administration of pneumococcal vaccine was not associated with reduced risk adjusted for propensity score of stroke (OR 1.14, 95% CI 1.00, 1.31) and of myocardial infarction (OR 1.09, 95% CI 0.98, 1.21). In contrast, in a prospective cohort of 6,171 subjects, Eurich et al. 2012⁶⁷ showed that administration of pneumococcal polysaccharide vaccine was associated with a decreased rate of the composite outcome of death or acute coronary syndrome-related hospitalization or of hospitalization due to acute coronary syndrome alone. Several other studies did not show a protective effect of pneumococcal vaccination for the occurrence of myocardial infarction (Siriwardena et al. 2010; Vila-Corcoles et al. 2012; Smeeth et al 2004).^{55, 56, 68} Finally, in a multi-center (40 countries) study, Johnston et al. (2012)⁵⁷ followed 31,546 subjects, aged 55 and above, and with a history of vascular disease or diabetes with documented end-organ damage between 2004 and 2007. The data were modeled using logistic regression and adjusted using propensity scores for influenza vaccination (demographics, body mass index, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination, use of a variety of medications). There was no association between pneumococcal vaccination and the risk of major vascular events during any of the influenza seasons. There were significant associations between vaccination and lower risk of non-cardiovascular deaths, cancer deaths, and deaths from other causes in all three (2004/05, 2005/06, 2006/07) cohorts studied.

Summary

Pneumococcal vaccines were not covered by the IOM report. We found no placebo-controlled trials of the currently available US versions in adults. Post-licensure studies focused on association of pneumococcal polysaccharide vaccines with cardiovascular and cerebrovascular events in older adults. Results consistently found vaccination was not associated with increased risk of these events. Strength of evidence is high. However, results were inconsistent as to whether these vaccines have a protective effect against these adverse events; strength of evidence is inconsistent.

No other adverse events or medical conditions were studied in case-control, self-controlled case series, or multivariate risk factor analyses regarding pneumococcal vaccines in adults.

Table 9. Post-marketing studies of pneumococcal vaccines in adults

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Tseng et al. 2010 ⁶⁶	N=84,170; Location=CA; Age=45-69 years; Setting=Kaiser Permanente Northern and Southern California health plans (California Men's Health Study)	Pneumococcal	Propensity score was created: age, race/ethnicity, region (northern vs. southern California Kaiser Permanente), household income, education, BMI, cigarette smoking, physical activity level, sedentary for more than 6.5 hours per day outside of work, alcohol consumption, number of influenza vaccines received, calorie intake, fat intake, fruit and vegetable consumption, history of diabetes, history of high blood pressure, history of high cholesterol, history of peripheral artery disease, history of other heart diseases, history of stroke, history of acute MI, and the log scale transformed number of outpatient visits in last 5 years	Adjusted hazard ratio Pneumococcal Vaccination and Incidence of MI and Stroke Acute MI All men: 1.09 (0.98-1.21) Stroke All men: 1.14 (1.00-1.31)	Association of Pneumococcal Vaccination and Incidence of MI and Stroke Age, years <65: 1.23 (1.08-1.40) >=65: 0.89 (0.80-1.01) High-risk groups Current smokers: 1.11 (0.83-1.47) Diabetes: 1.04 (0.87-1.24) Hypertension: 1.10 (0.97-1.25) Low-risk group: 0.98 (0.35-2.73), p=0.97 Influenza vaccine 0: 1.10 (0.70-1.72) 1-10: 1.10 (0.97-1.26) >10: 1.00 (0.83-1.21)
Eurich et al. 2012 ⁶⁷	N=6,171; Location=Edmonton (Alberta, Canada); Age=mean 59 years; Setting=Population-based cohort of adults presenting with community-acquired pneumonia (CAP) in Edmonton	Pneumococcal polysaccharide vaccination (PPV)	Pneumonia severity based on the PSI; comorbidities including chronic obstructive pulmonary disease, diabetes, ischemic heart disease (IHD); functional status, smoking status and cardiovascular and other medications Authors also completed a propensity (to receive PPV) score analysis	Adjusted HRs for fatal and non-fatal ACS events within 90 days according to pneumococcal vaccination status Primary analysis Death or ACS-related hospitalization: 0.42 (0.27 to 0.66) Death: 0.92 (0.32 to 2.63) Hospitalization due to ACS: 0.35 (0.21 to 0.57) Propensity score analysis Death or ACS-related Hospitalization: 0.46 (0.28 to 0.73) Death: 1.51 (0.42 to 5.34) Hospitalization due to ACS: 0.36 (0.21 to 0.61)	Not reported
Siriwardena et al.	N=78,706 (16,012 cases)	Influenza; pneumococcal	Model 1 adjusted for asthma or chronic obstructive pulmonary	Pneumococcal vaccination within previous year, OR for MI	None given, but subgroup results shows for the following

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
al. 2010 ⁵⁶	of myocardial infarction (MI), 62,964 controls); Location=UK; Age=40 to >=65; Setting=United Kingdom General Practice Research Database (GPRD), an extensively validated computerized database, representative of and comprising 5% of the population of England and Wales.	(study didn't specify types)	disease, chronic heart disease, stroke or transient ischemic attack, diabetes, splenectomy, chronic liver disease, chronic renal failure, immunosuppression and HIV, hyperlipidemia, family history of acute myocardial infarction, peripheral vascular disease, hypertension, smoking status, treatment with acetylsalicylic acid, treatment with statins, treatment with antihypertensives, and general practice consultations. Each type of vaccination was adjusted for the other type. Second set of models (Model 2) adjusted for all of the above	Model 1: 0.96 (0.91–1.02) Model 2: 0.98 (0.93-1.04)	categories: Pneumococcal < 65: Model 1: 0.83 (0.73–0.95) Model 2: 0.91 (0.79–1.05) ≥ 65: Model 1: 0.88 (0.83–0.93) Model 2: 0.97 (0.91–1.03)
Vila-Corcoles et al. 2012 ⁶⁸	N=27,204 (8,981 vaccinated, 18,223 unvaccinated); Location=Spain; Age=71.7 (mean at study start); Setting=nine primary care centers in the Health Region of Tarragona (a mixed residential-	Pneumococcal (PPV23)	The following variables were considered in all the initial models: age, sex, number of outpatient visits to family physician in 12-months before study start, influenza vaccination in prior autumn, history of coronary artery disease, history of stroke, history of chronic heart disease, chronic pulmonary disease, hypertension, hypercholesterolemia, obesity, diabetes mellitus, smoking status, alcoholism, chronic severe liver disease, chronic severe nephropathy, cancer, dementia and nursing-home residence. Age, sex and influenza vaccine status were judged epidemiologically relevant	Multivariate hazard ratio (95% CI) CAP: 0.85 (0.62-1.15) AMI: 0.83 (0.56-1.22) Ischemic Stroke: 0.65 (0.42-0.99) Death from any cause: 0.88 (0.75-1.03)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
	industrial urban area in the Mediterranean coast of Catalonia, Spain)		variables, being included in all the final models. Final Models: CAP: Adjusted for age, sex, number of outpatient visits in prior year, influenza vaccination in prior year, chronic pulmonary disease, chronic heart disease, smoking and nursing-home resident AMI: Adjusted for age, sex, number of outpatient visits in prior year, influenza vaccination in prior year, history of coronary artery disease, chronic heart disease, diabetes mellitus, hypercholesterolemia, smoking (confounder) and nursing-home resident Ischemic Heart Disease: Adjusted for age, sex, number of outpatient visits in prior year, influenza vaccination in prior year, history of coronary artery disease, history of stroke, smoking (confounder) and nursing-home resident Death from any cause: Adjusted for age, sex, number of outpatient visits in prior year, influenza vaccination in prior year, chronic pulmonary disease, chronic heart disease, diabetes mellitus, cancer, chronic nephropathy, dementia, hypertension, hypercholesterolemia, obesity, smoking, and nursing home-resident		
Smeeth et al. 2004 ⁵⁵	N=20,486 adults with first MI and 19,063 with first stroke who received influenza immunization in UK	Influenza, pneumococcal	Age	Incidence ratios of first disease incidence Pneumococcal Myocardial Infarction 1-3 days: 0.49 (0.19–1.32) 4-7 days: 1.11 (0.63–1.96) 8-14 days: 1.22 (0.81–1.84) 15-28 days: 1.15 (0.85–1.55) 29-91 days: 1.10 (0.95–1.28) Stroke	

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
				1-3 days: 1.29 (0.67–2.49) 4-7 days: 1.08 (0.58–2.01) 8-14 days: 1.18 (0.75–1.85) 15-28 days: 0.90 (0.63–1.30) 29-91 days: 1.15 (0.98–1.35) Influenza Myocardial Infarction 1-3 days: 0.70 (0.18–2.81) 4-7 days: 0.53 (0.13–2.10) 8-14 days: 1.34 (0.69–2.60) 15-28 days: 1.05 (0.62–1.79) 29-91 days: 1.42 (1.12–1.79) Stroke 1-3 days: 1.01 (0.25–4.04) 4-7 days: 1.13 (0.36–3.52) 8-14 days: 0.64 (0.21–2.00) 15-28 days: 1.06 (0.57–2.00) 29-91 days: 0.99 (0.72–1.35)	
Johnston et al. 2012 ⁵⁷	N=31,546; Location=40 countries; Setting=Participants in the ONTARGET TRANSCEND trials: at least 55 years old and a history of vascular disease or diabetes with document end-organ damage	Influenza, pneumococcal	Adjusted by propensity score for influenza vaccination (body mass index, age, sex, ethnicity, education, vitamin use, smoking history, alcohol use, history of pneumococcal vaccination), history of coronary artery disease, diabetes mellitus, hypertension, stroke, admission to a nursing home, or use of aspirin, beta-blocker, lipid-lowering drug, angiotensin-converting enzyme inhibitor, or angiotensin II inhibitor	Association Between Influenza Vaccination and Risk of Major Adverse Vascular Events During the Influenza Season Cohort 2003-2004: 0.96 (0.73–1.27) 2004-2005: 0.62 (0.50–0.77) 2005-2006: 0.69 (0.53–0.91) 2006-2007: 0.52 (0.42–0.65) Association Between Influenza Vaccination and Risk of the Major Adverse Vascular Events During the Non-influenza Season Cohort 2003-2004: 0.81 (0.61–1.09) 2004-2005: 0.64 (0.50–0.83) 2005-2006: 0.74 (0.56–0.98) 2006-2007: 0.50 (0.38–0.67) Association Between Influenza Vaccination and Risk of Non-	Not given

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
				cardiovascular Death During the Influenza Season Cohort 2004-2005 Non-cardiovascular deaths: 0.26 (0.16–0.40) Cancer deaths: 0.20 (0.10–0.39) Deaths resulting from other causes: 0.33 (0.18–0.60) 2005–2006 Non-cardiovascular deaths: 0.21 (0.10–0.46) Cancer deaths: 0.27 (0.10–0.69) Deaths resulting from other causes: 0.14 (0.03–0.58) 2006-2007 Non-cardiovascular deaths: 0.27 (0.18–0.41) Cancer deaths: 0.17 (0.10–0.31) Deaths resulting from other causes: 0.47 (0.25–0.86)	

MI = Myocardial Infarction; PPV = Pneumococcal Polysaccharide Vaccination; IHD = Ischemic Heart Disease; PSI = Pneumonia Severity Index; ACS = Acute Coronary Syndrome; OR = Odd Ratio; GPRD = General Practice Research Database; CI = Confidence Interval; CAP = Community-acquired Pneumonia; AMI = Acute Myocardial Infarction;

Zoster

Zoster vaccine (Zostavax) is recommended in the US for adults aged 60 and over. We identified eight trials of Zoster vaccine; results are summarized in Table 11.

One trial in Brazil, Costa Rica, Colombia, Mexico, Peru, Venezuela, and the Philippines⁶⁹ studied the vaccine in varicella-zoster virus sero-negative or low sero-positive adults. This trial included only 21 persons: 18 received the vaccine, while three received placebo. There were no AEs reported in the placebo group; thus, odds ratios could not be calculated. There were no serious AEs in the vaccine group.

Publications often reported only broad categories of AEs. A controlled clinical trial in North America and Europe⁷⁰ included 22,439 adults (62% female) who received one dose of the zoster (Zostavax) vaccine at baseline. Compared to the control group, vaccinated individuals were more likely to experience one or more injection-site AEs (OR 10.38, 95% CI 9.72-11.08), vaccine-related AEs (OR 8.39, 95% CI 7.88-8.92), and one or more systemic adverse events (OR 1.09, 95% CI 1.03-1.15). How AEs were determined to be related to vaccination was not described.

A smaller trial in the US and Netherlands⁷¹ included 210 older adults (63% female) who received two doses of Zostavax, one at baseline (Dose 1) and another 42 days later (Dose 2). Compared to the control group, vaccinated individuals were more likely to experience one or more adverse events post dose 1 (OR 3.06, 95% CI 1.73-5.41), systemic adverse events post dose 1 (OR 14.70, 95% CI 1.89-114.53), vaccine-related adverse events post dose 1 (OR 8.53, 95% CI 4.18-17.39), one or more adverse events post dose 2 (OR 4.06, 95% CI 2.28-7.24), and vaccine-related adverse events post dose 2 (OR 11.17, 95% CI 5.46-22.87). Another trial in the US⁷² included 101 adults (59% female) who received the Zostavax at study start and 28 days later. The study reported overall results and also results according to different subgroups. The only AE associated with vaccination in the overall study population was injection-site AE (OR 19.84, 95% CI 6.77-58.12). The vaccine was associated with “one or more adverse event” in patients over 60 years old (OR 5.37, 95% CI 2.61-11.05). A controlled clinical trial in the US⁷³ included older adults (41% female) who received one dose of zoster vaccine. Compared to the control group, vaccinated individuals were more likely to experience one or more adverse events at the injection site (OR 4.67, 95% CI 4.16-5.24) and one or more vaccine-related systemic adverse events (OR 1.30, 95% CI 1.05-1.60).

Two very large trials reported no association with AEs. A controlled clinical trial in the US, Canada, Spain, Germany, and the UK⁷⁴ included almost 12,000 older adults (59% female) who received one dose of Zostavax. No statistically significant differences in adverse events between vaccinated and unvaccinated groups were reported. A controlled clinical trial in the US⁷⁵ included 38,546 older adults who received one dose of zoster vaccine. No statistically significant differences in adverse events between vaccinated and unvaccinated groups were reported.

Regarding special populations, one controlled trial⁷⁶ included 209 older adults (63% female) who suffered from arthritis, hyperlipidemia, and hypertension. Individuals were given the zoster vaccine at study start (dose 1) and then 42 days later (dose 2). Compared to controls, the vaccinated group was more likely to experience any adverse event at dose 2 (OR 4.20, 95% CI 2.35-7.52), systemic adverse events at dose 1 (OR 14.86, 95% CI 1.91-115.80), general vaccine-related adverse events at dose 1 (OR 8.70, 95% CI 4.26-17.76), and vaccine-related adverse events at dose 2 (OR 11.44, 95% CI 5.58-23.45).

Table 10. Vaccinated vs. unvaccinated adults. Zoster vaccine

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Macaladad N. et al.,2007 ⁶⁹ Brazil, Costa Rica, Colombia, Mexico, Peru and Venezuela and the Philippines	Controlled Clinical Trial	2	Sample size : 21, Mean age: 38.1, Age range: 27 – 69, Percent female: 66.7%	Zoster, NR, 50,000 PFU/0.5 mL, Adjuvant: Not Reported, Preservative: Not reported, Delivery: injected	Dose1: 0 Days	Not calculated
Mills R. et al.,2010 ⁷² US	Controlled Clinical Trial	5	Sample size : 101, Mean age: 67.8 (approx.), Age range: 50 - 93, Percent female: 59.4%	Zoster, Zostavax, Merck, Lyophilized zoster vaccine (~89,000 plaque-forming units[PFU]/dose at release), Adjuvant: Not Reported, Preservative: Not reported, Delivery: Subcutaneous	Dose1: 0 Days Dose2: 28 Days	50-59y: Systemic AE: OR 0.245 (0.027-2.231) 50-59y: 1 or more AE: OR 1.899 (0.613-5.88) >=60y: Systemic AE: OR 1.664 (0.685-4.042) >=60y: 1 or more AE: OR 5.371 (2.609-11.054) ** Overall - Injection site AEs: OR 19.841 (6.773-58.123) **
Murray A. V. et al.,2011 ⁷⁴ US, Canada, Spain, Germany, UK	Controlled Clinical Trial	4	Sample size : 11,999, Mean age: 70.4, Age range: 60 - 99, Percent female: 58.6%	Zoster, Zostavax, Merck, Lyophilized ZV, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Subcutaneous	Dose1: 0 Days	Blood/Lymphatic disorders(1-182d): OR 1.253 (0.336-4.669) Cardiac disorders (1-182d): OR 1.016 (0.733-1.41) Cardiac disorders(1-42d): OR 1.002 (0.53-1.895) Death (1-182d): OR 1.417 (0.76-2.64) Death (1-42d): OR 1.203 (0.367-3.944) GI disorders (1-182d): OR 1.281 (0.787-2.085) GI disorders(1-42d): OR 1.337 (0.464-3.855) Neoplasms (1-182d): OR 1.317 (0.934-1.858) Neoplasms(1-42d): OR 1.672 (0.731-3.824) Nervous system(1-182d): OR 0.808 (0.476-1.369) Nervous system (1-42d): OR 0.716 (0.227-2.256) Psychiatric (1-182d): OR 60.2 (0.116-31171.904) Psychiatric (1-42d): OR 1.002 (0.141-7.118) Respiratory/Thoracic (1-182d): OR 1.123 (0.654-1.928) Respiratory/Thoracic (1-42d): OR 1.504 (0.424-5.333)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Oxman M. N. et al.,2005 ⁷³ USA	Controlled Clinical Trial	3	Mean age: 69 (median), Age range: 60 - >80, Percent female: 41%	Zoster, Merck, The estimated potency at vaccination of the 12 vaccine lots used in the study ranged from 18,700 to 60,000 plaque-forming units per dose. The median potency was 24,600 plaque-forming units, and more than 90 percent of vaccinated subjects received 32,300 plaque-forming units or less., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Subcutaneous	Dose1: 0 Days	Documented temperature 38.3°C or higher: OR 0.978 (0.572-1.67) One or more adverse events at injection site: OR 4.67 (4.164-5.237) ** One or more systemic adverse events: OR 1.058 (0.945-1.185) One or more vaccine-related systemic adverse events: OR 1.296 (1.049-1.601) ** Self-reports of feeling abnormal temperature: OR 1.203 (0.987-1.467)
Simberkoff M. S. et al.,2010 ⁷⁵ US	Controlled Clinical Trial	7	Sample size : 38,546, Mean age: NR, Age range: 60 - NR	Zoster, Merck, Median potency, 24600 plaque-forming units per dose, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Subcutaneous	Dose1: 0 Days	# of SAE (60-69y): OR 1.081 (0.847-1.38) # of SAE (70-80y): OR 0.909 (0.728-1.135) # of SAE (>=70y): OR 0.969 (0.793-1.185) # of SAE (>=80y): OR 1.301 (0.808-2.095) COSTART - Cardiovascular: OR 1.117 (0.835-1.496) COSTART - Digestive: OR 0.719 (0.481-1.075) COSTART - Endocrine: OR 0.25 (0.028-2.237) COSTART - Genitourinary: OR 0.941 (0.476-1.864) COSTART - Hemic/Lymphatic: OR 2.501 (0.485-12.894) COSTART - Metabolic/Nutritional: OR 1.667 (0.398-6.978) COSTART - Musculoskeletal: OR 1 (0.489-2.047) COSTART - Nervous Sys: OR 1.03 (0.642-1.652) COSTART - Skin: OR 0.903 (0.542-1.506) Diagnostic group - Cancer: OR 1.131 (0.76-1.683) Diagnostic group - Vascular (functional): OR 1.155 (0.752-1.774)
Schmader K. E. et al.,2012 ⁷⁰ North America and Europe	Controlled Clinical Trial	4	Sample size : 22,439, Mean age: 54.8, Age range: 50 - 59, Percent female: 61.9%	Zoster, Zostavax, Merck, lyophilized ZV with stabilizers, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Subcutaneous	Dose1: 0 Days	1 or more Injection-site AEs: OR 10.379 (9.722-11.081) ** SAE with death: OR 0.334 (0.035-3.209) Vaccine-related AEs: OR 8.385 (7.882-8.922) ** Vaccine relate systemic AEs: OR 0.43 (0.393-0.471) With vaccine related SAE: OR 0.002 (0-0.013) 1 or more Systemic AEs: OR 1.089 (1.031-1.151) **

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Vermeulen J. N. et al.,2012 ⁷¹ US and Netherlands	Controlled Clinical Trial	5	Sample size : 210, Mean age: 68.7 (Tx); 70.7 (Placebo), Age range: 58–90, Percent female: 62.85%	Zoster, Zostavax, Merck, lyophilized ZV (~23,000 plaque forming unit [PFU]/0.5 mL), Adjuvant: Not Reported, Preservative: Not reported, Delivery: Subcutaneous	Dose1: 0 Days Dose2: 42 Days	1 or more AEs (Post Dose 1): OR 3.062 (1.732-5.412) ** Systemic AEs (PD #2) -Rash: OR 2.019 (0.18-22.617) Systemic AEs (Post Dose 2): OR 0.825 (0.244-2.791) Systemic AEs (Post Dose 1): OR 14.696 (1.886-114.525) ** 1 or more AEs (Post dose 2): OR 4.063 (2.278-7.243) ** Vaccine-related AEs (Post Dose 1): OR 8.525 (4.179-17.389) **
Vermeulen J. N. et al.,2012 ⁷⁶	Controlled Clinical Trial	4	Sample size : 209, Mean age: 68.7/70.7 (vaccine/placebo), Age range: 58–90, Percent female: 63%, Conditions: Arthritis, hyperlipidemia, hypertension,	Zoster, NR, Lyophilized ZV (~23,000 plaque forming unit [PFU]/0.5mL, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Subcutaneous	Dose1: 0 Days Dose2: 42 Days	# of patients with any AE Dose 2: OR 4.203 (2.348-7.522) ** Rash Dose 2: OR 2.039 (0.182-22.841) Systemic AEs: OR 14.857 (1.906-115.797) ** Systemic AEs Dose 2: OR 0.833 (0.246-2.82) Vaccine-related AEs: OR 8.699 (4.26-17.763) ** Vaccine-related AEs Dose 2: OR 11.44 (5.582-23.446) **

NR = Not reported; PFU = Plaque Forming Units; Y = Year; D = Day; OR = Odds Ratio; = AEs = Adverse Events; PD = Post Dose; SAE = Serious Adverse Events; GI = Gastrointestinal; ZV = Zoster Vaccine

Two post-licensure studies evaluated adverse events following administration of adult herpes zoster vaccine. They are displayed in Table 11. Zhang et al. 2012⁷⁷ evaluated the efficacy and safety of zoster vaccine among Medicare beneficiaries 60 years and older who had inflammatory bowel disease, psoriatic arthritis, psoriasis or rheumatoid arthritis. Receipt of zoster vaccine was not associated with increased cases of varicella or herpes zoster within 42 days in the cohort as a whole and specifically in individuals who were receiving biologic immunomodulatory agents (principally agents targeted against Tumor Necrosis Factor). The authors also evaluated the relationship between vaccination and hospitalization for meningitis or encephalitis; no such cases were identified. With a median follow-up of two years, receipt of the zoster vaccine was associated with a decreased rate of incident cases of zoster. Lower rates were associated with vaccination in all patient subgroups. Using both a case-centered approach and a self-controlled case series analysis, Tseng et al 2012,⁷⁸ examined the relationship between receipt of zoster vaccine and various adverse events among a cohort of adults age 50 and above receiving care from eight managed-care organizations in the United States. Five specific groupings of events were examined: cerebrovascular events (Group 1), acute myocardial infarction, acute pericarditis, acute myocarditis, cardiomyopathy, heart failure (Group 2); meningitis encephalitis and encephalopathy (Group 3); Ramsay-Hunt syndrome and Bell's palsy (Group 4); and medically attended events, including cellulitis, pain and allergic reactions (Group 5). No increased risk was found for Groups 1 – 4 as a whole or for the any of the individual entities within these groups. An increased rate of cellulitis on days 1 – 7 was found using only the case-centered method (RR 1.30, 95% CI 1.18, 1.44) and an increase in allergic reactions was found by both the case centered analysis (RR 2.13, 95% CI 1.87, 2.40) and the self-controlled case series method (RR 2.32 95% CI 1.85, 2.91). No cases of anaphylaxis occurred with vaccine administration.

Summary

Zostavax is recommended for US adults over age 60; adverse events specific to this population were not covered by the IOM report. In the eight clinical trials we identified, dosage varied from 18,700 to 89,000 PFU (plaque-forming units) per 0.5 ml. Two trials did not report dosage. Although not always noted in the publications, studies using doses in the high end of the range are likely Phase II trials. The dosage currently licensed in the US is 19,400 PFU per 0.65 ml.

Adverse events were usually reported using broad categories such as “injection-related adverse events,” “systematic adverse events,” or “one or more adverse events.” Only one trial reported more specific events; this trial used broad categories such as “psychiatric” or “respiratory/thoracic.” Thus, there is insufficient evidence to make conclusions regarding the association of this vaccine with any adverse events other than injection site reactions. Strength of evidence is moderate for this non-serious adverse event. We found only two post-licensure studies; the only adverse events associated with Zoster vaccine were cellulitis and allergic reactions. (No cases of anaphylaxis were reported.) Strength of evidence is moderate; the events are non-serious.

