

Safety of Vaccines Used for Routine Immunization in the U.S. A Systematic Review

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Safety of Vaccines

Methods



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Started with IOM 2011 Consensus Report

- Searched for new studies of vaccines included in the report “Adverse Effects of Vaccines: Evidence and Causality”
 - Varicella
 - Influenza
 - Hepatitis A
 - Hepatitis B
 - HPV
 - MMR
 - Meningococcal
 - Tetanus
 - Diphtheria
 - Pertussis

Searched for Vaccines IOM Did Not Include

- Pneumococcal
- Rotavirus
- *Haemophilus influenzae* type b
- Inactivated poliovirus
- Zoster vaccines

Sources

- Searched electronic databases such as Medline[®]
- Reviewed ACIP statements, package inserts, and Scientific Information Packets requested from vaccine manufacturers by an AHRQ-funded Scientific Resource Center
- Scanned review articles for relevant references

Study Designs

- **Controlled clinical trial**
 - Human subjects are assigned prospectively, usually through randomization, to receive an intervention (in this case, a vaccine) or an alternative intervention (another vaccine) or placebo to determine safety and efficacy
- **Cohort study**
 - Follows two or more similar groups that differ with respect to whether they received a vaccine (the “exposure”) to determine how/whether the vaccination affects rates of one or more AEs (the “outcome”)
- **Case-control study**
 - Compares people who have a disease or adverse event with people who do not and compares exposure to vaccine in each group to determine the relationship between the vaccine and the disease/event

Study Designs (continued)

- **Self-controlled case series**
 - Includes only individuals who experienced the AE. Each individual serves as his or her own control. The analysis inherently controls for covariates that remain stable during the study period—for example, race and sex. SCCSs compare outcome event rates both postvaccination and prevaccination to calculate the relative incidence of AEs
- **Multivariate risk factor analysis**
 - Includes all active surveillance studies that used regression to control for confounders and test multiple relationships simultaneously. Data sources may include medical records, health insurance claims, and government registries

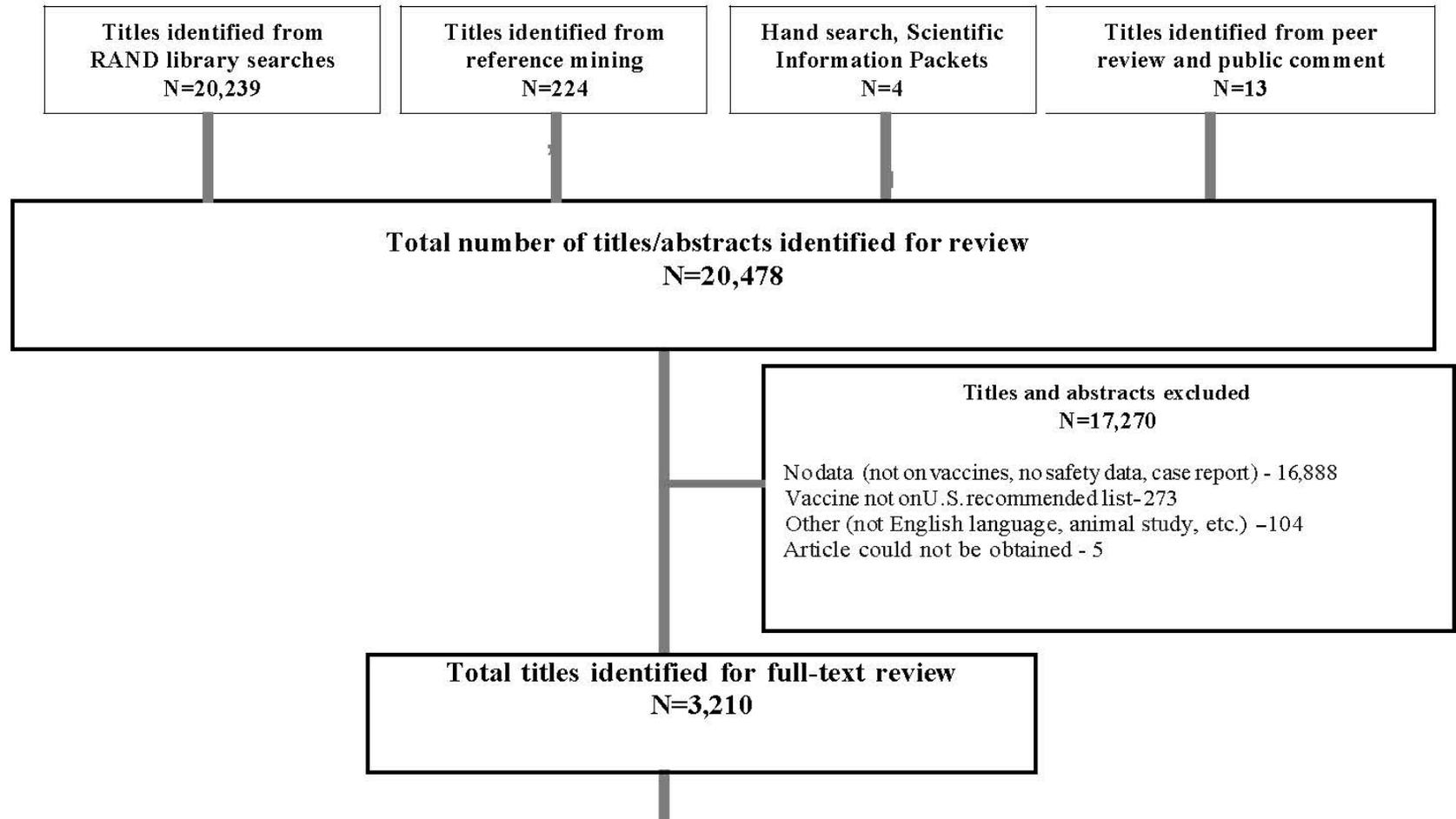
- Studies using passive surveillance (such as the U.S. Vaccine Adverse Event Reporting System) are not designed to assess a statistical association between a vaccine and an adverse event

Evaluation Methods