Table 11. Post-marketing studies of zoster vaccine

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Zhang et al. 2012 ⁷⁷	N=463,541(4,026 with ankylosing spondylitis, 66,751 with inflammatory bowel disease, 11,030 with psoriatic arthritis, 89,565 with psoriasis, and 292,169 with RA); Location=US; Age=74 years (mean at study start); Setting=US Medicare beneficiaries	Herpes zoster	Sex, race, immune-mediated disease, time varying concurrent medications, and time-varying health care utilization (hospitalization and physician visits)	<p>HR (95% CI) for Herpes Zoster Incidence</p> <p>Using ICD-9-CM diagnosis code+pharmacy claim definition for HZ case (Definition 1) HZ vaccination: 0.61 (0.52-0.71)</p> <p>Using ICD-9-CM diagnosis code only for HZ case (Definition 2) HZ vaccination: 0.67 (0.59-0.75)</p>	<p>Sex</p> <p>Men [Reference]</p> <p>Women Definition 1: 1.22 (1.17-1.28) Definition 2: 1.21 (1.17-1.26)</p> <p>Race</p> <p>White [Reference]</p> <p>Black Definition 1: 0.67 (0.62-0.73) Definition 2: 0.69 (0.64-0.74)</p> <p>Other Definition 1: 0.89 (0.81-0.97) Definition 2: 0.89 (0.83-0.95)</p> <p>Immune-mediated disease</p> <p>Rheumatoid arthritis [Reference]</p> <p>Ankylosing spondylitis Definition 1: 0.98 (0.77-1.25) Definition 2: 0.94 (0.77-1.13)</p> <p>Inflammatory bowel diseases Definition 1: 1.03 (0.97-1.10) Definition 2: 1.02 (0.97-1.07)</p> <p>Psoriatic arthritis Definition 1: 0.92 (0.80-1.05) Definition 2: 0.92 (0.83-1.02)</p> <p>Psoriasis Definition 1: 0.99 (0.93-1.05) Definition 2: 0.97 (0.93-1.02)</p> <p>Hospitalized in the previous 6 mo</p> <p>No [Reference]</p> <p>Yes Definition 1: 1.00 (0.95-1.05) Definition 2: 1.25 (1.20-1.29)</p> <p>No. of physician visits in the previous 6 mo Definition 1: 1.04 (1.04-1.04)</p>

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
					Definition 2: 1.04 (1.04-1.04)
Tseng et al. 2010 ⁷⁸	N=193,083 recipients of zoster vaccine in 8 US MCOs; Age≥50;	Zoster	No additional confounders controlled for in models	<p>Relative risk (RR) and 95% confidence interval (CI) of pre-specified adverse events within predefined risk windows following vaccination with a zoster vaccine</p> <p>Case-centered</p> <p><u>Day 1-14</u> Stroke: 1.03 (0.83–1.28) Acute myocardial infarction: 1.17 (0.92–1.48) Cardiomyopathy: 0.73 (0.51–1.03) Heart failure: 0.76 (0.46–1.24) Meningitis, encephalitis and encephalopathy: 0.54 (0.19–1.52) Ramsey-Hunt syndromes and Bell's palsy: 0.63 (0.29–1.38)</p> <p><u>Day 15-28</u> Stroke: 0.92 (0.73–1.16) Acute myocardial infarction: 1.04 (0.81–1.34) Cardiomyopathy: 1.11 (0.83–1.48) Heart failure: 1.08 (0.70–1.65) Meningitis, encephalitis and encephalopathy: 0.90 (0.40–2.05)</p> <p><u>Day 29-42</u> Stroke: 1.06 (0.85–1.31) Acute myocardial infarction: 0.97 (0.75–1.26) Acute pericarditis: 1.04 (0.13–8.05) Cardiomyopathy: 1.00 (0.74–1.36) Heart failure: 0.95 (0.60–1.49) Meningitis, encephalitis and encephalopathy: 0.62 (0.23–1.69)</p> <p><u>Day 1-42</u> Stroke: 1.00 (0.87–1.15) Acute myocardial infarction: 1.07 (0.92–1.26) Acute pericarditis: 0.27 (0.03–2.22) Cardiomyopathy: 0.94 (0.77–1.14) Heart failure: 0.91 (0.68–1.21) Meningitis, encephalitis, and encephalopathy: 0.66 (0.37–1.16) Mortality: 0.31 (0.23–0.40)</p> <p>Day 1-7</p>	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
				Cellulitis and infection: 1.30 (1.18–1.44) Allergic Reaction: 2.13 (1.87–2.40) Self-controlled case series <u>Day 1-14</u> Cerebrovascular diseases: 0.94 (0.70–1.28) Acute myocardial infarction: 1.22 (0.87–1.73) Cardiomyopathy: 0.70 (0.45–1.10) Heart failure: 0.77 (0.41–1.46) Meningitis, encephalitis, and encephalopathy: 0.80 (0.21–2.98) Ramsey-Hunt syndromes and Bell's palsy: 0.78 (0.29–2.09) <u>Day 15-28</u> Cerebrovascular diseases: 1.03 (0.74–1.42) Acute myocardial infarction: 1.24 (0.85–1.79) Cardiomyopathy: 1.05 (0.69–1.59) Heart failure: 0.92 (0.51–1.63) Meningitis, encephalitis, and encephalopathy: 0.86 (0.29–2.55) <u>Day 29-42</u> Cerebrovascular diseases: 0.97 (0.71–1.30) Acute myocardial infarction: 0.97 (0.67–1.39) Acute pericarditis: 1.00 (0.06–15.99) Cardiomyopathy: 0.86 (0.57–1.29) Heart failure: 0.64 (0.36–1.16) Meningitis, encephalitis, and encephalopathy: 0.80 (0.21–2.98) <u>Day 1-42</u> Cerebrovascular diseases: 0.99 (0.83–1.19) Acute myocardial infarction: 1.05 (0.86–1.29) Acute pericarditis: 0.50 (0.05–5.51) Cardiomyopathy: 0.94 (0.73–1.20) Heart failure: 0.88 (0.61–1.25) Meningitis, encephalitis, and encephalopathy: 0.78 (0.39–1.56) <u>Day 1-7</u> Cellulitis and infection: 1.10 (0.95–1.26) Allergic Reaction: 2.32 (1.85–2.91)	

CI = Confidence Interval; RA = Rheumatoid Arthritis; HR = Hazard Ratio; ICD = International Classification of Diseases; CM = Clinical Modification; HZ = Herpes Zoster; Mo = Month; RR = Relative Risk; MCOs = Managed Care Organizations;

Varicella

We identified only one study comparing varicella-vaccinated and unvaccinated adults, published after the IOM search dates. A study in the US⁷⁹ included 82 adults (35% female) who received varicella vaccine (Varivax) at baseline and 12 weeks later. No statistically significant differences in AEs between vaccinated and unvaccinated groups were reported.

Data are presented in Table 12.

Table 12. Vaccinated vs. unvaccinated adults. Varicella vaccine

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Weinberg, A., et al. 2010 ⁷⁹ US (No direct mentions)	Cohort	1	Sample size : 82, Mean age: NR, Age range: 18 - 65, Percent female: 35.3%, Conditions: HIV	Varicella, Varivax, Merck, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Not reported	Dose1: 0 Weeks Dose2: 12 Weeks	Dose 1: Influenza-like illness: OR 1.55 (0.242-9.94) Dose 1: Pruritis: OR 0.484 (0.042-5.618) Dose1: Systemic rash (non-zosteriform): OR 0.484 (0.042-5.618) Dose2: Liver enzyme elevation: OR 2.065 (0.178-23.943) Dose 2: Systemic rash (non-zosteriform): OR 1 (0.06-16.69)

CI = Confidence Interval; NR = Not reported; HIV = Human Immunodeficiency Virus; OR = Odds Ratio;

HPV

The IOM committee found the evidence “convincingly supports” no causal relationships with AEs, and “favors acceptance” of a causal relationship with anaphylaxis. The IOM committee found the evidence is “inadequate to accept or reject” a causal relationship between HPV vaccine and the following AEs: ADEM, transverse myelitis, neuromyelitis optica, MS, Guillain-Barre Syndrome, chronic inflammatory disseminated polyneuropathy, brachial neuritis, amyotrophic lateral sclerosis, transient arthralgia, pancreatitis, thromboembolic events, and hypercoagulable states. In the US, HPV vaccine is generally administered to patients between the ages of 9 and 26. Thus, the post-licensure studies are discussed in the section on children and adolescents.

We identified two trials of HPV vaccine in women aged 18 to 35. Both were administered some formulation of Cevarix at baseline, one month, and six months. The results are summarized in Table 13. A controlled trial in Hong Kong⁸⁰ included 300 women; compared to the control group, women who were vaccinated were more likely to experience the non-serious AEs, fatigue (OR 1.69, 95% CI 0.56-3.34) and myalgia (OR 1.71, 95% CI 1.03-2.82). A controlled trial in India⁸¹ included 337 adult women; compared to the placebo group, women who were vaccinated were more likely to experience Grade 3 (severe) pain (OR 6.19, 95% CI 2.63-14.54). In this study Grade 3 events were defined as those which limited typical daily activity. In this case, we do not regard this as a SAE.

We summarize the totality of the evidence on HPV in the section on children and adolescents.

Table 13. Vaccinated vs unvaccinated adults. HPV vaccine

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Bhatla N. et al.,2010 ⁸¹ India	Controlled Clinical Trial	7	Sample size : 337, Mean age: 28.4, Age range: 18 – 35, Percent female: 100%	Human papillomavirus (HPV), HPV-16/18 L1 virus-like particle (VLP) cervical ca, GlaxoSmithKline, HPV-16/18 L1 virus-like particle (VLP) cervical cancer vaccine containing the proprietary ASO4 (3-O-desacyl-4(1)-monophosphoryl lipid [MPL] [0 mcg MPL] adsorbed on aluminum [Al] hydroxide [500 mcg AL(+3)]) adjuvant system, Adjuvant: ASO 4-Aluminum, Preservative: Not reported, Delivery: Intramuscular	Dose1: 0 Month Dose2: 1 Month Dose3: 6 Month	Pain (Grade 3): OR 6.189 (2.634-14.54) ** Redness (>50 mm): OR 1 (0.063-15.882)
Ngan H. Y. S. et al.,2010 ⁸⁰ Hong Kong	Controlled Clinical Trial	7	Sample size : 300, Age range: 18 – 35, Percent female: 100%	Human papillomavirus (HPV), Cevarix, GlaxoSmithKline, Each dose (0.5 mL) of the HPV-16/18 vaccine contained 20 µg each of HPV-16 and -18 L1 (structural protein of HPV) virus-like particle (VLP) and adjuvanted with a proprietary AS04 (3-O-desacyl-4'-monophosphoryllipid [50 µg] adsorbed on aluminum hydroxide [Al(OH)3, 500 µg]), Adjuvant: ASO 4, Preservative: Not reported, Delivery: Intramuscular	Dose1: 0 Month Dose2: 1 Month Dose3: 6 Month	Arthralgia: OR 1.362 (0.556-3.336) Fatigue: OR 1.69 (1.049-2.721)** Fever: OR 0.734 (0.3-1.797) GI symptoms: OR 1.714 (0.86-3.415) Headache: OR 1.439 (0.822-2.519) Myalgia: OR 1.705 (1.031-2.82) ** Rash: OR 3.062 (0.476-19.708) Urticaria: OR 1 (0.199-5.036)

OR = Odds Ratio; CI = Confidence Interval; HPV = Human Papillomavirus; VLP = Virus-like Particle; MPL = Monophosphoryl Lipid; GI = Gastrointestinal;

Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis

The IOM studied diphtheria toxoid, tetanus toxoid, and acellular pertussis-containing vaccines alone and in combination, which are administered to both children and adults. Except where noted below, studies did not report specific AEs by age. The IOM committee found the evidence “convincingly supports” a causal relationship in the adult population between the tetanus toxoid vaccine and anaphylaxis.

We identified only one trial of adults that fell into this category published after the IOM search dates. A trial in Korea⁸² included only 20 individuals (all male) who received one dose of SK Td vaccine. No statistically significant differences in AEs between vaccinated and unvaccinated groups were reported. Data are displayed in Table 14.

We identified no post-license studies of vaccines against diphtheria, tetanus, or pertussis in adults published after the IOM searches.

Table 14. Vaccinated vs unvaccinated adults. Td (Tetanus/diphtheria) vaccine

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Lee S. et al.,2011 ⁸² Korea	Controlled Clinical Trial	5	Sample size : 20, Mean age: 28.1, Age range: NR, Percent female: 0%	Td, SK Td Vaccine Inj, SK Chemicals, Seongnam, Korea, >= 2 IU of diphtheria toxoid and >=20 IU of tetanus toxoid, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Intramuscular	Dose1: 0 Days	Hypoesthesia: OR 3.857 (0.326-45.572)

OR = Odds Ratio; CI = Confidence Interval; NR = Not reported; Td = Tetanus/Diphtheria; IU = International Unit

Other vaccines.

The IOM report made the following conclusions regarding other vaccines in adults.

MMR vaccine. The evidence⁸³⁻⁸⁶ “favors acceptance” of a causal relationship with transient arthralgia in women. The IOM committee found the evidence “inadequate to accept or reject” a causal relationship in the adult population between MMR vaccine and MS onset, Guillain-Barré Syndrome, chronic arthralgia in women, and chronic arthritis and arthropathy in men.

Hepatitis A. Evidence “neither convincingly supports nor favors acceptance” of any causal relationships between this vaccine and AEs. No epidemiological studies of the following AEs in adults were found: acute disseminated encephalomyelitis, transverse myelitis, MS, Guillain-Barre Syndrome, chronic inflammatory disseminated polyneuropathy, Bells’ Palsy, anaphylaxis, and autoimmune hepatitis. The IOM thus states that the evidence is “inadequate to accept or reject” a causal relationship with these AEs.

Hepatitis B. Although no epidemiological studies were identified, mechanistic evidence favored acceptance of a causal relationship between the vaccine and anaphylaxis in yeast-sensitive individuals. Epidemiological studies of the following AEs in adults had evidence “inadequate to accept or reject” a causal relationship: optic neuritis, MS onset or relapse, first demyelinating event, Guillain-Barré Syndrome, SLE, onset or exacerbation of vasculitis, polyarteritis nodosa, and onset or exacerbation of rheumatoid arthritis. No epidemiological studies of the following AEs in adults were found: encephalitis, encephalopathy, ADEM, transverse myelitis, neuromyelitis optica, chronic inflammatory disseminated polyneuropathy, brachial neuritis, erythema nodosum, onset or exacerbation of psoriatic arthritis, onset or exacerbation of reactive arthritis, and fibromyalgia. The IOM thus states that the evidence is “inadequate to accept or reject” a causal relationship with these AEs.

We found no additional trials of MMR, Hepatitis A vaccine, or Hepatitis B vaccine in adults published after the IOM searches.

Post-marketing studies of multiple vaccines / other vaccines. We found four post-marketing studies of multiple vaccines in adults published after the IOM searches, as presented in Table 15. Hedlund et al. 2003⁸⁷ compared one-year outcomes among 100,242 persons vaccinated with influenza and/or 23-valent pneumococcal vaccine versus 159,385 unvaccinated individuals; all subjects were aged 65 years or older. Among the vaccinated subjects, 76,177 had both vaccines, 23,224 received only the influenza vaccine, and 841 received only the pneumococcal vaccine. The incidence of hospital admissions for influenza, pneumonia, and invasive pneumococcal disease during one year after vaccination was significantly lower in the vaccinated than in the unvaccinated cohort. The vaccinated cohort had significantly lower rates of in-hospital mortality for pneumonia, COPD, and cardiac failure. The benefits of vaccination were greater during influenza season (December - May) than at other times of the year (June - November). No harms from vaccination were noted among the reported outcomes. Administration of tetanus or polysaccharide pneumococcal vaccination was not associated with any subsequent change in the age-adjusted rates of first and recurrent myocardial infarction or stroke.

In a case-control study of 189 young adults with Autism Spectrum Disorder and 224 controls, Uno et al. 2012⁸⁸ 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 a case-control study of 159 cases of psoriatic arthritis and 159 persons with psoriasis alone, Eder et al. 2011⁸⁹ found vaccination against any of the following diseases was not associated with onset of psoriatic arthritis: Hepatitis A, Hepatitis B, influenza, and pneumonia.

In a multivariate analysis of records from the Defense Medical Surveillance System, Duderstadt and colleagues⁹⁰ found that military personnel vaccinated for MMR were less likely to have new onset of Type 1 diabetes (RR 0.71, 95% CI 0.61, 0.83) than those who were not vaccinated. The same was true for military personnel who had received Hep B vaccine (RR. 0.83, 95% CI 0.72, 0.83).

Finally, in a case control study of 355 Graves' disease cases, 418 Hashimoto's thyroiditis cases, and 1,102 controls, Yu et al. 2007⁹¹ found that vaccination against Hepatitis B, influenza, MMR, Hepatitis A, or polio was not associated with an increase rate of Graves' disease or Hashimoto's thyroiditis.

Summary

MMR. Per the IOM's conclusions, we concur that MMR vaccine is associated with transient arthralgia in women; however, strength of evidence is low. We concur with the IOM findings that MMR vaccination in childhood is not associated with autism spectrum disorders at any age; strength of evidence is high due to number and size of studies, quality of studies, and consistency of results. MMR is not associated with onset of type 1 diabetes in adults; strength of evidence is moderate, per results of a very large recent high quality epidemiological study.

Hepatitis A. Per evidence presented in the IOM report and recent post-licensure studies, there is insufficient evidence regarding association of this vaccine with any adverse events or onset of medical conditions.

Hepatitis B. Per evidence presented in the IOM report and recent post-licensure studies, there is insufficient evidence regarding association of this vaccine with any short-term adverse events other than anaphylaxis in years-sensitive individuals. This event is considered serious. Hepatitis B vaccine is not associated with onset of type 1 diabetes in adults; strength of evidence is moderate, per results of a very large recent high quality epidemiological study. There is insufficient evidence regarding the association of Hepatitis B vaccine and onset of any other medical conditions.

Table 15. Post-marketing studies of multiple vaccines in adults

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Duders tadt et al. 2012 ⁹⁰	N=2,385,102 active military personnel, including 1,074 cases of type 1 diabetes; Location=US; Age=17-35 years;	Hepatitis B, MMR, smallpox, typhoid, yellow fever	Receipt of multiple vaccines, age, race, sex, service branch, military grade, occupation, deployment, and calendar year	Risk Ratios for Diabetes Type 1 Hepatitis B: 0.83 (0.72, 0.95) MMR: 0.71 (0.61, 0.83)	Not reported
Hedlund et al. 2003 ⁸⁷	N=100,242 vaccinated with influenza or pneumococcal vaccines, 159,385 unvaccinated controls, in Stockholm County, Sweden; Age>=65 years;	Influenza and 23-valent pneumococcal vaccine (PV)	Age and gender	Hospital admissions/100 000 individuals between 1 December 1998 and 30 November 1999 Influenza 0.68 (0.53-0.88) Pneumonia 0.78 (0.71-0.86) IPD: 0.46 (0.25-0.87) COPD: 1.04 (0.92-1.17) Cardiac failure: 0.95 (0.87-1.05) In-hospital mortality due to investigated diagnoses/100 000 individuals between 1 December 1998 and 30 November 1999 Influenza 1.20 (0.39-3.70) Pneumonia 0.55 (0.43-0.71) IPD: 0.53 (0.06-5.10) COPD: 0.53 (0.29-0.98) Cardiac failure: 0.72 (0.59-0.87) Hospital admissions/100 000 individuals per year between 1 December 1998 and 31 May 1999 Influenza: 0.66 (0.52-0.82) Pneumonia: 0.72 (0.65-0.79) IPD: 0.47 (0.24-0.93) COPD: 1.07 (0.94-1.23) Cardiac failure: 0.90 (0.80-1.01) Hospital admissions/100 000 individuals per year between 1 June and 30 November 1999 Influenza: 1.36 (0.58-3.17) Pneumonia: 0.88 (0.77-1.00) IPD: 0.45 (0.15-1.32) COPD: 1.00 (0.87-1.15)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Uno et al. 2012 ⁸⁸	N=413 (189 Autism Spectrum Disorder (ASD) cases, 224 controls); Location=Kanto area, Japan; Age=22.6 years (mean); Setting=Cases were patients of the Yokohama Psycho-Developmental Clinic (YPDC). Controls were volunteers from area schools.	MMR, diphtheria–pertussis–tetanus vaccine (DPT); the polio vaccine. Study did not specify whether DPT was acellular and did not specify whether polio was inactivated. Only MMR was included in controlled analyses.	Maternal hypertension, low Apgar score, obstetrical vacuum extraction or forceps delivery Cases/controls matched by sex and year of birth	Cardiac failure: 1.02 (0.93-1.11) Odds ratio for ASD: 1.10 (0.64–1.90)	Maternal hypertension: 4.19 (0.46–38.57) Low Apgar score: 2.06 (0.18–22.12) Obstetrical vacuum extraction or forceps delivery: 0.98 (0.50–1.92)
Yu et al. 2007 ⁹¹	N=1,875 (355 Graves' disease cases, 418 Hashimoto's thyroiditis cases, 1,102 controls); Vaccine Safety Datalink Project: Age=18–69 years; Setting=Three health maintenance organizations (HMOs) In US	Hepatitis B vaccine, influenza, MMR, Hepatitis A, polio	Controls were frequency-matched to cases by birth year, sex, and study site (HMO) All models adjusted for frequency-matching variables (age groups, sex, site, and index year), personal and family history of autoimmune disease, smoking status, race, and education	OR (95% CI) for Graves' disease Main analysis Hepatitis B: 0.90 (0.62–1.32) Influenza: 1.07 (0.80–1.42) MMR: 0.59 (0.29–1.20) Hepatitis A: 0.70 (0.43–1.13) Polio: 1.29 (0.76–2.17) OR (95% CI) for Hashimoto's thyroiditis Main analysis Hepatitis B: 1.23 (0.87–1.73) Influenza: 1.15 (0.89–1.48) MMR: 1.50 (0.79–2.86) Hepatitis A: 0.97 (0.64–1.46) Polio: 1.17 (0.73–1.86)	Not reported

MMR = Measles, Mumps, Rubella; PV = Pneumococcal Vaccine; IPD = Invasive Pneumococcal Disease; COPD = Chronic Obstructive Pulmonary Disease; ASD = Autism Spectrum Disorders; DPT = Diphtheria–pertussis–tetanus Vaccine; YPDC = Yokohama Psycho-Developmental Clinic; HMO = Health Maintenance Organization; CI = Confidence Interval

Key Question (KQ) 2: What is the evidence that vaccines included in the immunization schedules recommended for US **children and adolescents** in 2011²⁴ are safe in the short term (within 30–42 days following immunization) or long term (>42 days after immunization)?

- a. What AEs are collected in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?
- b. What AEs are reported in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?

Table 16 lists all AEs reported in trials of vaccines on the US routine recommended schedule for children and adolescents. We are uncertain if additional AEs were collected; we can rely only on what was reported in the literature. The list does not imply an association with vaccination, as it contains AEs regardless of whether they were reported in vaccinated or unvaccinated study participants. Later in this report, we describe the studies further and assess association.

Table 16. Adverse Events Reported in trials in children & adolescents

Human papillomavirus (HPV)	Rotavirus continued
Injection site reactions	Decreased appetite
Ear and eye and respiratory system	Dehydration
“Laboratory abnormality”	Diarrhea
Pruritus, severe	Eczema
Serious AE (any)	Femur fracture
Serious AE (vaccine-related)	Fever
Systemic AE (any)	Gastroenteritis
Systemic AE (vaccine-related)	Gastrointestinal disorders
Influenza (inactive)	General Body
Abnormal crying	General disorders and administration site conditions
Allograft rejection, acute	GERD
Appetite decrease	Head injury
Death	Hematochezia
Drowsiness	Hospitalization
Emesis	Hypovolemia/dehydration
Febrile illness, acute	Infections
Fever >=38C	Influenza
Flu virus infection	Intussusception
Irritability	Intussusception related Death
Influenza (live)	Irritability
Chills	Kawasaki disease
Cough	Kidney cyst
Febrile neutropenia	Leukocytosis
Fever >=100F	Meningitis
Headache	Meningitis, pneumococcal
Irritability	Mesenteric adenitis
Muscle ache	Nasal congestion
Rash	Nasopharyngitis
Runny nose	Nervous system disorders
Sore throat	Oral candidiasis - Grade 3
Tiredness	Otitis media, acute
Vomiting	Partial seizures
Haemoph. Influen. type b (Hib) protein conjugate	Pertussis
Areas of swelling measuring less than 2.54 cm in diameter	Pneumonia
Areas of redness measuring less than 2.54 cm in diameter	Pyelonephritis
Conjunctivitis	Pyrexia
Fever greater than or equal to 38 C	Reproductive system and breast disorders
Hospitalizations 30 days after vaccination	Respiratory
Serious adverse reactions	SAE (extreme preemie)
Viral infections	Sepsis
Pneumococcal conjugate	SIDS
Febrile seizure	Serious Adverse Event
Fever	Umbilical infection
Kawasaki Disease	“Unsolicited symptoms”
Local AE	Upper respiratory infection
Otitis media	Urinary Tract Infection
Rotavirus	Vaccine-related serious adverse event
Accidental drowning	Viral infections
Anal fissure	Vomiting
Anemia	Wheezing
“Any AE”	Withdrawal due to AE
Abdominal pain	Combination Vaccines
Apneic attack (extreme preemie)	Haemoph. Influen. type b (Hib) protein conjugate, Polio (inactivated only), Tdap
Asthma	Apnea/collapse/cyanosis/pallor
Bronchiolitis	Convulsion/fit/seizure
Bronchopneumonia	Crying
Constipation	Diarrhea
Convulsions	Feeding Problem

Cough/runny nose	Fever
Death	"Vaccine reaction"
Death due to SIDS	Vomiting
Death (Outside of 42 day safety window and not associated with vaccine)	

HPV = Human Papillomavirus; AE = Adverse Events; SIDS = Sudden Infant Death Syndrome; GERD = Gastroesophageal Reflux Disease; SAE = Severe Adverse Event; Hib = Haemophilus Influenzae Type B; Tdap = Tetanus, Diphtheria, and Acellular Pertussis Vaccine

Table 17 lists all AEs and medical conditions investigated in the case-control, self-controlled case series, and multivariate risk factor analyses in children and adolescents. The majority of these studies were designed to assess the association of a specific AE with vaccination. Again, the list does not imply an association.

Table 17. Adverse events investigated in post-marketing studies of children and adolescents

Influenza vaccines	Hep B
H1N1	Anaphylaxis (in yeast sensitive children)
Convulsion	Demyelinating Event, First
Flu-like symptoms	Multiple Sclerosis - Onset
Hospitalization or ER visit	Multiple Sclerosis - Relapse
HPV	Seizures
Hashimoto's Disease	MMR
Guillain-Barre Syndrome	Anaphylaxis
Rheumatoid Arthritis	Autism
Type 1 diabetes	Febrile seizures
Seizures	Hospitalization or ER visit
Stroke	Measles Inclusion Body Encephalitis
Syncope	Purpura
Venous thromboembolism	Transient Arthralgia
TIV	Rotavirus vaccines
GI event, acute	Intussusception
Respiratory infection, acute	
Sickle cell disease, exacerbation	
Urea cycle disorders	

ER = Emergency Room; HPV = Human Papillomavirus; TIV = Trivalent Influenza Vaccine; GI = Gastrointestinal; MMR – Measles, Mumps, Rubella

Key Question (KQ) 2: Children and adolescents

- c. What AEs are associated with these vaccines?
1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 3. For each AE associated with a particular vaccine, what are the risk factors for the AE (including age, sex, race/ethnicity, genotype, underlying medical condition, whether a vaccine is administered individually or in a combination vaccine product, schedule of vaccine administration, adjuvants, and medications administered concomitantly)?

Influenza vaccines

The IOM committee studied seasonal influenza vaccines. Such vaccines are administered in two forms: a live attenuated form, administered intranasally, and an inactivated form, administered intramuscularly. The IOM committee did not find evidence that “convincingly supports” causal relationships in the pediatric population for any conditions. They found the evidence is “inadequate to accept or reject” a causal relationship between influenza vaccine and the following: seizures, acute disseminated encephalomyelitis (ADEM), and transverse myelitis. The IOM committee also found evidence is “inadequate to accept or reject” a causal relationship between live attenuated influenza vaccine (LAIV) and asthma exacerbation or reactive airway disease (RAD) episodes in children younger than 5 years of age and 5 years of age or older.⁹²⁻⁹⁷

We identified three trials⁹⁸⁻¹⁰⁰ published after the IOM search and one cohort study.¹⁰¹ The studies included participants 2-17 years of age. Two studies looked at special populations, e.g., subjects with cancer⁹⁹ and subjects who had undergone transplants.¹⁰¹ The studies were set in the US and Japan. In the three trials, participants received 1-2 doses of either live⁹⁹ or inactive^{98,101} seasonal influenza vaccines which included an H1N1 strain.

In the studies of healthy patients, both inactivated seasonal influenza vaccine (including a strain of H1N1)⁹⁸ and monovalent H1N1¹⁰⁰ were associated with no AEs. Similarly, in the studies of children with cancer⁹⁹ and transplant patients,¹⁰¹ inactivated seasonal influenza vaccine (including a strain of H1N1) was associated with no AEs.

We identified two eligible trials of the Haemophilus influenza (Hib) vaccine,^{102, 103} one set in the US, the other in the Philippines. Results of the larger trial (N = 5,190) indicate that vaccination with Hib was associated with redness (OR 2.71, 95% CI 1.57, 4.67) and swelling (OR 9.44, 95% CI 4.90, 18.19). Vaccination was not associated with high fever in either trial. No other AEs were associated with vaccination. In the larger trial, vaccination was associated with a protective effect against viral infections.

Table 18. Vaccinated vs unvaccinated children or adolescents. Influenza vaccines

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Englund J. A. et al.,2010 ⁹⁸ US	Controlled Clinical Trial	6	Sample size : 1,375, Mean age: 9.1, Age range: 2 - 7	Influenza (inactivated), Fluzone, Sanofi, 0.25 mL dose contained 7.5 g hemagglutinin (HA) of A/New Caledonia/20/99(H1N1); A/New York/55/2004 (H3N2), and B/Jiangsu/10/2003, Adjuvant: Not Reported, Preservative: Preservative Free, Delivery: Intramuscular	Dose1: 0 Days Dose2: 1 Month	Abnormal crying (Dose 1): OR 1 (0.794-1.26) Abnormal crying (Dose 2): OR 1.042 (0.83-1.31) Any drowsiness (Dose 1): OR 1.093 (0.863-1.384) Any emesis (Dose 1): OR 1.294 (0.926-1.808) Any emesis (Dose 2): OR 0.193 (0.146-0.256)** Any irritability (Dose 1): OR 1.128 (0.858-1.483) Any irritability (Dose 2): OR 0.922 (0.736-1.156) Decreased appetite (Dose 1): OR 0.883 (0.703-1.109) Decreased appetite (Dose 2): OR 0.944 (0.723-1.234) Fever >=38C (Dose 1): OR 0.952 (0.67-1.352) Fever >=38C (Dose 2): OR 0.596 (0.313-1.135)
Gotoh K. et al.,2011 ¹⁰¹ Japan	Cohort	1	Sample size : 101, Mean age: 9.8, Percent female: 51.5%, Conditions: Transplant	Influenza (inactivated), NR, 15 Ig hemagglutinin per 0.5 mL of each of the following influenza strains: A/New Caledonia/20/99 (H1N1), A/Hiroshima/52/2005 (H3N2), and B/Malaysia/2506/2004 in the 2006–2007 season; A/SolomonIslands/3/2006 (H1N1), A/Hiroshima/52/2005 (H3N2), and B/Malaysia/2506/2004 in the 2007–2008 season; and A/Brisbane/59/2007 (H1N1), A/Uruguay/716/2007 (H3N2), and B/Florida/4/2006 in the 2008–2009 season. These inactivated vaccines did not contain adjuvant., Adjuvant: Adjuvant Free, Preservative: Not reported, Delivery: Not reported	Dose1: 0 Days	Acute febrile illness: OR 0.421 (0.16-1.11) Flu virus infection: OR 0.819 (0.143-4.703)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Halasa N. et al.,2011 ⁹⁹ US	Controlled Clinical Trial	2	Sample size : 20, Mean age: 12.2, Age range: 5 - 17, Percent female: 45%, Conditions: Cancer	Influenza (live), MedImmune, 2005-2005 prep: 106.5-7.5 TCID 50per dose for each of the following strains: A/New Caledonia/20/99 (A/NC/20/99; A/H1N1), A/Wyoming/3/2003(A/Fujian/411/02-like, A/Fuj/411/02; A/H3N2), and B/Jilin/20/2003(B/Shanghai/361/2002-like, Yam88 lineage; B/Yam/166/98; B2005-2006: contained an identical A/H1N1 strain, but the A/H3N2 isolate was updated to A/California/7/2004(A/Cal/7/04) and the B strain was replaced with B/Jiangsu/10/2003(B/Shanghai/361/2002-like, Yam88 lineage; B/Yam/166/98; B, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Intranasal	Dose1: 0 Days	Chills: OR 0.259 (0.022-3.063) Cough: OR 0.259 (0.022-3.063) Fever >=100C (0-42 days): OR 0.375 (0.051-2.772) Headache: OR 0.286 (0.045-1.821) Runny nose: OR 1.556 (0.244-9.913) Sore throat: OR 0.25 (0.034-1.819) Tiredness: OR 0.444 (0.074-2.66) Vomiting: OR 1.556 (0.244-9.913)
Mallory R. M. et al.,2010 ¹⁰⁰ US	Controlled Clinical Trial	3	Mean age: 9, Age range: 2 - 17, Percent female: 51%	Influenza - monovalent H1N1, not reported, MedImmune, derived by genetic reassortment of the hemagglutinin and neuraminidase genes from the wild-type A/California/7/2009virus and the remaining 6 gene segments from an attenuated master donor virus (in sucrose phosphate buffer and egg allantoic fluid, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Intranasal	Dose1: 1 Days Dose2: 29 Days	# with any AE Dose 1: OR 1.103 (0.537-2.267) # with any AE Dose 2: OR 0.985 (0.448-2.167) Ear and labyrinth Dose 2: OR 0.251 (0.015-4.066) GI Dose 1: OR 1.017 (0.367-2.818) GI Dose 2: OR 0.882 (0.281-2.774) Infections and infestations Dose 2: OR 1.821 (0.404-8.219) Injury, poisoning, procedural complications Dose 2: OR 0.759 (0.078-7.414)

OR = Odds Ratio; CI = Confidence Interval; HA = Hemagglutinin; TCID = Tissue Culture Infective Dose; GI = Gastrointestinal;

Table 19. Vaccinated vs unvaccinated children or adolescents. Hib vaccine

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Capeding M. R. Z. et al., 1996 ¹⁰³ Philippines	Controlled Clinical Trial	3	Sample size : 174, Mean age: 6.9 months, Age range: 5 – 8 months, Percent female: 37%	Haemophilus Influenza type b (Hib) protein conjugate, Routine Vaccines, Pedvax-Hib, Merck, PRP-OMP polysaccharide coupled to an outer membrane protein of Neisseria meningitidis group B. Lot 0957V., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Intramuscular	Dose1: 6-8 Weeks Dose2: 10-12 Weeks Dose3: 14-16 Weeks	Fever greater than or equal to 38 C: OR 1.246 (0.467-3.323)
Santosham M. et al., 1991 ¹⁰² United States	Controlled Clinical Trial	4	Sample size : 5,190, Mean age: 54.6 days, Age range: 35 – 196 days, Percent female: 49.4%	Haemophilus Influenza type b (Hib) protein conjugate, Routine Vaccines, PedvaxHIB, Merck, OMPC lots 1072, 1080, and 1085. After reconstitution with 0.1ml of diluent, each 0.5m of vaccine contained 15 micrograms of H. influenzae polysaccharide and 131 to 272 micrograms of group B meningococcal OMPC., Adjuvant: Aluminum, Preservative: Thimerosal, Delivery: Intramuscular	Dose1: 42-90 Days Dose2: 70-146 Days	Areas of redness measuring less than 2.54 cm in diameter: OR 2.713 (1.574-4.676)** Areas if swelling measuring less than 2.54 cm: OR 9.446 (4.905-18.19)** Conjunctivitis: OR 0.628 (0.408-0.968)** Fever above 38.9 C: OR 1.059 (0.685-1.638) Hospitalizations 30 days after vaccination: OR 0.986 (0.748-1.299) Viral infections: OR 0.285 (0.13-0.627)**

OR = Odds Ratio; CI = Confidence Interval; Hib = Haemophilus Influenza Type b;

We found three post marketing studies on H1N1 vaccine in children or adolescents; two of these also studied seasonal influenza vaccines. We also identified four other post-marketing studies on seasonal influenza vaccines (TIV and LAIV). These influenza vaccine studies are summarized in Table 20.

Convulsions. Stowe et al. (2011)¹⁰⁴ studied 2,366 cases of convulsions in children (age <10 years) between May 2000 and April 2010 using the UK's General Practice Research Database (GPRD). The monovalent H1N1 vaccine (MIV) was studied only during the 2009/10 influenza season and the TIV vaccine was studied during the other seasons. Both vaccination status and health outcomes were ascertained by a review of medical records. The children were followed up for an average of 5.1 years each (range 0.3–10.0 years). The analysis adjusted for age, period, and season. For both the H1N1 and TIV vaccines, the onset of a convulsion episode was not significantly associated with vaccine at any time point.

Hospitalization or ER visits. Aljadhey et al. (2012)¹⁰⁵ studied 359 (169 vaccinated, 190 control) children and adolescents (age 6-18 years). Research teams visited schools and offered H1N1 (Pandemrix) vaccines to students, and subsequent health outcomes were ascertained by a trained pharmacist over phone interviews. The data were analyzed using a logistic regression that was adjusted for age, sex, education, and use of medications. The results found that the children vaccinated with H1N1 were no more likely (OR 1.25, 95% CI 0.47, 3.35) to use the hospital or emergency department services for any reason, but were significantly less (OR 0.63, 95% CI 0.41, 0.99) likely to exhibit influenza-like symptoms, than controls.

Influenza-like illness. A case-control analysis studied 683 children and adolescents (age 1 month - 18 years) who were hospitalized through the emergency departments of eight hospitals in Italy between November 2009 and August 2010.¹⁰⁶ Vaccination for H1N1 was ascertained via parental report, and health outcomes were collected through active surveillance of both clinically defined and laboratory confirmed hospitalizations for Influenza-Like Illness (ILI) events. AEs were confirmed using parental reports. Data were modeled using logistic regression that adjusted for age, chronic conditions, and other seasonal influenza vaccines. Results indicate that children vaccinated with any influenza vaccine (OR 2.7, 95% CI 1.6, 4.7) or seasonal vaccine (OR 2.1, 95% CI 1.1, 4.1) were significantly more likely to show symptoms of ILI, while those vaccinated for H1N1 were not (OR 1.3, 95% CI 0.6, 3.1).

Gastrointestinal. Baxter et al. (2012)¹⁰⁷ examined 43,702 LAIV recipients, 43,702 TIV recipients, and 53,366 matched unvaccinated controls, 5-17 years of age between October 2003 and March 2008. Immunization status and health outcomes were confirmed by a review of Kaiser Permanente's electronic medical records. Data were analyzed using Cox proportional hazards model, and relative risks (RR) were calculated as the ratio of the incidence rates without adjustment for any covariate. Hazard ratios (HR) were also calculated adjusting for matching factors and seasonal changes in background rates. Results were significant in children aged 5 to 8 vaccinated with LAI—for acute GI event within 21 days (HR 1.36, 95% CI 1.05, 1.76) and 42 days (HR 1.30, 95% CI 1.08, 1.78) and for acute respiratory tract event in 21 days (HR 1.12, 95% CI 1.00, 1.25) and 42 days (HR 1.15, 95% CI 1.06, 1.24) compared to the unvaccinated same age cohort. The incidence rates of SAEs overall and by specific diagnosis were not significantly higher or lower in the LAIV recipients relative to control groups in any comparison.

In another self-controlled case series, Glanz et al. (2011)¹⁰⁸ studied 66,283 children aged 24-59 months who received TIV vaccine between 2002 and 2006 in the US. Immunization status and health outcomes were ascertained by a review of medical records. Data were modeled using conditional Poisson regression adjusted for calendar month (indicating influenza season) and age.

The results showed that influenza vaccination was significantly associated with medically confirmed GI tract disorders (RR 7.70, 95% CI 1.11, 53.52), fever (RR 1.71, 95% CI 1.64, 1.80), and GI tract symptoms like vomiting and diarrhea (RR 1.18, 95% CI 1.10, 1.25) in the risk windows of 0-2, 1-14, and 1-42 days after vaccination.

Urea cycle disorders. In a self-controlled case series, Morgan et al. (2011)¹⁰⁹ studied 169 US children under age 18 with urea cycle disorders between February 2006 and July 2009. The study included numerous vaccines but reported only results for the influenza vaccines. Vaccination status and health outcomes were ascertained from clinical records. Data were analyzed using conditional Poisson regression that was adjusted for age. Results indicate that the influenza vaccination was not associated with urea cycle disorders at any post vaccination risk period.

Sickle cell disease. In a matched case-control study, Ambridge et al. (2011)⁶⁰ studied 1,294 (269 cases, 1,025 controls) children and adolescents (age 6 months to 17 years) in the US using data from the 1999-2006 Vaccine Safety Datalink program. This study also included a self-controlled case series analysis. Cases were identified as children who had received the TIV and had been hospitalized due to sickle cell crisis. Medical records were reviewed to confirm vaccination and hospitalization. Data were modeled using a conditional logistic regression and cases and controls were matched on age, gender, location, and influenza season. Results from both the case-control study and the self-controlled case series indicated that TIV is not associated with hospitalizations due to sickle cell crises. The authors noted that children classified as not receiving vaccine may have received vaccine from an outside provider.

Summary

Seasonal influenza vaccines were not associated with SAEs in the short term in children with cancer or who have received organ transplants. Due to small number and size of trials, the strength of evidence is low.

In clinical trials of healthy children, seasonal influenza vaccines were not associated with SAEs in the short term. We concur with the IOM findings that there is insufficient evidence to accept or reject an association between influenza vaccines and seizures, ADEM, transverse myelitis, asthma exacerbation, or RAD in children, due to the dearth of studies on these issues.

In large, high quality post-licensure studies, both seasonal influenza vaccines and H1N1 vaccines were associated with mild gastrointestinal disorders, such as vomiting and diarrhea in children in the short-term. Strength of evidence is moderate. One large study 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).

Seasonal influenza vaccines were associated with influenza-like symptoms in children in the short term, but strength of evidence is low, given the inconsistency of results.

Table 20. Post-marketing studies of influenza vaccines in children and adolescents

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Stowe et al. (2011) ¹⁰⁴	N=2,366 cases of convulsions; Location=UK; Age=Under 10 years; Used General Practice Research Database (GPRD)	Monovalent H1N1 influenza vaccine during the 2009/10 influenza season or seasonal TIV	Age, period and season	Incidence rate ratio (IRR) estimates for the onset of a convulsion episode in relation to the timing of influenza vaccination and type of vaccine administered Vaccine, Period, IRR TIV 2 Weeks pre-vaccine: 1.00 (0.70–1.42) Day of vaccination: 1.23 (0.39–3.83) 1–3 Day post vaccine: 0.98 (0.47–2.07) 4–7 Days post vaccine: 0.96 (0.50–1.86) 0–7 Days post vaccine: 1.00 (0.64–1.59) Monovalent H1N1 vaccine 2 Weeks pre-vaccine 0.44 (0.25–0.76) Day of vaccination 1.83 (0.68–4.90) 1–3 Day post vaccine 1.08 (0.51–2.28) 4–7 Days post vaccine 0.70 (0.31–1.57) 0–7 Days post vaccine 0.99 (0.61–1.60) Incidence rate ratio (IRR) estimates for the onset of a convulsion episode in relation to the timing of monovalent H1N1 vaccine Dose 1 2 Weeks pre-vaccine: 0.37 (0.20–0.68) Day of vaccination: 1.52 (0.49–4.73) 1–3 Day post vaccine: 0.85 (0.35–2.04) 4–7 Days post vaccine: 0.77 (0.34–1.72) 0–7 Days post vaccine: 0.89 (0.53–1.52) Dose 2 2 Weeks pre-vaccine: 1.24 (0.40–3.88) Day of vaccination: 5.24 (0.73–37.41) 1–3 Day post vaccine: 3.48 (0.86–14.07) 4–7 Days post vaccine: 0 0–7 Days post vaccine: 1.96 (0.62–6.14)	Not reported
Aljadhey et al. (2012) ¹⁰⁵	N=359 (169 vaccinated group, 190 control); Location=Riyadh, Saudi Arabia; Age=6-18 years; Setting=Schools	H1N1 vaccine (Pandemrix)	Age, sex, education, use of medications	OR (95% CI) for Hospitalization or ED H1N1: 1.25 (0.47-3.35) OR (95% CI) for Flu-like symptoms H1N1: 0.63 (0.41-0.99)	Not reported
Italian Multicent	N=683 children aged 1 month to 18	A-H1N1 Seasonal	Age and chronic diseases; the ORs of	OR of influenza-like illness	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
er Study Group for Drug and Vaccine Safety in Children (2011) ¹⁰⁶	years, hospitalized through the emergency departments of eight pediatric hospitals/wards in Italy	influenza	A-H1N1 and seasonal vaccine were each adjusted for the other influenza vaccine	Any flu vaccine 2.7 (1.6 to 4.7) A-H1N1 1.3 (0.6 to 3.1) Seasonal vaccine 2.1 (1.1 to 4.1)	
Baxter, 2012 ¹⁰⁷	43,702 LAIV recipients, 53,366 matched unvaccinated controls, 43,702 TIV recipients Age: 5 to 17 years, Setting: Kaiser Permanente health system	LAIV, TIV, unvaccinated comparison group	Relative risks (RR) were calculated as the ratio of the incidence rates of the two comparison groups without adjustment for any covariate. Hazard ratios (HR) were also calculated adjusting for matching factors and seasonal changes in background rates.	The incidence rates of SAEs overall and by specific diagnosis were not significantly higher or lower in the LAIV recipients relative to control groups in any comparison.	Children aged 5 to 8 vaccinated with LAIV had higher risk of acute GI event in 21 days (HR 1.36, 10.05 - 1.76) and 42 days (HR 1.30, 1.08 - 1.78) than unvaccinated cohort same age. Children aged 5 to 8 also had higher risk of acute respiratory tract event in 21 days (HR 1.12, 1.00 - 1.25) and 42 days (HR 1.15, 1.06 - 1.24) than unvaccinated cohort same age.
Glanz et al. 2011 ¹⁰⁸	N=66,283 who received trivalent inactivated influenza vaccine (TIV); Location=US; Age=24-59 months; Setting=Seven US managed care organizations (Vaccine Safety Datalink)	TIV	Calendar month (season) and age	Medically Attended Events That Met the Screening Criteria in Risk Windows of 0 to 2, 1 to 14, and 1 to 42 Days After Vaccination Non-confirmed Cases From Electronic Data Analysis Potentially serious Nervous system disorder: 6.32 (0.96-41.65), Cardiac event: 3.56 (0.55-22.89) Hypotension: 5.52 (0.71-43.07) Gastrointestinal tract disorder: 2.75 (1.07-7.09) Cellulitis and skin reaction: 3.06 (0.89-10.53) Potentially less serious and common Rash: 2.33 (0.68-7.93) Limb soreness: 3.56 (1.30-9.75) Fever: 1.40 (1.09-1.80) Gastrointestinal tract symptoms (vomiting and diarrhea): 1.52 (1.18-1.95) Medical Record-Confirmed Cases Potentially serious Gastrointestinal tract disorder: 7.70 (1.11-53.52) Cellulitis and skin reaction: 3.27 (0.36-29.70) Potentially less serious and common Rash: 1.94 (0.44-8.63)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
				Fever: 1.71 (1.64-1.80) Gastrointestinal tract symptoms (vomiting and diarrhea): 1.18 (1.10-1.25)	
Morgan et al. 2011 ¹⁰⁹	N= 169 children with urea cycle disorders (USD); Location=US Age=0-18 years;	A number of vaccines were analyzed but influenza was only specific vaccine reported on	Age	Influenza only: Relative Incidences Risk Period: Days After Vaccination 1-7: 2.31 (0.73-7.30) 8-21: 0.78 (0.19-3.12) 1-21: 1.28 (0.52-3.15)	Not reported
Ambridge et al. 2011 ⁶⁰	N=1,294 (269 cases of hospitalization of sickle cell crisis, 1025 controls); Location=United States; Age=6 months to 17 years; Setting=8 managed care organizations that comprise the Vaccine Safety Datalink	TIV	Cases/controls matched on age category, gender, Vaccine Safety Datalink site, and season	Case-control study OR (95% CI) of hospitalization TIV: 1.3 (0.8-2.2) Self-controlled All children: 1.21 (0.75-1.95) Boys: 1.07 (0.50-2.28) Girls: 1.33 (0.72-2.44) 6-23 months: 1.23 (0.25-6.04) 60 mo to 17 yr: 1.38 (0.83-2.29)	Not reported

GPRD = General Practice Research Database; TIV = Trivalent Influenza; IRR = Incidence Rate Ratio; OR = Odds Ratio; CI – Confidence Interval; ED = Emergency Department; RR=Relative Risk; LAIV = Live Attenuated Influenza Vaccine, HR = Hazard Ratio; SAEs = Serious Adverse Events; USD = Urea Cycle Disorders; Mo = Month; Yr = Year;

Measles-Mumps-Rubella (MMR)

The IOM committee studied the MMR vaccine. They found the evidence “convincingly supports” causal relationships in the pediatric population between MMR and the following: measles inclusion body encephalitis; febrile seizures;¹¹⁰⁻¹¹⁷ and anaphylaxis. The IOM committee found the evidence “favors acceptance” of a causal relationship between MMR and transient arthralgia in the pediatric population.¹¹⁸⁻¹²⁴ They found the evidence “favors rejection” of a causal relationships between MMR and autism in the pediatric population.¹²⁵⁻¹²⁹ Finally, the IOM committee found the evidence is “inadequate to accept or reject” a causal relationship in the pediatric population between MMR and the following: encephalitis, encephalopathy, afebrile seizures, meningitis, cerebellar ataxia, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, neuromyelitis optica, MS onset, and chronic arthropathy.

We identified no additional trials and four post-marketing studies of MMR in children published after the IOM searches. Study designs included self-controlled case series and case-control. The studies were set in England, Denmark, Italy, Canada, and the US.

Purpura. Andrews et al. (2012)¹³⁰ studied 343 cases of thrombocytopenic purpura (TP) in children aged 12 to 23 months between 1990 and 2007. Vaccination status was ascertained using review of the immunization registry and health outcomes from hospital discharge data. This study presented data from both a case-control design and a self-controlled case series. The self-controlled case series was adjusted for age only. The results indicate that the relative risk of TP was significant 14-27 days (England: RR 3.13, 95% CI 1.44, 6.79; Denmark: RR 2.75, 95% CI 1.61, 4.69) after immunization and 0- 42 days after immunization in both England (RR 1.92, 95% CI 1.02, 3.59) and Denmark (RR 2.01, 95% CI 1.34, 2.99). The data from Denmark were used in a model adjusting for age (1-month intervals), calendar period (one year intervals), gender, place of birth, ethnicity of mother (Danish or not), and maternal age at birth. Similar results were obtained with a significant relative risk of TP at 14-27 days (RR 2.54, CI 95% 1.47, 4.37) and 0-42 days (RR 1.85, 95% CI 1.23, 2.78) after immunization with MMR.

Bertuola et al. (2010)¹³¹ studied 2,311 children from four pediatric hospitals in Italy between November 1999 and December 2007. The sample included 387 cases (mean age: 4.9 years) of idiopathic thrombocytic purpura (ITP) and 1,924 controls (mean age: 5.7 years) who had gastroduodenal lesions or neurological disorders. Vaccination with MMR was confirmed using physician self-report, and health outcomes were ascertained using emergency department and hospital records. Analysis adjusted for age and use of NSAIDs, acetaminophen, antibacterials, mucolytics, and corticosteroids. There was a statistically significant association between vaccination with MMR and ITP (OR 2.4, 95% CI 1.2, 4.7). Results were also significant for use of each medication except corticosteroids.

The VSD was used to study the association between several vaccines and ITP.¹³² (Details are displayed in Table 27 on studies of multiple vaccines.) MMR was associated with ITP in infants 12 to 19 months old (OR 5.48, 95% CI 1.61, 18.64).

Hospitalization or ER visits. In a self-controlled case series study, Wilson et al. (2011)¹³³ studied 413,957 Canadian children who were vaccinated against MMR at 12-18 months of age between 2006 and 2009. Vaccination status was ascertained by a review of records from the Ontario Health Insurance Plan database. Health outcomes were verified using national databases like the Discharge Abstract Database and the National Ambulatory Care Registration System. Data were analyzed using a fixed effects Poisson regression model. The results show that the relative risk of hospitalization/ED use was significant on days 4-12 (RR 1.33, 95% CI 1.29–1.38) following the 12-month vaccination, and during days 10 to 12 after the 18-month vaccination.

Summary

We concur with the IOM's assessment supporting causal relationships between MMR and anaphylaxis in children who may be allergic to ingredients. We also concur with the IOM's assessment of an association of MMR vaccine with febrile seizures and measles inclusion body encephalitis in children.

MMR vaccination was associated with thrombocytopenic purpura in children in the short term after vaccination. Strength of evidence is moderate, as findings have been consistent and odds ratios similar in three European countries, Canada and the US.

There is moderate strength of evidence that MMR vaccination is associated with increased emergency department visits within two weeks. This is consistent with the IOM's findings that MMR vaccine is associated with febrile seizures.

We concur with the IOM's findings that the evidence is "inadequate to accept or reject" a causal relationship in the pediatric population between MMR and the following: encephalitis, encephalopathy, afebrile seizures, meningitis, cerebellar ataxia, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, neuromyelitis optica, MS onset, and chronic arthropathy.

Finally, we concur with the IOM's findings favoring rejection of a causal relationship between MMR vaccination and autism.

Table 21. Post-marketing studies of Measles-Mumps-Rubella (MMR) vaccine in children and adolescents

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Andrews et al. (2012) ¹³⁰	N=343 cases of thrombocytopenic purpura (TP); Location=England, Denmark; Age=12–23 months;	MMR	Age Cohort study: Models were fitted just adjusting for age (1-month intervals) and calendar period (1 year intervals), and also adjusting for other covariates: child's gender, place of birth (classified according to degree of urbanization), ethnicity of mother (Danish or not), mother's age at birth (using age categories: ≤19, 20–24, 25–29, 30–34, 35–39, ≥40)	Relative incidence of TP after MMR vaccination in children aged 12–23 months in England using the self-controlled case series method (SCCS) and in Denmark using the SCCS and cohort methods Self-Controlled Case Series Period after MMR (days) 0–13 England: 1.10 (0.33–3.71) Denmark: 1.38 (0.68–2.78) 14–27 England: 3.13 (1.44–6.79) Denmark: 2.75 (1.61–4.69) 28–42 England: 1.53 (0.58–4.03) Denmark: 1.94 (1.04–3.62) 0–42 England: 1.92 (1.02–3.59) Denmark: 2.01 (1.34–2.99) Cohort (Denmark) Period after MMR (days) 0–13: 1.32 (0.65–2.68) 14–27: 2.54 (1.47–4.37) 28–42: 1.72 (0.92–3.22) 0–42: 1.85 (1.23–2.78)	Not reported
Bertuola et al. (2010) ¹³¹	N=2,311 (387 cases, 1924 controls); Location=Italy; Age=Mean (SD) case/control: 4.9 (3.5) / 5.7 (4.9); Setting=Four pediatric hospitals: Department of Paediatrics, University of Padua; Giannina Gaslini Pediatric Hospital, Genova; Bambino Gesù Hospital, Rome;	MMR	Age and use of multiple medications	OR 95% CI for idiopathic thrombocytopenic purpura (ITP): MMR 2.4 (1.2-4.7)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
	Santobono-Pausilipon Pediatric Hospital, Naples				
Wilson et al. (2011) ¹³³	N=413,957; Location=Ontario, Canada; Age=12 and 18 months;	Live MMR	None in the model	<p>Relative incidence of combined endpoint (hospital admission or emergency room visit) following 12 month vaccination, comparison is 20 to 28 days after vaccination.</p> <p>Risk interval: Relative Incidence (95% CI)</p> <p>Day 4: 1.15 (1.06–1.25) Day 5: 1.19 (1.10–1.29) Day 6: 1.20 (1.11–1.31) Day 7: 1.20 (1.10–1.30) Day 8: 1.62 (1.50–1.74) Day 9: 2.04 (1.91–2.17) Day 10: 1.84 (1.72–1.97) Day 11: 1.72 (1.60–1.84) Day 12: 1.32 (1.22–1.43) Days 4 to 12** (Combined risk interval): 1.33(1.29–1.38)</p> <p>Relative incidences of individual endpoints (emergency room visit, hospital admission, death) during highest risk interval compared to control period.</p> <p>12 months Emergency visits: 1.34 (1.29–1.39) Admissions: 1.08 (0.93–1.25)</p> <p>18 months Emergency visits: 1.25 (1.18–1.34) Admissions: 1.23 (0.94–1.59)</p>	Not reported

TP = Thrombocytopenic Purpura; MMR = Measles-Mumps-Rubella; SCCS = Self-controlled Case Series; SD = Standard Deviation; OR = Odd Ratio; CI = Confidence Interval; ITP = Idiopathic Thrombocytopenic Purpura;

Rotavirus Vaccines: RotaTeq and Rotarix

Vaccines against rotavirus were not included in the 2011 IOM report on adverse effects of vaccines. We identified 32 eligible trials of rotavirus vaccine.¹³⁴⁻¹⁶⁵ We also identified several Phase II trials which were excluded because the dosage used was not comparable to that currently used in the product. We also excluded studies of Rotashield, which was withdrawn from the market in 1999, because of concerns regarding risk of intussusception.

Participants in the accepted studies received 2-3 oral administered doses of Rotarix (18 studies) or RotaTeq (15 studies).

Most participants were between 4 and 20 months of age. Studies were set all over the world including North America, South America, Europe, and Asia. The number of participants ranged from 100 to over 60,000. In general, neither Rotarix nor RotaTeq was associated with increased risk of AEs other than cough, runny nose or irritability. The only exception was an association of RotaTeq with respiratory and thoracic disorders in a trial of children with HIV in Sub-Saharan Africa.¹⁴⁵

Table 22. Vaccinated vs. unvaccinated children or adolescents. Rotavirus vaccines

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Armah G. E. et al.,2010 ¹³⁴ Ghana, Kenya, Mali	Controlled Clinical Trial	5	Sample size : 5,560, Age range: 4 - 12, Conditions: HIV	Rotavirus, RotaTeq, Merck, 2×10 ⁷ infectious units per reassortant rotavirus, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 6 Weeks Dose2: 10 Weeks Dose3: 14 Weeks	Bronchiolitis: OR 1 (0.063-16.002) Bronchopneumonia: OR 1.669 (0.398-6.989) Gastroenteritis: OR 1 (0.51-1.964) One or more serious adverse event: OR 0.933 (0.61-1.425) Other: OR 0.714 (0.226-2.253) Pneumonia: OR 1.302 (0.57-2.974) Respiratory tract infection: OR 0.6 (0.143-2.512) Upper respiratory tract infection: OR 0.5 (0.045-5.518)
Block S. L. et al.,2007 ¹³⁵ United States, Finland	Controlled Clinical Trial	5	Sample size : 1,312, Age range: 6 - 13, Percent female: 47.8%	Rotavirus, RotaTeq, Merck, ©1.1X10 ¹⁰ infectious U per dose. Pentavalent (G1–G4, and P[8]) human bovine(WC3) reassortant rotavirus vaccine (PRV), Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Weeks Dose2: 4-10 Weeks Dose3: 8-20 Weeks	Bronchiolitis/bronchitis/bronchospasm: OR 1.162 (0.419-3.224) Decreased appetite: OR 1.015 (0.063-16.269) Dehydration: OR 0.253 (0.028-2.267) Gastroenteritis: OR 0.507 (0.046-5.605) Gastrointestinal system: OR 0.301 (0.083-1.1) Influenza: OR 0.507 (0.046-5.605) Pneumonia: OR 3.056 (0.317-29.453) Respiratory syncytial virus infection: OR 6.778 (0.03-1543.45) Respiratory: OR 1.905 (0.755-4.806) Serious Adverse Event: OR 0.783 (0.438-1.399)
Chang C.-C. et al.,2009 ¹³⁶ Taiwan	Controlled Clinical Trial	NC	Sample size : 189, Age range: 6 - 12, Percent female: 47.6%	Rotavirus, RotaTeq, Merck, five human-bovine reassortant rotaviruses, each of which contained the WC3 bovine strain backbone with different human viral surface proteins G1, G2, G3, G4 and P[8]. An estimated final concentration of 6.5 × 10 ⁷ IU to 1.2 × 10 ⁸ IU was included in a 2 mL dose solution, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Weeks Dose2: 4-10 Weeks Dose3: 8-20 Weeks	Diarrhea: OR 2.015 (0.972-4.178) Fever, rectal temperature > 38.0°C: OR 0.875 (0.492-1.555) Irritable crying: OR 0.979 (0.06-15.882) Vomiting: OR 1.13 (0.392-3.252)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Christie C. D. C. et al.,2010 ¹³⁷ Jamaica	Controlled Clinical Trial	4	Sample size : 1,804, Mean age: 7.7, Age range: 6 - 12, Percent female: 48.4%	Rotavirus, Routine Vaccines, RotaTeq, Merck, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Month Dose2: 2 Month Dose3: 2 Month	Bronchiolitis: OR 1.081 (0.475-2.463) Convulsions: OR 0.99 (0.139-7.044) Death: OR 0.329 (0.034-3.172) Femur fracture: OR 0.99 (0.062-15.854) Gastroenteritis: OR 0.99 (0.199-4.918) Otitis media: OR 1.322 (0.295-5.922) Urinary Tract Infection: OR 1.389 (0.439-4.393) Viral infections: OR 3.973 (0.443-35.62)
Dennehy P. H. et al.,2005 ¹³⁸ United States, Canada	Controlled Clinical Trial	6	Sample size : 529, Mean age: 8.7, Age range: 5 - 15, Percent female: 51%	Rotavirus, Routine Vaccines, RIX4414, GlaxoSmithKline, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Month Dose2: 2 Month	Bronchiolitis: OR 0.502 (0.1-2.532) Hypovolemia/dehydration: OR 0.507 (0.031-8.187)
Goveia M. G. et al.,2007 ¹³⁹ 11 countries	Controlled Clinical Trial	8	Sample size : 2,074, Mean age: NR, Age range: 6 - 12, Conditions: Premature babies	Rotavirus, RotaTeq, Merck, vaccine contained 5live human-bovine reassortant rotaviruses, each consisting of the WC3 bovine strain expressing a viral surface protein corresponding to human rotavirus serotypes G1, G2, G3, G4, or P1A, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Days Dose2: 4-10 Weeks Dose3: 4-10 Weeks	Apneic attack (extreme preemie): OR 1.056 (0.066-16.901) At least one SAE (extreme preemie): OR 0.702 (0.249-1.979) Bronchiolitis (all subjects, most frequent AE): OR 0.7 (0.354-1.383) Bronchiolitis (extreme preemie): OR 1.056 (0.148-7.509) Deaths (total, all subjects): OR 1.056 (0.148-7.509) Death due to SIDS (all subjects): OR 1.056 (0.066-16.901) Pneumonia (extreme preemie): OR 2.113 (0.191-23.345)
Grant L. R. et al.,2012 ¹⁴⁰ United States	Controlled Clinical Trial	5	Sample size : 1,003, Age range: 6 - 12	Rotavirus, RotaTeq, Merck, PRV is a live, pentavalent, vaccine that contains human bovine (WC3 strain) reassortant rotaviruses expressing the G1, G2, G3, G4, and P[8] human rotavirus antigens, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Weeks Dose2: 4-10 Weeks Dose3: 8-20 Weeks	Deaths, (Were outside of 42 day safety window and not associated with vaccine): OR 1.945 (0.176-21.517) Diarrhea, all events: OR 1.208 (0.939-1.555) Diarrhea, vaccine related: OR 1.113 (0.851-1.456) Fever, all events: OR 0.943 (0.736-1.21) Fever, vaccine related: OR 1.047 (0.804-1.364) Vomiting, all events: OR 1.097 (0.788-1.527) Vomiting, vaccine related: OR 1.384 (0.911-2.102)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Kawamura N. et al.,2011 ¹⁴¹ Japan	Controlled Clinical Trial	4	Sample size : 764, Mean age: 7.7, Age range: 6 - 14, Percent female: 50%	Rotavirus, Rotarix, GlaxoSmithKline, Each dose (1ml) of the lyophilized RIX4414 vaccine (Rotarix TM) contained at least 10-6.0 median Cell Culture Infective Dose (CCID50) of live attenuated human rotavirus RIX4414 strain, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Month Dose2: 1 Month	# of patients with any AE (31-day post vacc): OR 0.96 (0.71-1.299) Cough/runny nose: OR 1.045 (0.762-1.434) Diarrhea: OR 1.652 (0.866-3.153) Eczema: OR 1.299 (0.82-2.057) Fever: OR 1.421 (0.837-2.414) Irritability: OR 1.128 (0.835-1.523) Loss of appetite: OR 1.397 (0.895-2.179) Upper respiratory tract infection: OR 1.011 (0.61-1.678) Vomiting: OR 1.084 (0.706-1.664)
Kerdpanich A. et al.,2010 ¹⁴² Thailand	Controlled Clinical Trial	9	Sample size : 400, Age range: 6 - 12	Rotavirus, Routine Vaccines, Rotarix, GlaxoSmithKline, RIX4414 vaccine contained at least 106.0 cell culture infective dose 50 (CCID50) of the RIX4414 strain. CaCO3 buffer based reconstitution., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Month Dose2: 2 Month	Loss of appetite: OR 0.487 (0.205-1.16) SAE - UTI: OR 0.145 (0.009-2.384)
Kim D. S. et al.,2008 ¹⁴³ Korea	Controlled Clinical Trial	3	Sample size : 178, Age range: 6 - 12, Percent female: 42.7%	Rotavirus, RotaTeq, Merck, PRV contained 5 WC3 reassortant rotaviruses, each consisting of the WC3 bovine strain with viral surface proteins corresponding to human rotavirus serotypes G1, G2, G3, G4, and P1A_8 suspended in a liquid sodium citrate and phosphate buffer at an aggregate viral titer of approximately 6.9 _ 10 ⁷ to 8.6 _ 10 ⁷ infectious units per dose., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Weeks Dose2: 4-10 Weeks Dose3: 8-20 Weeks	One or more serious adverse events: OR 0.44 (0.141-1.373)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Kim J. S. et al.,2012 ¹⁴⁴ South Korea	Controlled Clinical Trial	5	Sample size : 684, Mean age: 8.8, Percent female: 45.3%	Rotavirus, Routine Vaccines, RIX4414, NR, >=10*6.0 median Cell Culture Infective Dose per ml, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 8 Weeks Dose2: 16 Weeks	Bronchiolitis (total study period): OR 0.409 (0.123-1.356) Bronchiolitis (unsolicited/31d): OR 0.77 (0.327-1.811) Gastroenteritis (total study period): OR 0.427 (0.113-1.61) Patients with unsolicited AE over 31d: OR 0.815 (0.565-1.176) URI (unsolicited/31d): OR 0.861 (0.371-2) gastroenteritis (unsolicited/31d): OR 0.843 (0.467-1.521) nasopharyngitis (unsolicited/31d): OR 0.563 (0.301-1.051)
Laserson K. F. et al.,2012 ¹⁴⁵ Kenya	Controlled Clinical Trial	7	Sample size : 297, Age range: 0 - 12, Percent female: 51.8%, Conditions: HIV	Rotavirus, RotaTeq, Merck, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 6 Weeks Dose2: 10 Weeks Dose3: 14 Weeks	Gastrointestinal disorders: OR 1.534 (0.968-2.431) General disorders and administration site conditions: OR 0.97 (0.599-1.57) Infections: OR 0.684 (0.332-1.412) Infections Dose 2: OR 0.524 (0.301-0.912)** One of more serious adverse events: OR 0.581 (0.286-1.179) Respiratory, thoracic and mediastinal disorders: OR 337.733 (45.817-2489.554)**
Madhi S. A. et al.,2010 ¹⁴⁶ South Africa and Malawi	Controlled Clinical Trial	3	Sample size : 4,939, Mean age: 6.4 in placebo and rotarix gro, Percent female: 49.6%, Conditions: HIV	Rotavirus, Routine Vaccines, Rotarix, GlaxoSmithKline, Calcium carbonate buffer, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 6 Weeks Dose2: 10 Weeks Dose3: 14 Weeks	Bronchiolitis: OR 1.027 (0.563-1.871) Bronchopneumonia: OR 0.995 (0.601-1.647) Deaths: OR 0.959 (0.661-1.393) Gastroenteritis: OR 0.779 (0.584-1.039) Overall SAE: OR 0.823 (0.68-0.995)** Pneumonia: OR 0.818 (0.564-1.185) Sepsis: OR 1.234 (0.722-2.11)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Narang A. et al.,2009 ¹⁴⁷ India	Controlled Clinical Trial	5	Sample size : 363, Mean age: 8.7, Age range: 8 - 10, Percent female: 47.1%	Rotavirus, Routine Vaccines, Rotarix, GlaxoSmithKline, Vaccine contained at least 106.0 median cell culture infectious dose (CCID50) of the vaccine strain per dose. The placebo contained the same constituents as the study vaccine but without the virus component. The lyophilized vaccine and placebo were reconstituted with a diluent containing Calcium Carbonate as a buffer., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Month Dose2: 1 Month	Cough/runny nose: OR 1.515 (0.276-8.315) Cough/runny nose: OR 4.472 (2.02-9.902)** Diarrhea: OR 1 (0.218-4.597) Diarrhea: OR 0.89 (0.366-2.164) Fever: OR 0.675 (0.346-1.319) GE episodes from dose 1 to one month post-dose 2: OR 0.94 (0.433-2.04) Irritability: OR 0.242 (0.031-1.913) Irritability: OR 2.316 (1.135-4.723)** Loss of appetite: OR 1.136 (0.5-2.584) Serious adverse event: OR 1.473 (0.241-8.988) Vomiting: OR 0.093 (0.034-0.256)**
Omenaca F. et al.,2012 ¹⁴⁸ France, Portugal, Poland and Spain	Controlled Clinical Trial	6	Sample size : 1,009, Mean age: 8.5, Age range: 5 - 14, Percent female: 49%, Conditions: Premature babies	Rotavirus, Rotarix, GlaxoSmithKline, A single dose of RIX4414 vaccine contained at least 106.0 median cell culture infective dose of the live-attenuated RIX4414 human rotavirus strain., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Days Dose2: 30-83 Days	At least 1 unsolicited symptom: OR 0.602 (0.458-0.792)** At least 1 unsolicited symptom (grade 3): OR 0.285 (0.142-0.573)** At least 1 unsolicited symptom (vaccine-related): OR 0.608 (0.401-0.92)** infection - Gastroenteritis: OR 0.744 (0.341-1.625) infection - Upper resp infection: OR 0.649 (0.291-1.448)
Phua K. B. et al.,2005 ¹⁴⁹ Singapore	Controlled Clinical Trial	3	Sample size : 2,464, Mean age: 13.3, Age range: 11 - 17, Percent female: 50.2%	Rotavirus, Routine Vaccines, Rotarix, GlaxoSmithKline, 10.7 ffu group. To produce RIX4414, the parent 89-12vaccine strain was further passaged in Vero cells and cloned [18, 20]. The vaccine was a lyophilized preparation supplied in single-dose vials with calcium carbonate buffer for reconstitution. Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Days Dose2: 1 Month	Severe Vomiting (Dose 1): OR 1 (0.312-3.203) Severe Vomiting (Dose 2): OR 1 (0.312-3.203)
Phua K. B. et al.,2009 ¹⁵⁰ Hong Kong, Singapore, Thailand	Controlled Clinical Trial	8	Sample size : 10,708, Mean age: 11.6, Age range: 5 - 20, Percent female: 49.1%	Rotavirus, Routine Vaccines, Rotarix, GlaxoSmithKline, contained at least 106.0 median cell culture infectious dose (CCID50) of the vaccine strain per dose, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Dose2: 1-2 Month	Death: OR 0.332 (0.035-3.195) Intussusception (from Dose 1 to age 2): OR 1.996 (0.601-6.632) Withdrawal due to AE: OR 0.581 (0.229-1.477)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Phua K. B. et al.,2012 ¹⁵¹ Singapore, Hong Kong, Taiwan	Controlled Clinical Trial	1	Sample size : 8,407, Mean age: 35.3, Age range: 23 - 44, Percent female: 49%, Percent pregnant: Percent Pregnant: 0%	Rotavirus, Routine Vaccines, Rotarix, GlaxoSmithKline, reconstitution of lyophilized vaccine in calcium carbonate buffer to a concentration of at least 10*6.0 cell culture infective dose (CCID50) of live-attenuated virus (median), Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: NR Dose2: 1-2 Month	Intussusception: OR 1.983 (0.18-21.878) gastroenteritis (failed treatment?): OR 1.487 (0.248-8.905)
Rodriguez Z. M. et al.,2007 ¹⁵² United States	Controlled Clinical Trial	1	Sample size : 1,358, Mean age: 9.35, Age range: 6 - 13, Percent female: 51.1%	Rotavirus, Routine Vaccines, RotaTeq, Merck, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Days Dose2: 28-70 Days Dose3: 56-140 Days	Cough: OR 1.027 (0.748-1.41) Diarrhea: OR 0.711 (0.535-0.946)** Fever: OR 0.901 (0.728-1.115) Nasal congestion: OR 0.957 (0.699-1.311) Nasopharyngitis: OR 0.891 (0.664-1.197) Otitis media: OR 0.786 (0.561-1.103) Upper respiratory infection: OR 0.827 (0.647-1.056) Vomiting: OR 0.747 (0.528-1.055)
Ruiz-Palacios G. M. et al.,2006 ¹⁵³ Finland, Argentina, Brazil, Chile, Colombia, the Dominican Republic, Honduras, Mexico,Nicaragua, Panama, Peru, Venezuela	Controlled Clinical Trial	6	Sample size : 63,225, Mean age: 8.2, Percent female: 49%	Rotavirus, Routine Vaccines, Rotarix, GlaxoSmithKline, Contained 10.5 median cell-culture infective doses of the RIX4414 vaccine strain. Vaccine was reconstituted with 1.3 ml of liquid calcium carbonate buffer., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 2 Month Dose2: 4 Month	Death: OR 1.298 (0.872-1.932) Definite intussusception, 31 days or less after dose 1: OR 0.498 (0.045-5.493) Definite intussusception, 31 days or less after dose 2: OR 0.996 (0.288-3.441) Definite intussusception, 31 days or less after either dose: OR 0.854 (0.287-2.541) Definite intussusception, between dose 1 and visit 3: OR 0.56 (0.248-1.268) Hospitalization: OR 0.877 (0.8-0.961)** Serious adverse events: OR 0.879 (0.804-0.962)**
Sow S. O. et al.,2012 ¹⁵⁴ Vietnam, Bangledash, Ghana, Kenya, Mali	Controlled Clinical Trial	5	Sample size : 1,960, Mean age: NR, Age range: 6 - 14, Percent female: 48.3%	Rotavirus, RotaTeq, Merck, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 6 Weeks Dose2: 10 Weeks Dose3: 14 Weeks	Bronchiolitis: OR 1.002 (0.063-16.044) Deaths: OR 0.6 (0.143-2.518) One or more serious adverse events: OR 0.834 (0.254-2.742) Pneumonia: OR 0.667 (0.111-4.003)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Steele A. D. et al.,2010 ¹⁵⁵ South Africa	Controlled Clinical Trial	4	Sample size : 475, Mean age: 6.3	Rotavirus, Rotarix, GlaxoSmithKline, RIX4414 developed from 89-12 parent vaccine strain that was cloned and passaged on Vero cells. Viral concentration of 1 dose contained at least 1x10 ⁶ .0 medial cell culture infective dose and lyophilized vaccine was reconstituted with calcium carbonate as buffer, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 10 Weeks Dose2: 14 Weeks	Serious adverse events (any): OR 1.011 (0.336-3.046)
Steele A. D. et al.,2011 ¹⁵⁶ South Africa	Controlled Clinical Trial	5	Sample size : 100, Mean age: 7, Age range: 6 - 10, Percent female: 53%, Conditions: HIV	Rotavirus, Rotarix, GlaxoSmithKline, Each dose of the vaccine contained at least 106.0 median cell culture infective dose(CCID 50) of the active virus strain. Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Month Dose2: 1 Month Dose3: 1 Month	At least 1 Grade 3 unsolicited symptom w/in 31 d): OR 1 (0.425-2.352) Bronchopneumonia: OR 1.872 (0.512-6.848) Bronchopneumonia - Grade 3: OR 1 (0.236-4.242) Cough: OR 1.43 (0.622-3.286) Fatality: OR 0.621 (0.203-1.899) GE: OR 2.136 (0.503-9.068) GE - Grade 3: OR 2.087 (0.365-11.949) Irritability: OR 1.17 (0.39-3.515) Oral candidiasis - Grade 3: OR 2.087 (0.365-11.949)
Tregnaghi M. W. et al.,2011 ¹⁵⁷ Argentina, Brazil, Colombia, Dominican Republic, Honduras, and Panama	Controlled Clinical Trial	4	Sample size : 6,568, Mean age: 8.6, Age range: 6 - 12	Rotavirus, Rotarix, GlaxoSmithKline, Contained at least 106.0 median Cell Culture Infective Dose (CCID50) of live attenuated human rotavirus RIX4414 strain. The lyophilized vaccine was reconstituted with the supplied buffer before oral administration., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Days Dose2: 1-2 Month	Bronchiolitis: OR 1.178 (0.874-1.588) Intussusception: OR 1 (0.183-5.464) Death: OR 2.503 (0.548-11.436) Gastroenteritis: OR 0.727 (0.529-1)** Pneumonia: OR 1 (0.699-1.43)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Vesikari T. et al.,2004 ¹⁵⁸ Finland	Controlled Clinical Trial	5	Sample size : 405, Mean age: 8.3, Age range: 6 - 12	Rotavirus, Rotarix, GlaxoSmithKline, The vaccine was a lyophilized product; it was reconstituted with a diluent containing calcium carbonate as buffer. Each reconstituted vaccine dose contained 104.7 focus forming units of the RIX4414 strain rotavirus vaccine, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Not reported	Dose1: 2 Month Dose2: 4 Month	Diarrhea, Dose 1: OR 1.652 (0.685-3.984) Diarrhea: OR 2.042 (0.538-7.745) Fever greater than or equal to 38.0°C, Dose 2: OR 1.11 (0.694-1.773) Fever greater than or equal to 38.0°C, Dose 1: OR 1.103 (0.578-2.105) Irritability, Dose 1: OR 1.088 (0.715-1.654) Irritability: OR 1.276 (0.845-1.928) Loss of appetite, Dose 1: OR 1.542 (0.914-2.602) Vomiting, Dose 1: OR 1.879 (0.788-4.48) Vomiting: OR 0.645 (0.299-1.393)
Vesikari T. et al.,2006 ¹⁵⁹ Finland	Controlled Clinical Trial	5	Sample size : 1,946, Age range: 2 - 8	Rotavirus, NR, Low-potency pentavalent RotaTeq G1, G2, G3, G4, P1A 2.41×10 ⁶ ., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Weeks Dose2: 4-8 Weeks Dose3: 8-16 Weeks	Post-vaccination fever greater than or equal to 38.1 C rectally after dose 1: OR 1.479 (0.982-2.229) Post-vaccination fever greater than or equal to 38.1 C rectally after dose 2: OR 1.171 (0.788-1.74) Post-vaccination fever greater than or equal to 38.1 C rectally after dose 3: OR 1.286 (0.873-1.894)
Vesikari T. et al.,2006 ¹⁶⁰ 11 countries	Controlled Clinical Trial	8	Sample size : 69,274, Mean age: 9.8, Age range: 6 - 12, Percent female: 49.3%	Rotavirus, RotaTeq, Merck, Pentavalent, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Days Dose2: 4-10 Weeks Dose3: 4-10 Weeks	Not calculable
Vesikari T. et al.,2011 ¹⁶¹ Finland	Controlled Clinical Trial	3	Mean age: 9.1, Age range: 6 - 12, Percent female: 50%	Rotavirus, Rotarix, GlaxoSmithKline, RIX4414 oral suspension (liquid formulation). Contained at least 10 ⁶ -median cell culture infective dose (CCID ₅₀) of live attenuated RIX4414 human rotavirus strain. The liquid formulation of RIX4414 contained sucrose as excipient and the content of sucrose in the liquid formulation is higher than one in the lyophilized formulation., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Days Dose2: 1 Month	Cough/runny nose: OR 0.959 (0.477-1.927) Diarrhea: OR 0.49 (0.066-3.639) Fever: OR 1.652 (0.381-7.173) Irritability: OR 1.199 (0.582-2.47) Loss of appetite: OR 0.778 (0.334-1.814) Vomiting: OR 1.098 (0.404-2.984)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Vesikari T. et al.,2004 ¹⁶² Belgium, Germany	Controlled Clinical Trial	5	Sample size : 59, Age range: 1 - 44	Rotavirus, Rotarix, GlaxoSmithKline, Derived from the parent strain 89-12single dose of a minimum of 10(6.1) focus forming unit (ffu) of RIX4414 or placebo, with prior administration of Mylanta® as buffer, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 0 Days	Not calculable
Zaman K. et al.,2009 ¹⁶³ Bangladesh	Controlled Clinical Trial	7	Sample size : 294, Mean age: 6.1, Age range: 6 - 7, Percent female: 53.4%	Rotavirus, Routine Vaccines, Rotarix, GlaxoSmithKline, 10.5 median cell culture infective dose of the G1P strain., Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 6 Weeks Dose2: 10 Weeks Dose3: 14 Weeks	fever: rectal temperature =38 °C: OR 0.3 (0.134-0.675)** Any diarrhea: =6/day: OR 0.66 (0.074-5.862) Gastroenteritis: OR 0.49 (0.03-8.001) Loss of appetite: OR 1.138 (0.553-2.341) Unsolicited symptoms: OR 0.603 (0.272-1.336) Vomiting: =1 episode of forceful emptying of partially digested stomach contents =1 h after feeding within a day: OR 1.377 (0.564-3.364)
Zaman K. et al.,2010 ¹⁶⁴ Bangladesh and Vietnam	Controlled Clinical Trial	8	Sample size : 2,035, Mean age: 8.9, Age range: 5.9 - 25.9, Percent female: 47%	Rotavirus, RotaTeq, Merck, Pentavalent rotavirus vaccine containing 5 human-bovine reassortant rotaviruses with the WC3 bovine strain as backbone and viral surface proteins corresponding to human rotavirus serotypes G1, G2 G3, G4, P1A[8], Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 6 Weeks Dose2: 10 Weeks Dose3: 14 Weeks	Death: OR 0.75 (0.167-3.36)
Zaman K. et al.,2012 ¹⁶⁵ Bangladesh	Controlled Clinical Trial	5	Sample size : 1,136, Mean age: 8.2, Percent female: 48.6%	Rotavirus, Routine Vaccines, RotaTeq, GlaxoSmithKline, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Oral	Dose1: 6 Weeks Dose2: 10 Weeks Dose3: 14 Weeks	Accidental drowning: OR 1 (0.062-16.027) Acute diarrhea: OR 1 (0.062-16.027) All Serious Adverse Events: OR 0.939 (0.47-1.878) Death, All causes: OR 3.011 (0.312-29.031) Pneumonia: OR 0.728 (0.331-1.599)

OR = Odds Ratio; CI = Confidence Interval; HIV = Human Immunodeficiency Virus; CCID = Cell Culture Infective Dose; PRV = Pentavalent Rotavirus Vaccine; IU = International Unit; SAE = Serious Adverse Events; AE = Adverse Event; ffu = Focus Forming Unit; h = Hour;

We found four post-licensure studies of vaccines against rotavirus (Buttery, 2011; Velazquez, 2012; Patel, 2011; Shui, 2012).¹⁶⁶⁻¹⁶⁹ The studies were set in Australia (Buttery, 2011), US (Shui, 2012), Mexico (Velazquez, 2012; Patel, 2011) Brazil (Patel, 2011). All studied intussusception, as an earlier brand of rotavirus vaccine (Rotashield) was withdrawn from the market in 1999 due to reports of this AE. Studies are displayed in Table 23.

Intussusception. Buttery et al. (2011)¹⁶⁶ studied children under the age of 24 months who received either RotaTeq (N=296,023) or Rotarix (302,455) between July 2007 and December 2008. Vaccination status was ascertained through a national vaccination registry. Health outcomes were collected using active surveillance: the Australian Pediatric Surveillance Unit (APSU), the Pediatric Active Enhanced Disease Surveillance (PAEDS), and from the active surveillance of four major tertiary pediatric hospitals. Relative risk ratios were estimated to compare observed and expected cases of intussusception by age. For the RotaTeq vaccine, in the 1-7 days post vaccination period, the risk of intussusception was significant after the first dose (RR 5.26, 95% CI 1.09, 15.4) but insignificant after the second and third doses. The overall relative risk of intussusception was insignificant (RR 1.15, 95% CI 0.37, 2.68) during this period. There was a similar decreasing trend in the risk of intussusception with each dose in the 21-day period after vaccination; only dose one had a significant association (RR 3.51, 95% CI 1.29, 7.64). In children vaccinated with Rotarix, risk of intussusception was insignificant for all doses; the overall relative risk was 1.58 (95% CI 0.51, 3.69) for the 7-day post vaccination period and 1.37 (95% CI 0.73, 2.34) for the 21-day period.

In a self-controlled case series, Velazquez et al. (2012)¹⁶⁷ studied 698 infants (age < 1 year) with intussusception between January 2008 and October 2010 in Mexico. Use of the Rotarix vaccine was confirmed using immunization cards or a review of all available medical records. In the absence of medical records, vaccination status was ascertained using parent/guardian reported data. Active surveillance identified cases of intussusception through reviews of admission and discharge logs from hospitals, emergency departments, pediatric, surgery and radiology wards. Episodes of intussusception were confirmed using radiography, surgery, or post mortem examination. Data were modeled using a conditional Poisson regression and adjusted for age as a potential confounder. The relative incidence of intussusception was significant after dose 1 during the 0-6 days (RR 6.49, 95% CI 4.17, 10.09), 0-15 days (RR 3.24, 95% CI 2.15, 4.87), and 0-30 days (RR 1.75, 95% CI 1.24, 2.48) post vaccination periods. The risk of intussusception after dose 2 was not significant for all three post vaccination periods studied.

Patel et al. (2011)¹⁶⁸ studied 2,665 infants (615 cases of intussusception, 2,050 controls), 45-245 days of age from 53 hospitals in seven states in Brazil and from 16 hospitals in 10 states in Mexico. This study reports two sets of results, one as a case-control study and the other as a self-controlled case series. Vaccination with Rotarix was ascertained by a review of medical records, and cases of intussusception were verified by a review of clinical records. Data were analyzed using a conditional logistic regression model that was matched by date of birth, and also controlled for age and sex. For the children studied in Mexico, the likelihood of intussusception in the case-control analysis was significant (OR 5.8, 95% CI 2.6, 13.0) at 1-7 days but not at 8-14 days or 15-21 days after vaccination. After the second dose, the likelihood of intussusception was significant 8-14 days (OR 2.3, 95% CI 1.2, 4.4) days after vaccination but not in the other periods. The case-control analysis of data from the children in Brazil showed no significant relationship between vaccine and intussusception at any time period after dose 1, but showed a significant association (OR 1.9, 95% CI 1.1, 3.4) within 1-7 days after dose 2.

The results of Patel's self-controlled case series analyses¹⁶⁸ showed a significant association of vaccination with intussusception in 1-7 days after the first dose (OR 5.3, 95% CI 3.0, 9.3) and 8-14

days (OR 2.2, 95% CI 1.2, 4.2) and 15-21 days (OR 2.2, 95% CI 1.2, 4.0) after the second dose in children in Mexico. In Brazil, the association with intussusception after the first dose was insignificant at each time period, but significant (OR 2.6, 95% CI 1.3, 5.2) 1-7 days after the second dose.

The only post-licensure study conducted in the U.S. (Shui, 2012)¹⁶⁹ found no association between RotaTeq and intussusception at any time after vaccination.

Summary

Vaccines against rotavirus were not included in the 2011 IOM report.

Both RotaTeq and Rotarix were associated with cough, runny nose and irritability in children. There is moderate strength evidence from several RCTs for these mild, short-term adverse events.

In clinical trials, there was no association between either of the two currently available vaccines (RotaTeq and Rotarix) and any serious adverse events, including intussusception, in the long or short-term.

However, a high quality epidemiological study (N = 296,023) found RotaTeq associated with intussusception in children 1 to 21 days following the first of three required doses. Strength of evidence is moderate given size and quality of that study, conducted in Australia.

Two case-control studies conducted in Latin America found an association RotaTeq with intussusception in children following the first of three required doses of Rotarix. Strength of evidence is low.

One study estimated Rotarix increases risk by 3.7 (95% CI 1.2, 7.3) additional cases per 100,000 person/years in Mexico. The other Latin American study estimated risk as one case per 51,000 vaccines in Mexico and one case per 68,000 vaccines in Brazil. These risks need to be placed in context with the morbidity and mortality prevented by vaccination in developing countries.

Table 23. Post-marketing studies of rotavirus vaccines in children and adolescents

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Buttery et al. (2011) ¹⁶⁶	Children under 24 months old receiving RotaTeq (N=296,023) or Rotarix (302,455) in Australia; Active surveillance mechanisms	Two states used RotaTeq, two states used Rotarix	No control for confounders	Observed and expected cases of intussusception by age in months in jurisdictions delivering RotaTeq 1–7 days post-vaccine Dose 1: 5.26 (1.09, 15.4) Dose 2: 1.33 (0.16, 4.82) Dose 3: 0.00 (0.00, 2.16) Total: 1.15 (0.37, 2.68) 1–21 days post-vaccine Dose 1: 3.51 (1.29, 7.64) Dose 2: 0.67 (0.14, 1.94) Dose 3: 0.00 (0.00, 0.89) Total: 0.77 (0.37, 1.41) Observed and expected cases of intussusception by age in months in jurisdictions delivering Rotarix 1–7 days post-vaccine Dose 1: 3.45 (0.71, 10.1) Dose 2: 1.05 (0.13, 3.80) Total: 1.58 (0.51, 3.69) 1–21 days post-vaccine Dose 1: 1.53 (0.42, 3.92) Dose 2: 0.88 (0.29, 2.05) Total: 1.37 (0.73, 2.34)	Not reported
Velazquez et al. (2012) ¹⁶⁷	N=698 infants < 1 year old in Mexico with intussusception Active surveillance across hospitals in Mexico from the Mexican Institute of Social Security	Rotarix	Age	Relative Incidence Dose and risk period (days after vaccination) Dose 1, 0-30 days: 1.75 (1.24–2.48) Dose 2, 0-30 days: 1.06 (0.75–1.48) Dose 1, 0-15 days: 3.24 (2.15–4.87) Dose 2, 0-15 days: 1.06 (0.69–1.61) Dose 1, 0-6 days: 6.49 (4.17–10.09) Dose 2, 0-6 days: 1.29 (0.80–2.11)	Not reported
Patel et al. (2011) ¹⁶⁸	N=2,665 (615 cases of intussusception, 2050 controls); Location=Mexico, Brazil; Age=45-245 days; Setting=53 hospitals in 7 states in Brazil and at	RV1, Rotarix	Matched by date of birth, also controlled for age, sex	OR (95% CI) for intussusception (Case-control) Mexico Either dose, any time before reference date 1.0 (0.6–1.7) First dose 1–7 days: 5.8 (2.6–13.0) 8–14 days: 1.0 (0.4–2.9)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
	16 hospitals in 10 states in Mexico			15–21 days: 0.8 (0.3–2.1) Second dose 1–7 days: 1.1 (0.6–2.2) 8–14 days: 2.3 (1.2–4.4) 15–21 days: 2.0 (1.0–3.8) Brazil Either dose, any time before reference date 1.7 (0.9–2.9) First dose 1–7 days: 1.4 (0.4–4.8) 8–14 days: 1.6 (0.5–4.7) 15–21 days: 0.6 (0.1–2.2) Second dose 1–7 days: 1.9 (1.1–3.4) 8–14 days: 0.9 (0.5–1.8) 15–21 days: 0.8 (0.4–1.6) OR (95% CI) for intussusception (Self-controlled case-series) Mexico First dose 1–7 days: 5.3 (3.0–9.3) 8–14 days: 1.1 (0.5–2.7) 15–21 days: 0.9 (0.3–2.2) Second dose 1–7 days: 1.8 (0.9–3.8) 8–14 days: 2.2 (1.1–4.2) 15–21 days: 2.2 (1.2–4.0) Brazil First dose 1–7 days: 1.1 (0.3–3.3) 8–14 days: 1.3 (0.5–3.4) 15–21 days: 0.2 (0.0–1.4) Second dose 1–7 days: 2.6 (1.3–5.2) 8–14 days: 1.4 (0.7–3.0) 15–21 days: 0.9 (0.4–2.0)	
Shui I. M. et al., 2012 ¹⁶⁹ USSui IM, et al. 2012 162	Children receiving RotaTeq in US (N=117,575)	1	Sample size : 117,575, Mean age: NR, Age range: 4 - 34	Rotavirus, RotaTeq, Merck, Adjuvant: Not Reported, Preservative: Not reported, Delivery: OralShui	Dose1: 0 Days Dose2: 2 Month Dose3: 2 Month

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
USA					
Haber et al. May 2013				http://pediatrics.aappublications.org/content/early/2013/05/08/peds.2012-2554	

OR = Odds Ratio; CI = Confidence Interval;

Hepatitis B vaccine

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 IOM found insufficient evidence to accept or reject a causal relationship with any other AEs.

We found no trials and one post-marketing study of Hepatitis B vaccine in children or adolescents.

Autism. Gallagher and Goodman (2010)¹⁷⁰ conducted a secondary analysis of 7,074 boys, age 3 to 17 years, born prior to 1999, using the National Health Interview Survey through 2002. Vaccination status and health outcomes were reported by parents in an interview with trained interviewers who asked them to gather vaccination records in advance. Data were analyzed using a logistic regression adjusted for race/ethnicity, two-parent household, and maternal education. Result was 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.”

We concur with the IOM’s conclusions regarding “insufficient” evidence of association of Hepatitis B vaccine with any short or long term adverse events in children. Based on the newly identified study discussed above, there is insufficient evidence of an association of the Hepatitis B with autism in children.

Table 24. Post-marketing study of Hepatitis B vaccine in children and adolescents

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Gallagher and Goodman 2010 ¹⁷⁰	N=7,074 (30 with autism, 7,044 without autism); Location=US; Age=boys 3 through 17 years born prior to 1999; Used National Health Interview Survey data	Hepatitis B	Race/ethnicity, two-parent household, maternal education	OR (95% CI) of autism diagnosis Received first dose of Hepatitis B vaccine during first month of life, compared with receipt after first month of life or not at all OR=3.00 (1.11-8.13)	Non-Hispanic white: 0.36 (0.15-0.88) Two-parent household 0.30 (0.12-0.75) Maternal education, high school or higher 2.32 (0.85-6.30)

OR = Odds Ratio, CI – Confidence Interval;

HPV

The IOM committee studied the HPV vaccine, which is administered to children, adolescents, and young adults. Except where noted below, studies did not report specific AEs by age. The IOM committee did not find evidence that “convincingly supports” causal relationships for any conditions. The IOM committee found the evidence “favors acceptance” of a causal relationship between the HPV vaccine and anaphylaxis. The IOM committee found the evidence is “inadequate to accept or reject” causal relationships between the HPV vaccine and the following: ADEM, transverse myelitis, neuromyelitis optica, MS, Guillain-Barré syndrome, chronic inflammatory disseminated polyneuropathy, brachial neuritis, amyotrophic lateral sclerosis, transient arthralgia, pancreatitis, thromboembolic events, and hypercoagulable states.

We found nine additional reports of trials of the HPV vaccine in children and adolescents; seven¹⁷¹⁻¹⁷⁷ were original trials, and two^{178, 179} were longitudinal follow ups of clinical trials. Participants were between 7 and 27 years of age and received three doses of vaccine (either Cervarix or Gardasil) or placebo. The trials were conducted in North America, South America, Asia, Europe, Australia, and Africa. Most participants were female; there was one trial in males¹⁷¹ with a later follow-up.¹⁷⁷ The study of males found a significant association between vaccination with Gardasil and respiratory and thoracic disorders in the 15 days post-vaccination (OR 20.78, 95% CI 7.09, 60.89). One study of Gardasil¹⁷⁴ included only children with HIV; that trial found no AEs associated with vaccination. Only one other trial¹⁷⁵ found an association with medically significant adverse conditions (OR 1.94, 95% CI 1.23, 3.07). This trial, conducted in 208 women in Korea, found a relationship between Cervarix and the following Grade 3 (severe) adverse events: arthralgias (OR 2.68, 95% CI 1.29, 5.59), fatigue (OR 1.96, 95% CI 1.39, 2.77), GI symptoms (OR 2.41, 95% CI 1.39, 4.19), and rash (OR 2.67, 95% CI 1.23, 5.80). In this study, Grade 3 events were defined as severe enough to prevent normal daily activity.

Table 25. Vaccinated vs. unvaccinated children or adolescents. HPV vaccine

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Block S. L. et al.,2010 ¹⁷² Asia, Europe, Latin America, North America	Controlled Clinical Trial	7	Sample size : 21,480, Mean age: NR, Age range: 9 - 26, Percent female: 94%	Human papillomavirus (HPV), Gardasil/Silgard, Merck, HPV-6/11/16/18, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Not reported	Dose1: 1 Days Dose2: 2 Month Dose3: 6 Month	Cardiac: OR 2.472 (0.257-23.766) Death: OR 1.295 (0.502-3.341) Discontinuation due to AE: OR 1.099 (0.596-2.025) Gastrointestinal: OR 1.648 (0.302-8.998) Infections/infestations: OR 1.295 (0.662-2.532) Injury/poisoning/procedural: OR 0.669 (0.398-1.123) Musculoskeletal/connective tissue: OR 0.412 (0.037-4.543) Neoplasms benign malignant, unspecified: OR 0.824 (0.052-13.172) Nervous system: OR 0.824 (0.238-2.846) Pregnancy/puerperium/perinatal: OR 0.736 (0.463-1.17) Psychiatric: OR 1.236 (0.206-7.397) Renal/urinary: OR 0.824 (0.116-5.849) Reproductive system/breast: OR 0.824 (0.206-3.294) Respiratory/thoracic/mediastinal: OR 1.03 (0.276-3.836) Vascular: OR 164.803 (0-178246427.81)
De Carvalho N. et al.,2010 ¹⁷⁸ Brazil	Controlled Clinical Trial, Followup	3	Sample size : 433, Mean age: 26.5, Percent female: 100%, Percent Pregnant: 9.5%	Human papillomavirus (HPV), Cervarix, GlaxoSmithKline, 20 µg of HPV-16 L1 virus-like particle and 20 µg of HPV-18 L1 virus-like particle. Each type of virus-like particle was produced on Spodoptera frugiperda Sf-9 and Trichoplusia ni Hi-5 cell substrate with AS04 adjuvant containing 500 µg aluminum hydroxide and 50 µg 3-deacylated monophosphoryl lipid A (MPL, Corixa, Montana, USA) provided in a monodose vial, Adjuvant: ASO 4-Aluminum, Preservative: Not reported, Delivery: Intramuscular	Dose1: 0 Month Dose2: 1 Month Dose3: 6 Month	Medically significant adverse event (any): OR 1.344 (0.641-2.816)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Giuliano A. R. et al.,2011 ¹⁷⁷ 18 countries	Controlled Clinical Trial, follow-up	4	Sample size : 3,895, Mean age: 20.5, Age range: 15 - 27, Percent female: 0%	Human papillomavirus (HPV), Gardasil or Silgard, Merck, Quadrivalent HPV types 6, 11, 16, 18. Low-dose contained 20 ug type 6, 40 ug type 11, 40 ug type 16, 20 ug type 18, with 225 ug aluminum adjuvant. Adjuvant: Aluminum, Preservative: Not reported, Delivery: Intramuscular	Dose1: 1 Days Dose2: 2 Month Dose3: 6 Month	Death (entire study period): OR 0.3 (0.082-1.091)
Khatun S. et al.,2012 ¹⁷⁶ Bangladesh	Controlled Clinical Trial	2	Sample size : 67, Mean age: 12, Age range: 9 - 13, Percent female: 100%	Human papillomavirus (HPV), Cervarix, GlaxoSmithKline, HPV16/18 ASO4-adjuvanted cervical cancer vaccine. Purified L1 VLPs of HPV16/18 at 20/20-g per dose formulated on ASO4 adjuvant comprising 500 gm of aluminum hydroxide and 50 gm of 3-deacylated monophosphate lipid A, Adjuvant: ASO 4, Preservative: Not reported, Delivery: Not reported	Dose1: 0 Days Dose2: 1 Month Dose3: 6 Month	Not calculable

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Kim S. C. et al.,2011 ¹⁷⁵ Korea	Controlled Clinical Trial	8	Sample size : 208, Mean age: 22, Age range: 15 - 25, Percent female: 100%	Human papillomavirus (HPV), Cervarix, GlaxoSmithKline, HPV-16/18 contained 20 mcg each of HPV-16 and -18 L1 (structural protein of HPV) virus like particle, adjuvanted with the proprietary immunostimulant ASO4 adjuvant system (comprising 3-O desacyl-4(1)-MPL [50 mcg] adsorbed on aluminum hydroxide [Al(OH) ₃ , 500 mcg]), Adjuvant: ASO 4- Aluminum, Preservative: Not reported, Delivery: Intramuscular	Dose1: 0 Month Dose2: 1 Month Dose3: 6 Month	Medical significant adverse condition: OR 1.942 (1.227-3.073)** New onset chronic diseases: OR 0.41 (0.199-0.846)** Solicited - Arthralgias (Grade 3): OR 2.682 (1.287-5.591)** Solicited - Fatigue (Grade 3): OR 1.959 (1.388-2.766)** Solicited - Fevers (Grade 3): OR 1.725 (0.355-8.377) Solicited - GI symptoms (Grade 3): OR 2.405 (1.381-4.19)** Solicited - Headache (Grade 3): OR 1.633 (1.101-2.422)** Solicited - Myalgia (Grade 3): OR 2.275 (1.582-3.272)** Solicited - Rash (Grade 3): OR 2.668 (1.228-5.8)** Solicited - Urticaria (Grade 3): OR 2.156 (0.608-7.651) Unsolicited - Breast and reproductive system: OR 2.651 (0.763-9.208) Unsolicited - Infections and infestations: OR 2.149 (0.927-4.983) Unsolicited - any AE (Grade 3): OR 0.078 (0.026-0.232)**
Levin M. J. et al.,2010 ¹⁷⁴ US (not stated explicitly)	Controlled Clinical Trial	7	Sample size : 126, Mean age: NR, Age range: 7 - 12, Conditions: HIV	Human papillomavirus (HPV), Gardasil, Merck, Quadrivalent human papillomavirus (QHPV) (types 6, 11, 16, 18) recombinant vaccine, 0.5 mL, intramuscular, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Intramuscular	Dose1: 0 Weeks Dose2: 8 Weeks Dose3: 24 Weeks	Ear and eye and respiratory system: OR 0.305 (0.019-5.034) Laboratory abnormality: OR 0.935 (0.094-9.343) Systemic reactions: OR 0.617 (0.054-7.053)
Li R. et al.,2012 ¹⁷³ China	Controlled Clinical Trial	4	Sample size : 600, Mean age: 24.6, Age range: 9.0 - 45.8, Percent female: 83.3%	Human papillomavirus (HPV), Gardasil/Silgard, Merck, Says to see ref 19. But ref 19 is of a different trial where multiple formulations were used. Cannot ascertain useful information., Adjuvant: Not Reported, Preservative: Not Reported, Delivery: Intramuscular	Dose1: 1 Days Dose2: 2 Month Dose3: 6 Month	Systemic AE (any): OR 1.122 (0.81-1.553) Systemic AE (vaccine-related): OR 1.066 (0.747-1.522)

Author- Year- Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Moreira Jr E. D. et al.,2011 ¹⁷¹ 18 countries including Brazil, Germany, Mexico, US, South Africa, Australia, Canada	Controlled Clinical Trial	7	Sample size : 4,065, Mean age: NR, Age range: 16 - 26, Percent female: 0%	Human papillomavirus (HPV), Gardasil/Silgard, Merck, Quadrivalent HPV (type6/11/16/18) L1 VLP vaccine with amorphous aluminum hydroxyphosphate sulfate (AAHS) adjuvant, Adjuvant: Aluminum, Preservative: Not reported, Delivery: Intramuscular	Dose1: 1 Days Dose2: 2 Month Dose3: 6 Month	Death (entire study period): OR 0.3 (0.083-1.093) Dizziness(1-15 days): OR 1.061 (0.555-2.027) Gastrointestinal Disorders(1-15 days): OR 1.049 (0.81-1.359) General Disorders(1-15 days): OR 0.953 (0.761-1.194) Influenza (1-15 days): OR 0.958 (0.625-1.469) Injury, Poisoning and Procedural Complications(1-15 days): OR 1.259 (0.734-2.162) Musculoskeletal and Connective Tissue Disorders(1-15 days): OR 1.232 (0.844-1.801) Nasopharyngitis(1-15 days): OR 0.881 (0.585-1.328) Nervous System Disorders(1-15 days): OR 0.889 (0.729-1.084) Oropharyngeal pain(1-15 days): OR 1.032 (0.654-1.63) Pharyngitis(1-15 days): OR 1.106 (0.602-2.033) Respiratory, Thoracic And Mediastinal Disorders(1-15 days): OR 20.774 (7.088-60.889)** Skin And Subcutaneous Tissue Disorders(1-15 days): OR 0.84 (0.497-1.421) Upper respiratory tract infection(1-15 days): OR 1.361 (0.761-2.434) Discontinuation due to SAE (entire study period): OR 0.3 (0.083-1.093)
Roteli-Martins C. M. et al.,2012 ¹⁷⁹ Brazil	Controlled Clinical Trial, followup	NC	Sample size : 436, Mean age: 26.5, Age range: 15 - 25, Percent female: 100%, Percent Pregnant: 17%	Human papillomavirus (HPV), HPV-16/18, GlaxoSmithKline, Described in another study, Adjuvant: ASO 4, Preservative: Not reported, Delivery: Reported in previous study	Dose1: 0 Month Dose2: 1 Month Dose3: 6 Month	Medically Significant Adverse Events: OR 1.721 (0.998-2.97) New Onset Autoimmune Disease: OR 0.955 (0.133-6.84) New Onset Chronic Disease: OR 2.42 (0.464-12.609) Serious Adverse Events: OR 1.382 (0.516-3.699)

OR = Odds Ratio; CI = Confidence Interval; HPV = Human papillomavirus; MPL = Monophosphoryl Lipid; Al(OH)₃ = Aluminium hydroxide; GI = Gastrointestinal; HIV = Human Immunodeficiency Virus; QHPV = Quadrivalent Human Papillomavirus; AE = Adverse Event; AAHS = Amorphous Aluminum Hydroxyphosphate Sulfate; SAE = Serious Adverse Events;

We found two post-marketing studies of HPV vaccine in adolescents / young adults published after the IOM report. Both were conducted using the VSD and included hundreds of thousands of vaccine recipients.

Various illnesses. Between August 2006 and March 2008, Chao et al. (2012)¹⁸⁰ followed 189,629 females, aged 9 to 26 years, who had received the HPV vaccine from two MCOs. Immunization with HPV vaccine was ascertained by a review of health records and health outcomes were identified through electronic health records followed by in-depth case review by a panel of experts. Data were analyzed to generate incidence rate ratio (IRR) estimates of onset of select autoimmune conditions in the vaccinated group compared to unvaccinated female populations of similar age. Vaccinated patients had a significantly lower incidence of juvenile rheumatoid arthritis (IRR 0.36, 95% CI 0.14, 0.71) and Type 1 diabetes (IRR 0.54, 95% CI 0.45, 0.70), they had a higher incidence of Hashimoto's disease (IRR 2.02, 95% CI 1.65, 2.60); the authors report that an investigation of a temporal relationship and biological plausibility revealed no consistent evidence of a safety signal.

Gee et al. (2011)¹⁸¹ studied the administration of 600,558 doses of HPV4 in females age 9 to 26 years in seven large MCOs between August 2006 and October 2009. Vaccination status and health outcomes were confirmed using weekly standardized data files from participating MCOs. Case ascertainment was limited to the first episode in a particular time period. Data were analyzed using Poisson based maximized sequential probability ratio test (maxSPRT) and a logistic regression model (appendicitis only). The logistic regression was adjusted for sex, age, and seasonality. No statistically significant increased risk for any of the pre-specified adverse events (appendicitis, Guillain Barré Syndrome, seizures, stroke, syncope, venous thromboembolism) was detected after vaccination.

Summary

We concur with the IOM committee's finding that evidence "favors acceptance" of a causal relationship between the HPV vaccine and anaphylaxis in children and adolescents who may be allergic to ingredients.

We found moderate strength evidence that HPV vaccine is not associated with onset of juvenile rheumatoid arthritis or Type 1 diabetes. We found insufficient strength evidence that HPV vaccine may be associated with onset of Hashimoto's disease. Although we identified only one post-licensure study on these AEs, it was of high quality and included a very large population, and authors investigated cases closely.

Strength of evidence is moderate that HPV vaccine is not associated with appendicitis, Guillain Barré Syndrome, seizures, stroke, syncope, or venous thromboembolism. Although we identified only one post-licensure study on these AEs, it was of high quality and included a very large population, thus the moderate rating.

We concur with the IOM committee findings that the evidence is "inadequate to accept or reject" causal relationships between the HPV vaccine and the following: ADEM, transverse myelitis, neuromyelitis optica, MS, chronic inflammatory disseminated polyneuropathy, brachial neuritis, amyotrophic lateral sclerosis, transient arthralgia, pancreatitis, thromboembolic events, and hypercoagulable states. We found no studies of these conditions.

Table 26. Post-marketing studies of HPV vaccine in children and adolescents

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Chao et al. 2012 ¹⁸⁰	N=189,629 females who received HPV Age=9–26 years; Setting=Two managed care organizations in California	HPV4	Not reported	<p>Incidence rate ratio (IRR) and 95% confidence interval (CI) of select autoimmune conditions in the vaccinated vs. non-vaccinated female populations of similar age in Kaiser Permanente Southern California</p> <p>Rheumatologic/autoimmune: Immune thrombocytopenia: 1.24 (0.91–2.02) Systemic lupus erythematosus: 1.10 (0.71–1.66) Rheumatoid arthritis: 0.70 (0.41–1.60) Juvenile rheumatoid arthritis: 0.36 (0.14–0.71) Autoimmune hemolytic anemia - excluded</p> <p>Endocrine: Type 1 diabetes: 0.54 (0.45–0.70) Hashimoto’s disease: 2.02 (1.65–2.60) Graves’ disease: 0.76 (0.42–1.10)</p> <p>Neurological/ophthalmic: Multiple sclerosis: 1.37 (0.74–3.20) Other demyelinating diseases of central nervous system: 0.71 (0.38–2.13) Optic neuritis: 1.45 (1.00–2.91) Uveitis: 1.28 (0.53–6.39)</p>	Not reported
Gee et al. 2011 ¹⁸¹	N=600,558 doses of HPV4; Females age 9-26 years in 7 large managed care organizations (MCOs) in US	HPV4	Logistic regression: sex, age, and seasonality	No statistically significant increased risk for any of the pre-specified adverse events (Appendicitis, Guillain Barré Syndrome, Seizures, Stroke, Syncope, Venous Thromboembolism) after vaccination was detected.	Not reported

HPV = Human papillomavirus; IRR = Incidence Rate Ratio; CI = Confidence Interval; MCOs = Managed Care Organizations;

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,¹⁸² 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;¹⁸³ and anaphylaxis.¹⁸² The IOM committee found the evidence “favors acceptance” of causal relationships for no other conditions. Finally, the IOM committee found the evidence is “inadequate to accept or reject” a causal relationship between the varicella virus vaccine and the following: seizures, ADEM, transverse myelitis, Guillain-Barré syndrome, small fiber neuropathy, onset or exacerbation of arthropathy, and thrombocytopenia.

We found no additional studies in children.

Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis-Containing Vaccines

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.¹⁸⁴⁻¹⁸⁸ The IOM committee found the evidence is “inadequate to accept or reject” causal relationships between diphtheria toxoid-, tetanus toxoid- or acellular pertussis-containing vaccine and the following: infantile spasms; seizures; cerebellar ataxia; autism; ADEM; transverse myelitis; MS relapse in children; serum sickness; immune thrombocytopenic purpura; and SIDS.

We found no additional studies in children published after the IOM search date.

Meningococcal Vaccine

ACIP guidelines recommend the MPSV4 for individuals 2-10 years of age. The IOM committee found the evidence “convincingly supports” a causal relationship with anaphylaxis in children who may be allergic to ingredients. The committee found the evidence “inadequate to accept or reject” causal relationships between meningococcal vaccine and the following: encephalitis, encephalopathy, ADEM, transverse myelitis, MS, Guillain-Barre syndrome, CIDP, and chronic headache. We concur with these findings.

We found no additional trials or post-licensure studies of meningococcal vaccine in children.

Studies of combination vaccines or multiple vaccines

Allergies / Asthma. We identified five post-marketing studies on allergic symptoms, wheezing, or asthma, that were not included in the IOM report. A study in the Netherlands using parent questionnaires to ascertain vaccination status and health outcomes found no association between receipt of a combined DTP-IPV vaccine and asthma, hay fever, eczema, food allergy or atopic disorders (Bernsen, 2006).¹⁸⁹ A case-control study of over 2,000 children with atopic dermatitis and a family history of allergy in twelve Western countries (Gruber, 2008)¹⁹⁰ found 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. The study also found that a significant relationship between Hepatitis B vaccine in the first 6 months of life with elevated total IgE (OR 1.48, 95% CI 1.03, 2.13). Varicella vaccine seemed to have a protective effect against elevated total IgE. A German study (Mommers, 2004)¹⁹¹ found no relationship between vaccination against pertussis, measles, rubella, or Hib and atopic disease. A self-controlled case series of premature infants born in the US (Mullooly, 2007)¹⁹² 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 fact, some of the vaccines had a protective effect in the week after vaccination. Finally, Thomson¹⁹³ found no association of MMR vaccine with asthma in an Australian cohort. (Two diphtheria-tetanus vaccines not currently used in the US were also studied; no association with asthma was found.)

Seizures. Sun, 2012¹⁹⁴ examined national registry data on over 378,000 children who received a combined DTap-IPV-Hib vaccine in Denmark from 2003-2009. They assessed the association of vaccination with febrile seizures, controlling for birth circumstances, demographics, and family history of epilepsy. In both a cohort analysis and self-controlled case series (SCCS), risk of febrile seizures on the day of vaccination was significant (cohort – first vaccination, HR 6.02, 95% CI 2.86, 12.65; cohort – second vaccination, HR 3.94, 95% CI 2.18, 7.10; SCCS - first vaccination, HR 6.49, 95% CI 3.10, 13.61; SCCS – second vaccination, HR 3.97, 95% CI 2.20, 7.16). An American study (Chen, 1997)¹⁹⁵ investigated the relationship between DTP and MMR vaccines and seizures in children from four HMOs in the US. For DTP, the relative risk for seizures was elevated on the day of vaccination (RR 2.20, 95% CI 1.50, 3.40). For MMR, the risk was elevated on days 4 to 7 (RR 1.80, 95% CI 1.20, 2.70) and 8 to 14 (RR 2.50, 95% CI 2.20, 3.30) after vaccination. The authors also investigated the relationship between Td vaccination and emergency department visit or hospitalization. They found that risk of emergency department visit was elevated within 14 days of vaccination.

Gold, 2010¹⁹⁶ also studied the relationship between DTP and MMR vaccines and seizures. They used Australian registry data and medical records to ascertain vaccination status and health outcomes. For MMR, the risk for seizures was elevated between days 6 to 11 after exposure (IRR 2.11 95% CI 1.43, 3.10). For DTP, the risk was not elevated during any time period studied.

Bell's Palsy. A small self-controlled case series of 233 Bell's Palsy cases in Northern California (Rowhani, 2012)¹⁹⁷ found no association with vaccination with TIV or Hepatitis B vaccine.

Leukemia. Groves and colleagues¹⁹⁸ 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 than the 439 cases. Data collection forms were completed by mothers using vaccination records. 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. (Ma, 2005)¹⁹⁹ 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 (MacArthur, 2008)²⁰⁰ 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 (Pagaoa, 2011)²⁰¹ found that several vaccines may have a protective effect against acute lymphoblastic leukemia.

Diabetes. Hummel²⁰² conducted a secondary analysis of data from the BABYDIAB study in Germany to investigate the possible association of many factors (breast feeding, vaccinations, environmental, infections) and development of islet antibodies before the age of two. They included vaccines for Hib, measles, mumps, and rubella (separately) in their analyses; no association with the vaccines was found.

Purpura. A recent analysis 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. (O’Leary, 2012)¹³² In children from 12 to 19 months of age, MMR vaccine was associated with purpura (IRR 5.48, 95% CI 1.61, 18.64). None of the vaccines were associated with purpura in children aged two to six years. Purpura were associated with vaccination against Hepatitis A in children aged 7 to 17 years (IRR 23.14, 95% CI 3.59, 149.30) and a vaccination against varicella in children aged 11 to 17 (IRR 12.14, 95% CI 1.10, 133.96).

Encephalitis. Pahud, 2012 investigated whether various factors were associated with encephalitis in California children and adolescents.²⁰³ Of 1,434 cases, immunization records were requested for over 800 and received for only 246. Of these, 136 were excluded due to incomplete records or no vaccinations in the one-year observation period. In the 110 encephalitis cases included, there was no association with either measles virus-containing vaccines or pertussis antigen-containing vaccines.

Summary of studies of multiple vaccines

Strength of evidence is insufficient to determine an association between polio vaccine in newborns and sensitivity to food allergens. Strength of evidence is also insufficient to determine an association between Hepatitis B vaccine in the first 6 months of life and elevated total IgE. These associations were reported in one medium size study (N = 2,173) of children with a family history of food allergy living in 12 countries in multiple continents.

Strength of evidence of association of DTaP-IPV-Hib vaccination with febrile seizures in children in the short-term is moderate, based on a very large, high quality study. As reported in an earlier section, strength of evidence of association of MMR vaccination with febrile seizures in children in the short-term is moderate, based on another large high quality study.

There is high strength evidence that vaccinations recommended for children in the US are not associated with childhood leukemia. Multiple large epidemiological studies have assessed MMR, DTaP, Td, Hib, Hep B, and polio vaccine and have found no association.

In the short-term, purpura were associated with vaccination against Hepatitis A in children aged 7 to 17 years, vaccination against varicella in children aged 11 to 17, and MMR in children from 12 to 19 months of age. Strength of evidence is moderate. Cases were rare (one or two per age group), and the majority were mild.

Table 27. Post-marketing studies of combination vaccines or multiple vaccines in children and adolescents

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Bensen et al. 2006 ¹⁸⁹ Retrospective Cohort	N=1,875; Location=Netherlands; Age=8-12 years; Setting=Orthodox Reformed (Protestant) primary schools	DTP-IPV (diphtheria-tetanus-pertussis-(inactivated) poliomyelitis vaccination)	A variable was included in the multivariate model if it changed the univariate point estimate by at least 10%. Following confounders were assessed: Season of birth; Birth order; Gender; Gestational age; Birth weight; Age of the mother at the time of delivery; Exposure to smoking (prenatally, during the first year of life and currently); Breast feeding for four months or more (yes/no); Housing in the first year of life (rural and living on a farm with livestock/rural, other/city); Pet keeping (furry pets or birds yes/no) during the first year of life and currently; Day care starting at age 6 months or less (yes/no); Current age; Asthma and/or allergy of the parents and/or siblings; Highest educational level of the parents; Family income; Current level of urbanization (five levels); Living on a farm with livestock (yes/no); Sibship size; Mold in the child's bedroom in the past year; Frequent (more than 5 days/week) consumption of fruit (yes/no) (raw or cooked) vegetables (yes/no) anti-oxidants (yes/no) unskimmed dairy products (yes/no) wholegrain bread (yes/no); Frequent (at least 1 day/week) consumption of fish; Frequent exercise (school gym at least once a week and playing games with physical activity for at least half an hour a day and either being a member of a sporting club or	OR (95% CI) for Atopic disorders Asthma: 1.04 (0.76–1.42) Hay fever: 0.79 (0.55–1.12) Eczema: 0.87 (0.66–1.14) Food allergy: 1.13 (0.71–1.81) Any atopic disorder: 1.00 (0.80–1.24) OR (95% CI) for Physician diagnosed atopic disorders Asthma: 1.03 (0.72–1.46) Hay fever: 1.06 (0.59–1.90) Eczema: 0.96 (0.73–1.25) Food allergy: 1.13 (0.71–1.81) Any atopic disorder: 1.04 (0.82–1.31)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
			walking or cycling from home to school vice versa for at least 1 h a day); Body mass index; Hib vaccination.		
Gruber et al. 2008 ¹⁹⁰ Retrospective cohort	N=2,173 (cases with atopic dermatitis and family history of allergy); Location=12 countries, Australia, Austria, Belgium, Czech Republic, France, Germany, Italy, the Netherlands, Poland, South Africa, Spain, and the UK; Age=1-2 years; Setting=97 study centers in 10 European countries, South Africa and Australia	Diphtheria, tetanus, pertussis, polio, Haemophilus influenzae Type B, Hepatitis B, mumps, measles, rubella, varicella, BCG, meningococci and pneumococci	Total assessed: country, age, gender, birth weight, maternal age, family history of atopy, presence of siblings, breastfeeding, parental smoking, day care, exposure to pet animals and SCORAD total index	R (95% CI) for IgE-sensitivity to aeroallergens Infants immunized against Hepatitis B at birth were less likely to be IgE-sensitized to aeroallergens (adjusted Hepatitis B at birth: 0.54 (0.32, 0.90) No effect was seen for Hepatitis B immunization later on in life. OR (95% CI) for sensitivity to food allergens Newborns immunized against polio: 2.60 (1.08–6.25,) Immunization against polio later in life: NS OR (95% CI) for elevated total IgE Hepatitis B vaccine (first 6 months): R 1.48 (1.03–2.13), OR (95% CI) for elevated total IgE varicella immunization in the first year: 0.27 (0.08–0.87) varicella immunization in the 3 months before screening: 0.28 (0.14–0.56) varicella immunization since birth: 0.37 (0.21–0.65) rubella immunization since birth: 0.79 (0.63–0.99) pneumococci immunization since birth: 0.49 (0.27–0.92) No significant association of vaccination status and atopy (as defined by any positive IgE test) was found. OR (95%CI) for a moderate to severe SCORAD index immunization against polio in the first 6 months: 0.66 (0.45–0.97) pertussis immunization in the first year: 0.30 (0.10–0.89) OR (95% CI) for eczema severity varicella immunization in the first year: 0.34 (0.12–0.93) varicella immunization since birth: 0.56 (0.33–	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Mommers et al. 2004, ¹⁹¹ Case-control	N=510; Location=Dutch-German borderland; Age=7-8 years; Setting=Study on respiratory health in children conducted in the Dutch-German borderland, involving the Municipal Health Services of Kreis Heinsberg, Germany and of the Westelijke Mijnstreek, the Netherlands	Bacille Calmette-Guérin (BCG), pertussis, measles/mumps, rubella, and Haemophilus influenzae type b (Hib)	Gender, birth order, country of residence, socioeconomic status, breastfeeding, exposure to environmental tobacco smoke, home dampness, pets, and childhood infections (measles, mumps, rubella, varicella, and scarlet fever). Analyses stratified according to country of residence or respiratory status were additionally performed.	0.93) Odds Ratios and 95% Confidence Intervals for Association Between Risk Factors and Atopic Disease Pertussis Respiratory symptoms 0.83 (0.45–1.52) Allergic sensitization 0.89 (0.47–1.70) Sensitized against grasses 0.84 (0.38–1.84) Sensitized against HDM 1.02 (0.46–2.25) Measles Respiratory symptoms 0.93 (0.30–2.90) Allergic sensitization 1.51 (0.43–5.35) Sensitized against grasses 2.85 (0.45–18.08) Sensitized against HDM 1.93 (0.38–9.95) Rubella Respiratory symptoms 1.17 (0.65–2.10) Allergic sensitization 0.85 (0.46–1.57) Sensitized against grasses 0.75 (0.36–1.56) Sensitized against HDM 0.89 (0.41–1.92) Hib Respiratory symptoms 1.39 (0.60–3.19) Allergic sensitization 0.74 (0.30–1.79) Sensitized against grasses 0.55 (0.19–1.58)	Gender (male vs. female) Respiratory symptoms 1.68 (1.13–2.49) Allergic sensitization 2.68 (1.76–4.09) Sensitized against grasses 3.44 (2.05–5.76) Sensitized against HDM 2.90 (1.69–4.96) Birth order Only younger siblings Respiratory symptoms 1.06 (0.54–2.08) Allergic sensitization 0.57 (0.29–1.13) Sensitized against grasses 0.52 (0.24–1.12) Sensitized against HDM 0.74 (0.30–1.83) 1 older sibling Respiratory symptoms 0.91 (0.47–1.76) Allergic sensitization 0.47 (0.24–0.92) Sensitized against grasses 0.44 (0.20–0.95) Sensitized against HDM 0.75 (0.31–1.82) 2 older siblings Respiratory symptoms 1.63 (0.74–3.60) Allergic sensitization

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
				<p>Sensitized against HDM 1.14 0.33–3.89</p> <p>Frequencies of BCG, Pertussis, Measles, Rubella, and Hib Vaccination in Children With Respiratory Symptoms and in Sensitized Children</p> <p>Respiratory symptoms Pertussis: 0.85 (0.60–1.19) Measles: 0.86 (0.36–2.06) Rubella: 0.94 (0.64–1.38) Hib: 1.14 (0.82–1.58)</p> <p>Allergic sensitization Pertussis: 1.04 (0.73–1.47) Measles: 1.59 (0.61–4.17)</p> <p>Rubella: 0.80 (0.54–1.19) Hib: 0.94 (0.67–1.32)</p>	<p>0.40 (0.18–0.91) Sensitized against grasses .40 (0.16–1.02) Sensitized against HDM 0.69 (0.24–1.97) >2 older siblings Respiratory symptoms 0.95 (0.30–3.02) Allergic sensitization 0.33 (0.09–1.15) Sensitized against grasses 0.20 (0.04–1.13) Sensitized against HDM 0.29 (0.05–1.71)</p>
Mullooly et al. 2007 ¹⁹² Case-control	N=1,074 (844 atopy cases, 230 controls); Location=West Coast; Age=6-16 years; Setting=Kaiser Permanente Northwest (KPNW) HMO	DTP, MMR, HBV, IPV, HIB	<p>Covariates associated with atopy at $p < 0.20$ in bivariate analyses were included in the regression models.</p> <p>controls for age at skin test, gender, race, maternal/family history of atopy, low birth weight, maternal age at birth, breast feeding at 2 months, household smoking, dogs in home, calendar period of skin test (1978–93, 1994–99, 2000–01)</p>	<p>OR (95% CI) for atopy All cases versus all controls No. of pertussis doses 1.06 (0.89–1.27) No. of measles doses 0.85 (0.56–1.29) No. of HIB doses 0.93 (0.81–1.08) No. of HBV doses 1.15 (0.88–1.49)</p> <p>All cases versus asthma controls No. of pertussis doses 0.98 (0.74–1.29) No. of measles doses 0.80 (0.42–1.53) No. of HIB doses 0.88 (0.73–1.07) No. of HBV doses 1.04 (0.75–1.45)</p> <p>Asthma cases versus asthma controls</p>	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
				No. of pertussis doses 0.95 (0.71–1.29) No. of measles doses 0.69 (0.36–1.35) No. of Hib doses 0.88 (0.72–1.08) No. of HBV doses 1.05 (0.73–1.50)	
Thomson et al. 2010 ¹⁹³ Prospective cohort	N=488; Location=Australia; Age=2-6 years (outcomes ascertained at 6 years); Setting=Melbourne Atopy Cohort Study (MACS), an ongoing prospective cohort study initiated in 1989	Triple antigen [diphtheria, tetanus and pertussis (DTP)], combined diphtheria and tetanus (CDT), measles mumps rubella (MMR)	Parental socio-demographics, allergic disease, parental smoking history; parental education; gender of child and older siblings, pet ownership of at least one dog and/or cat	RR (95% CI) for Asthma Triple antigen (DTP) 1st year: 4.75 (0.88, 25.58) 2nd year: 0.74 (0.56, 0.96) Combined diphtheria and tetanus 1st year 1.88 (1.28, 2.77) 2nd year 1.00 (0.57, 1.74) Measles mumps rubella 2nd year 0.78 (0.61, 1.00)	RR (95% CI) for Asthma Socio-demographics child Gender (male) 1.61 (1.21, 2.14) Older siblings (at least 1) 1.27 (1.17, 1.38) Characteristics mother Education (tertiary) 0.94 (0.67, 1.31) Marital status (married) 0.75 (0.45, 1.24) Smoking (never) 0.70 (0.47, 1.03) Asthma 1.43 (1.07, 1.90) Eczema 1.32 (1.02, 1.72) Allergic rhinitis 0.87 (0.65, 1.17) Food allergy .14 (0.84, 1.53) Drug allergy 1.33 (1.02, 1.74) Characteristics father Education (tertiary) 1.11 (0.78, 1.58) Smoking (never) 0.99 (0.71, 1.40) Asthma 1.34 (1.01, 1.79) Eczema

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
					1.16 (0.84, 1.61) Allergic rhinitis 1.37 (1.04, 1.81) Food allergy 0.73 (0.50, 1.08) Drug allergy 0.89 (0.44, 1.81) Pet ownership Dog 0.84 (0.61, 1.14) Cat 1.05 (0.78, 1.42)
Sun et al. 2012 ¹⁹⁴ Prospective cohort study and self-controlled case series	N=378,834 (cohort study), 7811 children with febrile seizures (cases); Location=Denmark; Age=0-7 years; Cohort was identified by using information from the Danish Civil Registry	DTaP-IPV-Hib	Cohort: child's sex, multiple births, calendar year of birth, season, gestational age, birth weight, parity of the mother, parental history of epilepsy, maternal education, and family income at the time of birth. Season was included as a time-varying variable. SCCS: age of the child (1-week interval) and the season of the observation period	Cohort analysis - Adjusted HR Time After DTaP-IPV-Hib Vaccination First Vaccination 0 days: 6.02 (2.86-12.65) 1-3 days: 1.38 (0.58-3.31) 4-7 days: 0.41 (0.10-1.69) 0-7 days: 1.64 (0.93-2.88) Second Vaccination 0 days: 3.94 (2.18-7.10) 1-3 days: 1.57 (0.91-2.72) 4-7 days: 0.52 (0.23-1.18) 0-7 days: 1.36 (0.93-1.98) Third Vaccination 0 days: 1.07 (0.73-1.57) 1-3 days: 0.89 (0.70-1.14) 4-7 days: 1.06 (0.87-1.28) 0-7 days: 0.99 (0.86-1.15) SCCS analysis Relative IR Time After DTaP-IPV-Hib Vaccination First Vaccination 0 days: 6.49 (3.10-13.61) 1-3 days: 1.47 (0.62-3.50) 4-7 days: 0.44 (0.11-1.81) 0-7 days: 1.65 (0.94-2.90) Second Vaccination 0 days: 3.97 (2.20-7.16) 1-3 days: 1.52 (0.88-2.64) 4-7 days: 0.49 (0.22-1.11) 0-7 days: 1.32 (0.90-1.92) Third Vaccination	Differences between boys and girls not significant.

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
				0 days: 1.07 (0.73-1.57) 1-3 days: 0.89 (0.70-1.14)	
Chen et al. 1997 ¹⁹⁵ Prospective cohort	N=~242,000 (Location=US; Age=0-6 years; Setting=Vaccine Safety Datalink (VSD) project (4 HMOs, Group Health Cooperative (GHC) of Puget Sound in Washington, Northwest Kaiser Permanente (NWK) in Oregon, Northern California Kaiser (NCK), and Southern California Kaiser (SCK) Permanente	DTP, MMR,	stratified by HMO and birth date, adjusted for other vaccines	Relative risk (and 95% confidence interval) of seizures and persistent seizure disorders DTP Interval days post vaccination 0 days: 2.20 (1.50-3.40) 1-3 days: 1.00 (0.70-1.40) 4-7 days: 0.80 (0.50-1.00) 8-14 days: 0.85 (0.60-0.90) 15-30 days: 0.84 (0.70-0.90) MMR Interval days post vaccination 0 days: 0.80 (0.30-1.90) 1-3 days: 0.50 (0.20-1.00) 4-7 days: 1.80 (1.20-2.70) 8-14 days: 2.50 (2.20-3.30) 15-30 days: 1.00 (0.90-1.20) On crude analysis, a possible association was found 8 to 14 days after vaccination MMR. After adjustment the association with MMR persisted (2.42 (1.8-3.2)).	Not reported
Gold et al. 2010 ¹⁹⁶ Self Controlled Case Series	N= 323 cases of febrile seizures Location=South Australia; Age=0-7 years;	MMR, DTP	SCCS method accounted for exposure period and age	IRR for febrile seizures MMR vaccine Exposure period -1 to -14 days: 0.58 (0.33-1.02) Exposure period 6 to 11 days: 2.11 (1.43-3.10) Exposure period 15 to 35 days: 0.90 (0.65-1.25) DTP vaccine Exposure period -1 to -14 days: 0.56 (0.33-0.94) Exposure period 0 to 3 days: 0.59 (0.24-1.45) Exposure period 4 to 7 days: 0.94 (0.46-1.91) Exposure period 8 to 14 days: 0.93 (0.54-1.62)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Rowhani-Rahbar et al. 2012 ¹⁹⁷ Case-centered	N=233 cases of Bell's Palsy; Age= \leq 18 years; Setting=Kaiser Permanente Northern California population	TIV, Hepatitis B	Not reported	OR, 95% CI TIV Days 1-14: 1.0 (0.2, 5.0) Days 1-28: 0.7 (0.2, 2.8) Days 29-56: 1.2 (0.3, 4.8) Hep B Days 1-14: 1.3 (0.4, 4.5) Days 1-28: 0.8 (0.2, 2.4) Days 29-56: 0.9 (0.3, 2.6)	Not reported
Groves et al. 1999 ¹⁹⁸ Case-control	N=878; Location=nine Midwestern and Mid-Atlantic states; Age=0-14 years; Setting=Patients with acute lymphoblastic leukemia (ALL), diagnosed between 1989 and 1993. Subjects who resided in Illinois, Indiana, Iowa, Michigan, Minnesota, New Jersey, Ohio, Pennsylvania, or Wisconsin at the time of diagnosis were eligible for the vaccination component of the study.	Oral or injected poliovirus vaccine, trivalent diphtheria–tetanus–pertussis vaccine, bivalent diphtheria–tetanus vaccine, bivalent tetanus–diphtheria vaccine, monovalent tetanus vaccine, trivalent measles–mumps–rubella vaccine, Haemophilus influenzae group b (Hib) vaccines, Hepatitis B virus vaccine and other vaccines	Age at censoring, year of birth, sex, race, family income, parental education and attendance at day-care and/or preschool	Effect of vaccination (ever vs. never) on subsequent risk of childhood acute lymphoblastic leukemia (439 matched pairs) OR (95% CI) Measles–mumps–rubella: 1.19 (0.67–2.10) Oral poliovirus: 1.05 (0.41–2.67) Diphtheria–tetanus–pertussis: 0.66 (0.27–1.65) Tetanus (all): 0.75 (0.26–2.16) Diphtheria (all): 0.75 (0.26–2.16) Haemophilus influenzae b (Hib): 0.73 (0.50–1.06) (Presumptive) polysaccharide vaccine: 1.13 (0.64–1.98) (Presumptive) conjugate vaccine: 0.57 (0.36–0.89)	Not reported
Ma et al. 2005, ¹⁹⁹ Case-control	N=732; Location=California; Age=0-14 years; Setting=Northern California Childhood Leukemia Study	DPT, polio, MMR, Hib, Hepatitis B	Matched on date of birth, sex, mother's race and Hispanic status Adjusted for maternal education and annual household income	Vaccinations and the risk of childhood leukemia—adjusted odds ratios Each dose before the reference date DPT Leukemia: 0.97 (0.74, 1.28) ALL: 0.96 (0.72, 1.28)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
	(major pediatric clinical centers)			<p>Polio Leukemia: 1.14 (0.88, 1.47) ALL: 1.08 (0.82, 1.41)</p> <p>MMR Leukemia: 1.06 (0.69, 1.63) ALL: 0.87 (0.55, 1.37)</p> <p>Hib Leukemia: 0.81 (0.68, 0.96) ALL: 0.81 (0.66, 0.98)</p> <p>Hepatitis B Leukemia: 0.97 (0.77, 1.23) ALL: 1.01 (0.78, 1.31)</p>	
MacArthur et al. 2008 ²⁰⁰ Case-control	N=798; Location=Canada; Age=0-15 years; Setting=Canadian pediatric oncology centers and population-based cancer registries	Measles, mumps, and rubella (MMR), diphtheria, tetanus, and pertussis (DTP), poliomyelitis, hepatitis, or Bacillus Calmette-Guerin (BCG)	Maternal education, annual household income, ethnicity, maternal age at birth, and number of residences since birth. Multivariate models relied on strata formed by the following matching factors: province, gender, and age.	Vaccinations in childhood and risk of childhood leukemia, the Cross-Canada Childhood Leukemia Study, 1990–1994 OR (95% CI) Mumps: 0.83 (0.39-1.75) Measles 0.88 (0.41-1.90) Rubella 0.85 (0.42-1.70) Diphtheria 0.85 (0.29-2.49) Pertussis 0.71 (0.27-1.85) Tetanus 0.74 (0.27-2.03) Polio 0.90 (0.35-2.29) Hepatitis 1.09 (0.34-3.52) Other vaccine 0.81 (0.58-1.13)	Not reported
Pagaoo et al. 2011 ²⁰¹ Case-control	N=14,000(2,800 cancer cases, 11,200 controls); Location=Texas; Age=2 to 17 years;	DTaP, IPV, MMR, Hib, Hepatitis B, Varicella Zoster, 4-3-1 (Four doses of DTaP, 3 doses	Stratified analyses with infant sex, race/ethnicity, maternal age at birth, birth weight, and parity. Subjects matched on sex and birth year	OR (95% CI) for total cancer cases DTaP: 0.92 (0.80-1.07) IPV: 0.93 (0.81-1.07) MMR: 0.92 (0.82-1.02) Hib: 0.84 (0.70-1.00)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
	Setting=Texas Cancer Registry combined with birth certificate data to identify eligible participants	of IPV, 1 dose of MMR, 4-3-1-3 (Four doses of DTaP, 3 doses of IPV, 1 dose of MMR, 3 doses of Hib), 4-3-1-3-3, 4-3-1-3-3-1	Adjusted for sex, child's birth year, child's ethnicity, child's birth weight, mother's age at child's birth	<p>4-3-1: 0.90 (0.80-1.03) 4-3-1-3: 0.98 (0.87-1.11) OR (95% CI) for acute lymphoblastic leukemia DTaP: 0.82 (0.63-1.06) IPV: 0.83 (0.63-1.09) MMR: 0.87 (0.71-1.08) Hib: 0.58 (0.42-0.82) 4-3-1: 0.77 (0.60-1.00) 4-3-1-3: 1.04 (0.74-1.47) OR (95% CI) for Non-Hodgkin Lymphoma DTaP: 0.88 (0.58-1.32) IPV: 1.01 (0.59-1.74) MMR: 0.99 (0.63-1.55) Hib: 0.65 (0.26-1.59) 4-3-1: 0.98 (0.59-1.64) 4-3-1-3: 1.18 (0.70-1.98) OR (95% CI) for Medulloblastoma DTaP: 1.11 (0.71-1.73) IPV: 1.49 (0.89-2.52) MMR: 1.10 (0.70-1.72) Hib: 1.45 (0.75-2.80) 4-3-1: 1.39 (0.85-2.27) 4-3-1-3: 1.46 (0.90-2.36) County-level vaccination rates: OR (95% CI) for total cancer cases DTaP: 1.20 (0.90-1.60) IPV: 0.88 (0.74-1.05) MMR: 1.10 (0.84-1.45) Hib: 0.92 (0.82-1.04) Hepatitis B: 0.81 (0.67-0.98) Varicella Zoster: 1.03 (0.92-1.16) 4-3-1: 1.00 (0.89-1.11) 4-3-1-3-3: 0.90 (0.74-1.09) 4-3-1-3-3-1: 0.98 (0.88-1.10) OR (95% CI) for acute lymphoblastic leukemia DTaP: 1.02 (0.61-1.72) IPV: 0.67 (0.49-0.92) MMR: 0.84 (0.51-1.39) Hib: 0.76 (0.54-1.08) Hepatitis B: 0.63 (0.46-0.88) Varicells Zoster: 1.07 (0.78-1.47) 4-3-1: 0.73 (0.51-1.06)</p>	

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
				4-3-1-3-3: 0.62 (0.44-0.87) 4-3-1-3-3-1: 0.77 (0.50-1.17) OR (95% CI) for Non-Hodgkin Lymphoma DTaP: 2.34 (0.93-5.90) IPV: 0.73 (0.31-1.72) MMR: 2.81 (1.27-6.22) Hib: 0.98 (0.59-1.64) Hepatitis B: 0.77 (0.32-1.81) Varicella Zoster: 0.97 (0.58-1.62) 4-3-1: 1.13 (0.71-1.82) 4-3-1-3-3: 1.22 (0.40-3.69) 4-3-1-3-3-1: 0.84 (0.51-1.38) OR (95% CI) for Medulloblastoma DTaP: 1.43 (0.44-4.63) IPV: 1.47 (0.73-2.96) MMR: 1.20 (0.37-3.88) Hib: 1.62 (1.00-2.62) Hepatitis B: 1.39 (0.67-2.91) Varicella Zoster: 0.90 (0.54-1.51) 4-3-1: 1.14 (0.60-2.18) 4-3-1-3-3: 1.58 (0.76-3.30) 4-3-1-3-3-1: 1.12 (0.58-2.17)	
Hummel et al. 2000 ²⁰² Prospective cohort	N=823; Location=Germany; Age=0-2 years; Setting=German BABYDIAB Study	Bacille Calmette-Guérin [BCG]; haemophilus influenzae (HIB); diphtheria, tetanus, and pertussis (DTP); poliomyelitis; tick-borne encephalitis (TBE); and measles, mumps, and rubella (MMR)	Not reported	Risk (odds ratio) for developing islet antibodies with respect to environmental factors. (Estimates from figure) Hib: 1.4 (0.07-4.00) Measles: 1.6 (0.07-7.00) Mumps: 1.2 (0.08-3.50) Rubella: 1.3 (0.07-4.00)	Not reported
O'Leary et al. 2012 ¹³² Retrospective cohort	N=1.8 million from 5 managed care organizations; Location=Colorado, Hawaii, Georgia, Northern CA,	MMR, Hepatitis A, varicella, Tdap, Hib	Not reported	IRR for immune thrombocytopenic purpura (ITP) 6 wk to 11 mo Hib: 0.53 (0.14, 1.94) PCV: 0.58 (0.15, 2.18) 6 to 23 mo TIV: 2.69 (0.81, 8.88)	Not reported

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
	Massachusetts; Age=6 weeks to 17 years;			12 to 19 mo MMR: 5.48 (1.61, 18.64) MMRV: 2.87 (0.78, 10.56) DTaP: 1.00 (0.21, 4.81) Hib: 0.75 (0.16, 3.63) PCV: 0.72 (0.14, 3.97) 12 to 23 mo Hep A: 0.22 (0.03, 1.82) 2 to 6 years TIV: 1.86 (0.41, 8.38) Hep A: 1.14 (0.34, 3.86) 4 to 6 years MMR: 3.06 (0.42, 22.30) VAR: 4.39 (0.46, 41.65) DTaP: 2.57 (0.53, 12.37) IPV: 1.37 (0.23, 8.32) 7 to 17 years Hep A: 23.14 (3.59, 149.30) TIV: 5.95 (0.54, 65.96) 11 to 17 years VAR: 12.14 (1.10, 133.96) HPV: 9.71 (0.87, 108.92) MCV: 6.02 (0.64, 56.18) Tdap: 20.29 (3.12, 131.83)	
Pahud et al. 2012, Case-centered method	N=110 encephalitis cases; Location=CA; Age= 6 months to 18 years	Many analyzed, measles virus-containing vaccines and pertussis antigen containing vaccines reported	Not reported	Association with pre-defined risk windows Measles virus-containing vaccines 5–15 days: OR=1.31 (0.30–5.77) Pertussis antigen-containing vaccines 0–3 days: OR=1.37 (0.33–5.78)	Not reported

DTP-IPV = Diphtheria-tetanus-pertussis-(inactivated) Poliomyelitis Vaccination; OR = Odds Ratio; CI = Confidence Interval; Hib = Haemophilus Influenzae Type b; BCG = Bacillus Calmette–Guérin; HDM = House dust mite; HMO = Health Maintenance Organization; HBV = Hepatitis B Vaccine; MACS = Melbourne Atopy Cohort Study; DTP = Diphtheria, Tetanus and Pertussis; CDT = Combined Diphtheria and Tetanus; MMR = Measles, Mumps, Rubella; SCCS = Self-controlled Case Series; VSD = Vaccine Safety Datalink; GHC = Group Health Cooperative; NWK = Northwest Kaiser Permanente; NCK = Northern California Kaiser; SCK = Southern California Kaiser; TBE = Tick-born Encephalitis; IRR = Incidence Rate Ratio; ITP = Immune Thrombocytopenic Purpura; HPV = Human papillomavirus; MCV = Measles-Containing Vaccine; IPV = Polio Vaccine; VAR – Varicella; Hep A = Hepatitis A;

Key Question (KQ) 3: What is the evidence that vaccines recommended for pregnant women²⁵ are safe both for the woman and for her fetus/infant?

- a. What AEs are collected in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?
- b. What AEs are reported in clinical studies (phases I–IV) and in observational studies containing a control/comparison group?

Table 28 lists AEs reported in trials of vaccines in pregnant women, abstracted verbatim. Again, we are uncertain if additional AEs were collected; we can only rely on what was reported. The list does not imply an association with vaccination, as it contains AEs regardless of whether they were reported in vaccinated or unvaccinated study participants. Later we describe the studies further and assess association.

Table 28. Adverse Events Reported in Trials of Pregnant Women

Influenza (inactive)	Influenza - monovalent H1N1 continued
Chest tightness or difficulty breathing	Hypospadias
Cough	Intrauterine Growth Restriction (IUGR)
Death	Inferior vena cava (IVC) syndrome
Fever	Imperforate lacrimal duct
Infant: Dermatitis contact	Infections
Infant: Hyperbilirubinemia neonatal	Laryngomalacia
Infant: Respiratory distress	Limb pain
Infant: Seborrheic dermatitis	Malaise
Infant: Upper respiratory tract infection	Mild pulmonary artery stenosis
Malaise	Miscarriage
Maternal: At least one adverse event	Myalgia
Maternal: Fever, cough, runny nose, nasal congestion, and skin itching	Nausea, Influenza, Pain, viral infection
Maternal: Severe adverse event	Neonatal death (1 st , 2 nd and 3 rd Tri)
Myalgia/Arthralgia	Neonatal pathologies
Sore throat, hoarseness, or pain swallowing	Premature rupture of membranes (PROM)
Swelling of the face	Pelvic kidney
Influenza - monovalent H1N1	Persistent arterial duct
5min APGAR score <7	Pharyngitis
Allergy	Prematurity
Congenital anomalies	Preterm birth
Auricle defect	Preterm labor
Chest infection	Pulmonary valve stenosis
Chest pain	Pyelitic dilatation
Cleft palate	Pyrexia
Clubfoot	Rash
Coryza	Right pyelitic hypotension
Cough	Sinusitis
Death	Skin tag on finger
Diarrhea	Small for gestational age
Downs Syndrome	Spontaneous abortion (1 st , 2 nd and 3 rd Tri)
Dyspnea	Stillbirth (01 st , 2 nd and 3 rd Tri)
Ebstein's anomaly	Talipes calcaneus
Fetal death	Trisomy 21#
Flu-like symptoms	Umbilical hernia
Gestational diabetes	Unilateral cryptorchidism
Headache	Varus equines
Hip dysplasia	Ventriculomegaly
Hydrocephalus	Very preterm (<32w)
Hypertension	

IUGR = Intrauterine Growth Restriction; IVC = Inferior vena cava; PROM = Premature Rupture of Membranes;

Table 29 lists all AEs and medical conditions investigated in the case-control, self-controlled case series, and multivariate risk factor analyses in pregnant women. The majority of these studies were designed to assess the association of a specific AE with vaccination. Again, the list does not imply an association.

Table 29. Adverse events investigated in post-marketing studies of pregnant women

Influenza vaccines
H1N1
Spontaneous abortion / fetal loss
TIV
Premature birth
Small for gestational age

Key Question (KQ) 3: Pregnant women

- c. What AEs are associated with these vaccines in women?
 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 3. For each AE associated with a particular vaccine, what are the risk factors for the AE (including age, sex, race/ethnicity, genotype, underlying medical condition, whether the vaccine is administered individually or in a combination vaccine product, the schedule of vaccine administration, adjuvants, and medications administered concomitantly)?

- d. What AEs are associated with these vaccines in the fetus/infant?
 1. For each AE associated with a particular vaccine, what is the average severity (grade 1/mild; grade 2/moderate; grades 3 and 4/severe)?
 2. For AEs without statistically significant associations with a particular vaccine, what is the level of certainty?
 3. For each AE associated with a particular vaccine, what are risk factors for the AE (including age, gender, race/ethnicity, genotype, underlying medical condition, whether vaccine administered individually or in a combination vaccine product, vaccine schedule of administration, adjuvants, medications administered)?

Influenza vaccines

We identified only three studies comparing vaccinated and unvaccinated pregnant women. All administered H1N1 influenza vaccines during the 2009/2010 pandemic. The results are summarized in Table 29.

A cohort study in Taiwan²⁰⁴ in 396 pregnant women receiving AdimFlu-S influenza A (H1N1) between October 2009 and February 2010 or no vaccine reported no SAEs. A comparison of the medical records of the age-matched groups showed that significantly fewer women in the vaccinated group experienced at least one adverse event during the study period women (OR 0.37, 95% CI 0.22, 0.68). In addition, one statistically significant adverse event difference in the infants was observed: hyperbilirubinemia was much less common in the vaccinated group (OR 0.08, 95% CI 0.03, 0.2).

A Canadian cohort study²⁰⁵ included 55,570 pregnant women who delivered a single baby during the 2009/2010 influenza season. Women vaccinated during pregnancy with monovalent H1N1 influenza vaccines were statistically less likely to experience a fetal death (OR 0.60, 95% CI 0.44-0.81), preterm birth defined as below 37 weeks gestational age (OR 0.92, 95% CI 0.85, 0.98), infants small for their gestational age (OR 0.74, 95% CI 0.66, 0.83), or delivering infants before gestation week 32 (OR 0.72, 95% CI 0.58, 0.88).

A Scottish cohort study²⁰⁶ evaluated a mass vaccination program for high risk groups such as pregnant women during the 2009/2010 pandemic. The study compared 3,754 women vaccinated with monovalent H1N1 (Celvapan or Pandemrix) and 312 women who were offered the vaccine but were not vaccinated. The study analyzed self-reported serious adverse events and pregnancy outcomes and did not identify any statistically significant differences between the groups.

Table 30. Vaccinated vs. unvaccinated pregnant women. Vaccine H1N1

Author-Year-Country	Study Design	McHarm Score	Population	Vaccine	Timing	OR, 95% CI, versus unvaccinated group
Fell D. B. et al.,2012 ²⁰⁵ Canada	Cohort	4	Sample size : 55,570, Mean age: NR, Age range: <18 - 40+, Percent female: 100%	Influenza - monovalent H1N1, NR, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Not reported	Dose1: NR	5min APGAR score <7: OR 0.925 (0.794-1.078) Fetal Death: OR 0.595 (0.439-0.806)** Preterm birth (<37w): OR 0.915 (0.853-0.981)** Small for gestational age: <10th percentile: OR 0.836 (0.788-0.887)** Small for gestational age: <3rd percentile: OR 0.74 (0.66-0.829)** Very preterm (<32w): OR 0.717 (0.584-0.879)**
Lin T. H. et al.,2012 ²⁰⁴ Taiwan	Cohort	7	Sample size : 396, Mean age: 32.4, Percent female: 100%	Influenza (inactivated), AdimFlu-S®, Adimmune Corporation, Taichung, Taiwan, The vaccine evaluated in this study was produced by Adimmune Corporation (Taichung, Taiwan) using standard techniques for the production of seasonal inactivated influenza vaccines. The vaccine is a monovalent, unadjuvanted, inactivated, split-virus vaccine. One shot (0.5ml) of AdimFlu-Influenza (H1N1) vaccine contains 15 µg of New York Medical College X-179A reassortant of the A/California/7/2009 (H1N1) like strain. Adjuvant: Adjuvant Free, Preservative: Not reported, Delivery: Intradermal	Dose1: 0 Days	Infant: Dermatitis contact: OR 1.882 (0.682-5.194) Infant: Hyperbilirubinemia neonatal: OR 0.083 (0.032-0.214)** Infant: Respiratory distress: OR 0.66 (0.183-2.375) Infant: Seborrheic dermatitis: OR 2.042 (0.605-6.895) Infant: Upper respiratory tract infection: OR 0.742 (0.253-2.18) Maternal: At least one adverse event: OR 0.371 (0.202-0.68)**
Mackenzie I. S. et al.,2012 ²⁰⁶ Scotland	Cohort	2	Sample size : 4,066, Mean age: 53.6, Percent female: 57.9 (>=16 years))%, Percent pregnant: 3.2%, Conditions: multiple	Influenza - monovalent H1N1, Celvapan /Pandemrix, see above, Adjuvant: Not Reported, Preservative: Not reported, Delivery: Not reported	Dose1: NR Dose2: NR Dose3: NR	Chest infection: OR 0.879 (0.349-2.216) Coryza: OR 0.997 (0.235-4.24) Chest pain: OR 0.581 (0.071-4.738) Death: OR 0.498 (0.06-4.149) Dyspnea: OR 0.914 (0.118-7.103)

OR = Odds Ratio; CI = Confidence Interval; NR = Not Reported;

We found only two post-marketing studies of pregnant women that met our inclusion criteria. One focused on inactivated influenza vaccine and one on the H1N1 vaccine. AEs in mother and fetus / infant are discussed below.

The study (Omer, 2011)²⁰⁷ on inactivated influenza vaccine included 4,168 pregnant women and their newborns in the US followed during the 2004/05 and 2005/06 flu seasons. Vaccination status and health outcomes were ascertained using self-reported data. The analysis adjusted for potential confounders including various types of influenza activity periods, maternal health, and demographic variables. Results showed that infants born during the vaccine season to women who were vaccinated were less likely to be premature compared to infants born in the same period to unvaccinated mothers (adjusted OR 0.60, 95% CI 0.38, 0.94). This relationship increased (adjusted OR 0.44, 95% CI 0.26, 0.73) during periods of local influenza activity, and was at its greatest during periods of widespread influenza activity. Results also indicate that during widespread influenza activity periods, newborns of vaccinated mothers had 69% lower odds of being small for gestational age (adjusted OR 0.31, 0.13 to 0.75) compared with newborns of unvaccinated mothers.

Regarding H1N1, (Xu, 2012)²⁰⁸ studied data were obtained from 198 pregnant women who enrolled before 20 weeks of gestation in the US Vaccine and Medication in Pregnancy Surveillance System study. The aim of this study was not to assess the effect of H1N1 on childbirth outcomes, but to illustrate the use of survival analysis methods. Data were analyzed using time-independent (naive) and time-dependent covariate Cox models to account for left-truncation (due to possible enrollment later than conception). The model was adjusted for time of vaccine exposure (1st, 2nd trimester), previous spontaneous abortion events, maternal smoking habits, age, and the presence of asthma. Vaccination was not statistically associated with spontaneous abortions during any trimester.

Summary

We found moderate strength evidence that both H1N1 vaccine and seasonal influenza vaccine (inactivated) are not associated with serious adverse events in pregnant women or their offspring.

No other vaccines were studied in pregnant women.

Table 31. Post-marketing studies of influenza vaccines in pregnant women

Author / Year	Population	Vaccines	Adjusted for these confounders	Results re vaccine	Results re risk factors
Omer et al. 2011 ²⁰⁷	4,168 pregnant women and their newborns enrolled in Georgia Pregnancy Risk Assessment Monitoring System (PRAMS), mean age not reported but 11.5% were <19, 12.5% were >35, and 76% were 19-35. Recruitment occurred in the flu seasons of 2004-2006.	Inactivated influenza	Influenza activity period (pre-influenza activity period, periods of least local/regional influenza activity, period of widespread influenza activity) maternal variables (age, multiple births, medical risk factors, labor/delivery complications, birth defects, smoking during pregnancy, hypertension, insurance coverage, maternal diabetes, use of multivitamins, alcohol use during pregnancy, black race, education, marital status) Covariates were tested for the separate multivariate models by testing which potential confounders moved the relationship between immunization and birth outcome closer to 1.	Prematurity was defined as birth < 37 weeks gestation; SGA was defined as birth weight <10th percentile for gestational age. Infants born during the putative vaccine season to women who were vaccinated were less likely to be premature compared to infants born in the same period to unvaccinated mothers (adjusted OR 0.60, 95% CI 0.38 to 0.94) During the period of local influenza activity, this relationship increased (adjusted OR 0.44, 95% CI 0.26 to 0.73)) During the widespread influenza activity period, this relationship was greatest: adjusted OR 0.80, 95% CI 0.11. to 0.74) Also during the widespread influenza activity period, compared with newborns of unvaccinated mothers, newborns of vaccinated mothers had 69% lower odds of being SGA (adjusted OR 0.31, 0.13 to 0.75).	Not reported
Xu et al. 2012 ²⁰⁸	198 pregnant women who enrolled before 20 weeks gestation; US/Vaccine and Medication in Pregnancy Surveillance System study	H1N1	Vaccine exposure (1st or 2nd trimester) Previous spontaneous abortion (SAB) events (0, 1, 2, >=3) smoking maternal age asthma Dependent variable: SAB	SAB RR (time-independent): 1.13(0.13, 10.24) RR (time-dependent): 1.13(0.13, 10.24) Vaccination during 1st trimester (n=119) SAB RR (time-independent): 0.48(0.08, 2.70) RR (time-dependent): 0.79(0.19, 3.23) Vaccination during 2nd trimester (by definition, fetal loss>20weeks is still-birth, not SAB)(n=34) No. SAB: 0 Vaccination during 1st or 2nd trimester (n=153) SAB RR (time-independent): 0.58(0.10, 3.24) RR (time-dependent): 0.97(0.24, 3.94)	Not reported

PRAMS = Pregnancy Risk Assessment Monitoring System; SGA = Small for Gestational Age; OR = Odds Ratio; CI = Confidence Interval; SAB = Spontaneous Abortion; RR = Risk Ratio

Summary and Discussion

At the request of AHRQ and the Office of the Assistant Secretary for Health (OASH) we conducted an assessment of the evidence for the safety of vaccines recommended for routine use in the US among adults, children, and pregnant women, according to ACIP guidelines. We conducted an extensive literature search for clinical trials and observational studies meeting our inclusion criteria: cohort studies comparing vaccinated and unvaccinated groups, case-control studies, self-controlled case series, and multivariate risk factor analyses. In this chapter, we describe the limitations of our review and present our conclusions. We also discuss the implications of our findings for future research.

Limitations

Our literature search procedures were extensive; however, some unpublished trial results may not have been identified. An independent Scientific Resource Center (SRC) under contract with AHRQ requested Scientific Information Packets (SIPs) from the manufacturers of all vaccines routinely recommended in the US. (The research team was prohibited from contacting manufacturers directly.) Only two companies responded; both manufacture vaccines against seasonal influenza.

We excluded non-English language studies. Although we were considering only vaccines approved for use in the US, it is possible relevant epidemiological studies have been published in non-English journals.

An important limitation common to systematic reviews is the quality of the original studies included. We used a quality-rating instrument²⁸ developed by another Evidence-based Practice Center specifically to evaluate studies reporting harms. The scores are presented in the results tables and taken into consideration when rating the strength of the evidence. Studies that reported timing and severity, and defined AEs using standard, precise definitions were rated higher than those that did not. Epidemiological studies that used medical records to ascertain vaccination and health outcomes were also rated higher than those that relied on patient or parent report.

Studies using passive surveillance such as the US Vaccine Adverse Event Reporting System (VAERS),¹⁶ are crucial in identifying signals regarding adverse events post-licensure. However, because by definition they do not consider the rate of such events in non-vaccinated populations, they are not designed to assess a statistical association between a vaccine and an adverse event, so they were excluded from this project. Thus, there may be important adverse event signals not identified in this report that warrant future research.

We included controlled trials that used formulations currently approved in the US. We tried to exclude Phase II studies that used dosages that were never licensed and/ or formulations available only in other countries. Some studies reported the potency of the vaccines under study in a different manner or unit than that reported in other studies or the product materials. We assessed these findings to the best of our capabilities. We point out discrepancies in our results text.

Except where explicitly stated in the text, controlled trials of vaccines are conducted in healthy patients. Thus, persons who may be more susceptible to AEs may be excluded from trials, yet eligible to receive a vaccine after it is licensed. In addition, trials are generally underpowered to detect very rare events. For example, a trial of 1,000 patients may not detect an

AE with an expected incidence of one in 5,000. Trials may also be underpowered to assess risk factors for the AEs they do detect.

Post-licensure epidemiological studies are conducted to investigate possible associations between vaccines and AEs reported in passive surveillance or multiple case reports. Such studies often do not limit their investigation to a particular brand or formulation. They may lump vaccines against a specific disease together. For example, a study might investigate the effect of “seasonal influenza vaccines” in general. Formulations of seasonal influenza vaccines change each season, the vaccine comes in inactivated or live form, and a particular batch may or may not contain a strain of H1N1. It is difficult to assess the applicability of studies that do not report specific details about vaccines.

In many studies, the severity of AEs was not reported. Our researchers coded the severity according to CATAE classification when possible. Severity is listed in our tables where available.

Most studies did not investigate potential risk factors for AEs that were found to be associated with vaccination.

Some post-licensure surveys use patient or parent recall for ascertainment of vaccination or health outcomes, rather than medical records. Subjects may not have copies of their vaccination or medical records, introducing recall bias. Advanced health information technology (HIT) systems that contain vaccination and medical records make surveys unnecessary, leading to higher quality studies. In the US, the Vaccine Safety Datalink (VSD) uses data obtained through such systems at eight very large MCO, enabling high quality studies. Nations with single payer healthcare often have electronic registries, which allow even larger epidemiological studies of entire populations.

Conclusions

Table 32 summarizes our conclusions, given the caveats described in the Limitations section. The table displays the strength of evidence (SOE) regarding statistical association of each vaccine type with key AEs. The term “null” next to the SOE indicates evidence that a) the vaccine is not associated with the AE or b) the vaccine is associated with a protective effect against the AE.

Table 32. Summary: Safety of Vaccines Used for Routine Immunization of Adults (Including Pregnant Women) and Children

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
Adults			
Influenza Vaccines	<p>High – arthralgia, myalgia, malaise, fever, pain at injection site, anaphylaxis</p> <p>High (null) - cardiovascular or cerebrovascular events in the elderly</p> <p>High – H1N1 with Guillain-Barré Syndrome (GBS)</p> <p>Moderate (null) - Serious Adverse Events in renal patients</p> <p>Insufficient - Multiple Sclerosis (MS)</p>	<p>Studied two forms of influenza vaccines: live attenuated form, administered intranasally (LAIV), and inactivated form (TIV), administered intramuscularly.</p> <p>Evidence “convincingly supports” a causal relationship between influenza vaccines and anaphylaxis</p>	<p>Many clinical trials reported that influenza vaccines are associated with arthralgia, myalgia, malaise, fever, and pain in the short-term in adults. These adverse events (AEs) were not considered serious; severity was graded mild to moderate – odds of experiencing these events were 1.5 to 2 times higher in vaccinated patients than in unvaccinated. Risk factors were not discussed in the trials.</p> <p>Post-licensure studies report mixed results regarding association of seasonal influenza vaccines, including those containing H1N1 strains, with Guillain-Barré Syndrome (GBS) in adults. A high quality meta-analysis published as this report was finalized found an association with monovalent H1N1 vaccine in the 42 days post vaccination;¹⁸³ results translate to about 1.6 excess cases per million vaccinated.</p> <p>Post-licensure studies have found inconsistent evidence associating influenza vaccines with onset or exacerbation of MS in adults.</p> <p>Post-licensure studies have found influenza vaccines are NOT associated with increased risk of cardiovascular or cerebrovascular events in the elderly.</p> <p>Post-licensure studies have shown that influenza vaccines are NOT associated with increased risk of serious AEs (SAEs) in renal patients.</p>
Pneumococcal Polysaccharide Vaccine	High (null) - cardiovascular or cerebrovascular events in the elderly	Not covered	We found no placebo-controlled trials of the current US version. (We did find studies of the current version vs older versions, but these did not include a placebo group)

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
			Post-licensure studies of pneumococcal polysaccharide vaccine found vaccination was NOT associated with increased risk of cardiovascular events in older adults.
Zoster Vaccine	Moderate – injection site reactions, cellulitis, allergic reactions Insufficient – Serious Adverse Events	Recommended for US adults over age 60; AEs specific to this population were not covered by the IOM report.	In clinical trials, adverse events were often reported only in broad categories such as “injection–related adverse events,” “systematic adverse events,” or “serious adverse events” rather than specifying type or severity. This made assessing specific serious adverse events impossible. Vaccination was associated with injection site reactions in clinical trials. In post-licensure studies, vaccination was associated with cellulitis and allergic reactions, such as redness and swelling; 1 to 7 days post vaccination. These mild AEs occurred in less than 1% of patients, and were more likely in the younger (aged 50-59) vaccines. ⁷⁸
Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis Vaccines	High - anaphylaxis	Evidence “convincingly supports” a causal relationship in the adult population between the tetanus toxoid vaccine and anaphylaxis.	We identified one additional trial of adults. No association with AEs was reported. We identified no additional post-licensure studies of vaccines against diphtheria, tetanus, or pertussis in adults.
MMR Vaccine	Moderate (null) – Type 1 diabetes Low - transient arthralgia in women	Evidence “favors acceptance” of a causal relationship with transient arthralgia in women. Evidence is “inadequate to accept or reject” a causal relationship with MS onset, Guillain-Barré Syndrome, chronic arthralgia in women, and chronic arthritis and arthropathy in men.	MMR was NOT associated with onset of type 1 diabetes in adults in a very large recent high quality epidemiological study. ⁹⁰ RR=0.71 (95% CI 0.61, 0.83)
Hepatitis A Vaccine	Insufficient - Serious Adverse Events	Evidence “neither convincingly supports convincingly supports nor favors acceptance favors acceptance” of any causal relationships with AEs the committee was tasked with investigating: acute disseminated encephalomyelitis, transverse myelitis, MS, Guillain-Barre Syndrome, chronic inflammatory disseminated polyneuropathy, Bells’ Palsy, anaphylaxis,	We identified one additional post-licensure study; there was no evidence regarding association of this vaccine with any adverse events or onset of medical conditions.

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
Hepatitis B Vaccine	Insufficient Serious Adverse Events	<p>and autoimmune hepatitis.</p> <p>Although no epidemiological studies were identified on anaphylaxis, mechanistic evidence “favours acceptance” of a causal relationship between the vaccine and anaphylaxis in yeast-sensitive individuals.</p> <p>Epidemiological studies of the following AEs in adults had evidence “inadequate to accept or reject” a causal relationship: optic neuritis, MS onset or relapse, first demyelinating event, Guillain-Barré Syndrome, SLE, onset or exacerbation of vasculitis, polyarteritis nodosa, and onset or exacerbation of rheumatoid arthritis. No epidemiological studies of the following AEs in adults were found, evidence is also “inadequate to accept or reject” a causal relationship: encephalitis, encephalopathy, ADEM, transverse myelitis, neuromyelitis optica, chronic inflammatory disseminated polyneuropathy, brachial neuritis, erythema nodosum, onset or exacerbation of psoriatic arthritis, onset or exacerbation of reactive arthritis, and fibromyalgia.</p>	We found no additional studies that met our inclusion criteria.
Children and Adolescents			
Influenza Vaccines	<p>Moderate - mild gastrointestinal disorders</p> <p>Low (null) – Serious Adverse Events in the short term in children with cancer or who have received organ transplants</p> <p>Low - influenza-like symptoms</p> <p>Insufficient – asthma exacerbation, seizures, ADEM,</p>	<p>The IOM committee studied seasonal influenza vaccines. The influenza vaccine is administered in two forms: a live attenuated form, administered intranasally, and an inactivated form, administered intramuscularly.</p> <p>Evidence was “inadequate to accept or reject” a causal relationship in the pediatric population between seasonal influenza vaccines and the following: seizures, acute disseminated encephalomyelitis (ADEM), and transverse myelitis.</p> <p>Evidence was “inadequate to accept or reject” a causal relationship between live attenuated influenza vaccine (LAIV) and asthma exacerbation or reactive airway disease (RAD) episodes.</p>	<p>Seasonal influenza vaccines were NOT associated with any serious adverse events in the short term in immunocompromised children (one study each of children with malignancy and children who had received organ transplants).</p> <p>Both seasonal influenza vaccines and H1N1 vaccines were associated with mild gastrointestinal disorders, such as vomiting and diarrhea in children in the short-term in several large post-licensure studies. One large study¹⁰⁷ 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).</p> <p>Both live and inactivated seasonal influenza vaccines were associated with influenza-like</p>

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
	transverse myelitis		symptoms in children in the short term in multiple studies, while not associated in others.
Hib	Low (null) – serious adverse events	Not covered	No serious adverse events associated in two clinical trials.
Measles-Mumps-Rubella	<p>High (null) – Autism Spectrum Disorders</p> <p>High - anaphylaxis in children who may be allergic to ingredients, febrile seizures, measles inclusion body encephalitis</p> <p>Moderate – Transient arthralgia</p> <p>Low - thrombocytopenic purpura</p>	<p>Evidence “convincingly supports” causal relationships with measles inclusion body encephalitis, febrile seizures, and anaphylaxis.</p> <p>Evidence “favours acceptance” of a causal relationship between MMR and transient arthralgia</p> <p>Evidence “favours rejection” of a causal relationship between MMR and autism.</p> <p>Evidence is “inadequate to accept or reject” a causal relationship with encephalitis, encephalopathy, afebrile seizures, meningitis, cerebellar ataxia, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, neuromyelitis optica, MS onset, and chronic arthropathy.</p>	Four additional post-marketing studies were identified. Vaccination was associated with thrombocytopenic purpura in the short term. ¹³⁰⁻¹³² MMR vaccination was associated with increased emergency department visits within two weeks, ¹³³ this is consistent with the IOM's findings that MMR vaccine is associated with febrile seizures.
Rotavirus Vaccines: RotaTeq and Rotarix	<p>Moderate – mild adverse events (e.g. cough, runny nose, irritability)</p> <p>Low – intussusception for RotaTeq, Rotarix</p>	Not covered.	<p>In clinical trials, both RotaTeq and Rotarix were associated with cough, runny nose and irritability in children in the short-term. In clinical trials, there was no association between either of the two currently available vaccines (RotaTeq and Rotarix) and any serious adverse events, including intussusception in the long or short-term.</p> <p>A high quality epidemiological study in Australia found RotaTeq was associated with intussusception 1 to 21 days following the first of three required doses in infants 1 to 3 months of age. However, a post-licensure study in the US¹⁶⁹ found no association. Two case-control studies^{167, 168} conducted in Latin America found an association of Rotarix with intussusception in</p>

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
			children following the first of three required doses. One of these studies estimated a risk of 3.7 (95% CI 1.2,7.3) additional cases per 100,000 person/year in Mexico. The other estimated a risk of about 1 per 51,000 vaccines in Mexico and 1 per 68,000 vaccines in Brazil.
Hepatitis B Vaccine	Insufficient – Serious adverse events Insufficient – food allergy	Although no epidemiological studies were identified by the IOM, mechanistic evidence avored acceptance of a causal relationship between the vaccine and anaphylaxis in yeast-sensitive individuals. The IOM found insufficient evidence to accept or reject a causal relationship with any other AEs.	Hepatitis 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.
HPV Vaccine	Moderate –(null) juvenile rheumatoid arthritis, Type 1 diabetes, appendicitis, Guillain Barré Syndrome, seizures, stroke, syncope, venous thromboembolism Moderate - anaphylaxis Insufficient - ADEM, transverse myelitis, neuromyelitis optica, MS, onset of Hashimoto’s disease, chronic inflammatory disseminated polyneuropathy, brachial neuritis, amyotrophic lateral sclerosis, transient arthralgia,	Evidence “ favours acceptance ” of a causal relationship between the HPV vaccine and anaphylaxis. Evidence is “ inadequate to accept or reject ” causal relationships between HPV vaccines and the following: ADEM, transverse myelitis, neuromyelitis optica, MS, Guillain-Barré syndrome, chronic inflammatory disseminated polyneuropathy, brachial neuritis, amyotrophic lateral sclerosis, transient arthralgia, pancreatitis, thromboembolic events, and hypercoagulable states.	A large post-licensure study found HPV vaccine was NOT associated with onset of juvenile rheumatoid arthritis or Type 1 diabetes. ¹⁸⁰ This study reported an IRR of 1.29 (95% CI 1.08, 1.56) of onset of Hashimoto’s disease. However, investigation of a temporal relationship and biological plausibility revealed no consistent evidence of a safety signal. A large post-licensure study found HPV vaccine was NOT associated with Guillain Barré Syndrome, seizures, stroke, syncope, or venous thromboembolism. ¹⁸¹

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
	pancreatitis, thromboembolic events, and hypercoagulable states		
Varicella Vaccine	<p>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</p> <p>Insufficient – seizures, ADEM, transverse myelitis, Guillain-Barré syndrome, small fiber neuropathy, onset or exacerbation of arthropathy, thrombocytopenia.</p>	<p>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.</p> <p>The evidence is “inadequate to accept or reject” a causal relationship between the vaccine and seizures, ADEM, transverse myelitis, Guillain-Barré syndrome, small fiber neuropathy, onset or exacerbation of arthropathy, and thrombocytopenia.</p>	We found no additional studies that met our inclusion criteria.

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis-Containing Vaccines	<p>Moderate (null) – type 1 diabetes</p> <p>Insufficient - infantile spasms, seizures, cerebellar ataxia, autism, ADEM, transverse myelitis, MS relapse, serum sickness, immune thrombocytopenic purpura, and SIDS.</p>	<p>Evidence “favours rejection” of a causal relationship between vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens and type 1 diabetes.</p> <p>Evidence is “inadequate to accept or reject” causal relationships between vaccination and the following: infantile spasms, seizures, cerebellar ataxia, autism, ADEM, transverse myelitis, MS relapse in children, serum sickness, immune thrombocytopenic purpura, and SIDS.</p>	We found no additional studies that met our inclusion criteria.
Meningococcal Vaccines	<p>Moderate – anaphylaxis</p> <p>Insufficient - encephalitis, encephalopathy, ADEM, transverse myelitis, MS, Guillain-Barre syndrome, CIDP, chronic headache.</p>	<p>Evidence “convincingly supports” a causal relationship with anaphylaxis in children who may be allergic to ingredients.</p> <p>Evidence is “inadequate to accept or reject” causal relationships between meningococcal vaccine and the following: encephalitis, encephalopathy, ADEM, transverse myelitis, MS, Guillain-Barre syndrome, CIDP, and chronic headache.</p>	We found no additional studies that met our inclusion criteria.
Inactivated polio vaccine	Insufficient – food allergy	Not covered	One post-licensure study reported association between polio vaccine in newborns and sensitivity to food allergens.
Studies of combination vaccines or multiple vaccines	<p>Moderate - DTaP-IPV-Hib vaccination with febrile seizures</p> <p>High – (null) association of childhood leukemia with MMR, DTaP, Td, Hib, Hep B, and polio vaccines</p> <p>Moderate –</p>	Not covered	<p>Association of DTaP-IPV-Hib vaccination with febrile seizures in children was found in a very large, high quality post-licensure study.¹⁹⁴ Rate for first dose was estimated as 5.5 cases per 100,000 person/days. Rate for second dose was estimated as 5.7 cases per 100,000 person/days.</p> <p>Multiple large epidemiological studies¹⁹⁸⁻²⁰¹ have assessed MMR, DTaP, Td, Hib, Hep B, and polio vaccine and have found no association with childhood leukemia.</p>

Vaccine	EPC Conclusions: Strength of Evidence and Association	IOM findings	Additional findings from EPC
	Hepatitis A, MMR, and varicella vaccine with purpura		In a large post-licensure study of over 1.8 million vaccines, ¹³² purpura were associated with vaccination against Hepatitis A in children aged 7 to 17 years, vaccination against varicella in children aged 11 to 17, and MMR in children from 12 to 19 months of age. These results were based on one or two cases per vaccine type/age group. According to the authors most cases were mild and acute.
Pregnant Women			
Influenza Vaccines	Moderate (Null) – Serious adverse events	Results not specific to pregnant women	In comparison studies, H1N1 vaccine and seasonal influenza vaccine (inactivated) were not associated with serious adverse events in pregnant women or their offspring. No other vaccines were studied in pregnant women.

IOM = Institute of Medicine; GBS = Guillain-Barré Syndrome; TIV = Trivalent Influenza Vaccine; LAIV = Live Attenuated Influenza Vaccine; MMR = Measles, Mumps, Rubella Vaccine; MS = Multiple Sclerosis; SLE = Systemic Lupus Erythematosus; AEs – Adverse Events; ADEM = Acute Disseminated Encephalomyelitis; RAD = Reactive Airway Disease; HPV = Human Papillomavirus; VZV = Varicella-Zoster Virus; SIDS = Sudden Infant Death Syndrome; CIDP = Chronic Inflammatory Demyelinating Polyneuropathy; DTaP = Diphtheria, Tetanus, and Pertussis Vaccine; Td = Tetanus-Diphtheria; Hib = Haemophilus Influenzae Type B; Hep B = Hepatitis B

Research Gaps

While this report undergoes peer review and public comment, we will conduct a search update and incorporate new studies into our final report. During our current literature search, we identified the following research gaps.

Adults. We found insufficient evidence regarding the association of influenza vaccines with both onset or exacerbation of MS. The field could benefit from future research, using studies powered adequately to determine risk factors such as demographic and health characteristics of patients, and formulations of vaccine. There is particular concern regarding monovalent H1N1 vaccine and trivalent influenza vaccines that include H1N1 strains.

A late-breaking meta-analysis on H1N1 vaccine published as this report was written provided high strength evidence that H1N1 vaccine is associated with Guillain Barré Syndrome in adults. As the vaccine is associated with only 1.6 excess cases per million vaccinated, it will be very difficult to assess risk factors.

Published trials of zoster vaccine were not always transparent in reporting AEs. They often reported only broad categories such as “injection–related adverse events,” “systemic adverse events,” “one or more adverse events” or “serious adverse events” rather than specifying type or severity. Vaccinated groups often had significantly higher risk of these “categorical” events. Unfortunately, it is impossible to determine the rate of any particular serious adverse event from the information reported in the peer-reviewed publications. In the future, data from these trials could be re-analyzed and presented in a standard and transparent format. Two large, high quality post-licensure studies of zoster vaccine met our inclusion criteria; both used the Vaccine Safety Datalink (VSD). One investigated post-vaccination herpes zoster incidence in patients with pre-existing conditions; another investigated serious adverse events (such as acute myocardial infarction, stroke, and Bell’s Palsy) in the weeks following vaccination in healthy patients. Both found no association between vaccination and the adverse events studied. Additional studies might be conducted using the VSD if signals arise from passive surveillance systems.

Both MS and GBS are concerns regarding vaccines for MMR and hepatitis A and B. Further post-licensure studies are suggested.

Children. There is insufficient evidence regarding the associations between influenza vaccines and asthma exacerbation, seizures, acute disseminated encephalomyelitis (ADEM), and transverse myelitis. The field would benefit from additional post-licensure studies.

Febrile seizures, transient arthralgia, and importantly, measles inclusion body encephalitis were associated with MMR vaccine. Large scale studies are needed to determine patient risk factors. Purpura were also associated with MMR as well as with vaccination against varicella and hepatitis A; however, most cases were considered mild and acute.

Post-licensure studies in foreign countries have associated both Rotarix and RotaTeq with intussusception 21 days following vaccination. However, a large U.S. study found no association. The risk with Rotarix could be investigated further in US populations, unless there are known underlying factors that would make children in Latin American more vulnerable to this medical condition or the dosage / formulation differs from that used in the US. One study estimated the risk as 1 case per 51,000 vaccinations; the morbidity and mortality prevented through vaccination maybe valued by policy makers more than the risk of this rare event.

Strong evidence for a lack of association of HPV vaccines with several serious medical conditions (juvenile rheumatoid arthritis, type 1 diabetes, GBS) has been found in large post-licensure studies. However, there is insufficient evidence regarding other serious conditions such

as MS, chronic inflammatory disseminated polyneuropathy, amyotrophic lateral sclerosis, and pancreatitis. These issues warrant further study.

There is insufficient evidence to determine the possible association, if any, between vaccines such as DTaP, meningococcal vaccine, and varicella vaccine and the onset of nervous system conditions such as ADEM, transverse myelitis, MS, and GBS. Large scale epidemiological studies are needed to investigate further.

Pregnant women. Only vaccines against influenza were studied in pregnant women. Given the relatively recent introduction of the recommendation to administer the Tdap vaccine during pregnancy, passive surveillance systems might be regularly monitored for AEs in this population. This is a particular concern for women with multiple pregnancies over a period of a few years. Preliminary analyses of VSD could also identify adverse events associated with the vaccine and possible related risk factors.

Advanced health information technology (HIT) systems that contain both vaccination and health outcome records can be used to conduct high quality epidemiological studies. In the US, the VSD uses data obtained through such systems at nine very large MCOs. Nations with single payer healthcare systems often have electronic registries, which allow even larger epidemiological studies of entire populations. Future studies would benefit from such databases rather than relying on surveys that use patient / parent recall for ascertainment of vaccination or health outcome. Not only are such surveys subject to recall bias, but there may be no way of determining the formulation or brand of vaccination.

Independent abstraction and systematic reassessment of the studies included in the Institute of Medicine consensus report *Adverse Effects of Vaccines: Evidence and Causality* may be a useful future endeavor. Odds ratios could be calculated for each event reported in each study, and, where appropriate, meta-analysis conducted to calculate overall odds ratios for each AE and each vaccine type. If these additional studies were abstracted, the totality of data abstracted could be used for secondary analyses to explore additional hypotheses and issues beyond the scope of the current report.

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Abbreviations / Acronyms

ACIP	Advisory Committee on Immunization Practices
ADEM	Acute disseminated encephalomyelitis
AEs	Adverse Events
AHRQ	Agency for Healthcare Research and Quality
ALL	Acute lymphoblastic leukemia
CAP	Community-acquired pneumonia
CCTs	Controlled Clinical Trials
CDC	Centers for Disease Control and Prevention
CER	Comparative Effectiveness Review
CI	Confidence Interval
CIDP	Chronic inflammatory demyelinating polyneuropathy
COPD	Chronic obstructive pulmonary disease
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular Disease
DPT	Diphtheria–Pertussis–Tetanus vaccine
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
GBS	Guillain–Barre Syndrome
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
GPRD	General Practice Research Database (UK)
Hib	Haemophilus influenzae type b
HMO	Health Maintenance Organization
HPV	Human Papilloma Virus
HR	Hazard ratios
HZ	Herpes Zoster
ICD	International Classification of Diseases
IHD	Ischemic heart disease
ILI	Influenza-Like Illness
IOM	Institute of Medicine
IPD	Invasive pneumococcal disease
IPV	Inactivated polio vaccine
IRR	Incidence rate ratio
ITP	Idiopathic thrombocytic purpura
KQs	Key Questions
LAIV	Live attenuated influenza vaccine
maxSPRT	Maximized sequential probability ratio test

MCO	Managed Care Organization
MCV	Meningococcal conjugate vaccine
MI	Myocardial infarction
MIV	Monovalent inactivated pandemic H1N1 vaccine
MMR	Measles, mumps, and rubella
MPSV	Meningococcal polysaccharide vaccine
MS	Multiple Sclerosis
NIH	National Institute of Health
OASH	Office of the Assistant Secretary for Health
OHSU	Oregon Health Sciences University
OR	Odds ratio
PAEDS	Pediatric Active Enhanced Disease Surveillance
PCV13	Pneumococcal conjugate vaccine
PPV	Pneumococcal polysaccharide vaccination
PRAMS	Pregnancy Risk Assessment Monitoring System
PV	Pneumococcal vaccine
RAD	Reactive airway disease
RCTs	Randomized Controlled Trials
RR	Relative risk
SAE	Serious adverse events
SAS	SAS Institute Inc., Cary, NC
SCCS	Self-controlled case series
SD	Standard deviation
SIDS	Sudden Infant Death Syndrome
SIPs	Scientific Information Packets
SLE	Systemic lupus erythematosus
SRC	Scientific Resource Center
Td	Tetanus, diphtheria
Tdap	Tetanus, diphtheria, and acellular pertussis vaccine
TEP	Technical Expert Panel
TIV	Trivalent influenza vaccine
TOO	Task Order Officer
TP	Thrombocytopenic purpura
USD	Urea cycle disorders
VAERS	Vaccine Adverse Event Reporting System
VICP	Vaccine Injury Compensation Program
VSD	Vaccine Safety Datalink
VZV	Varicella-Zoster Virus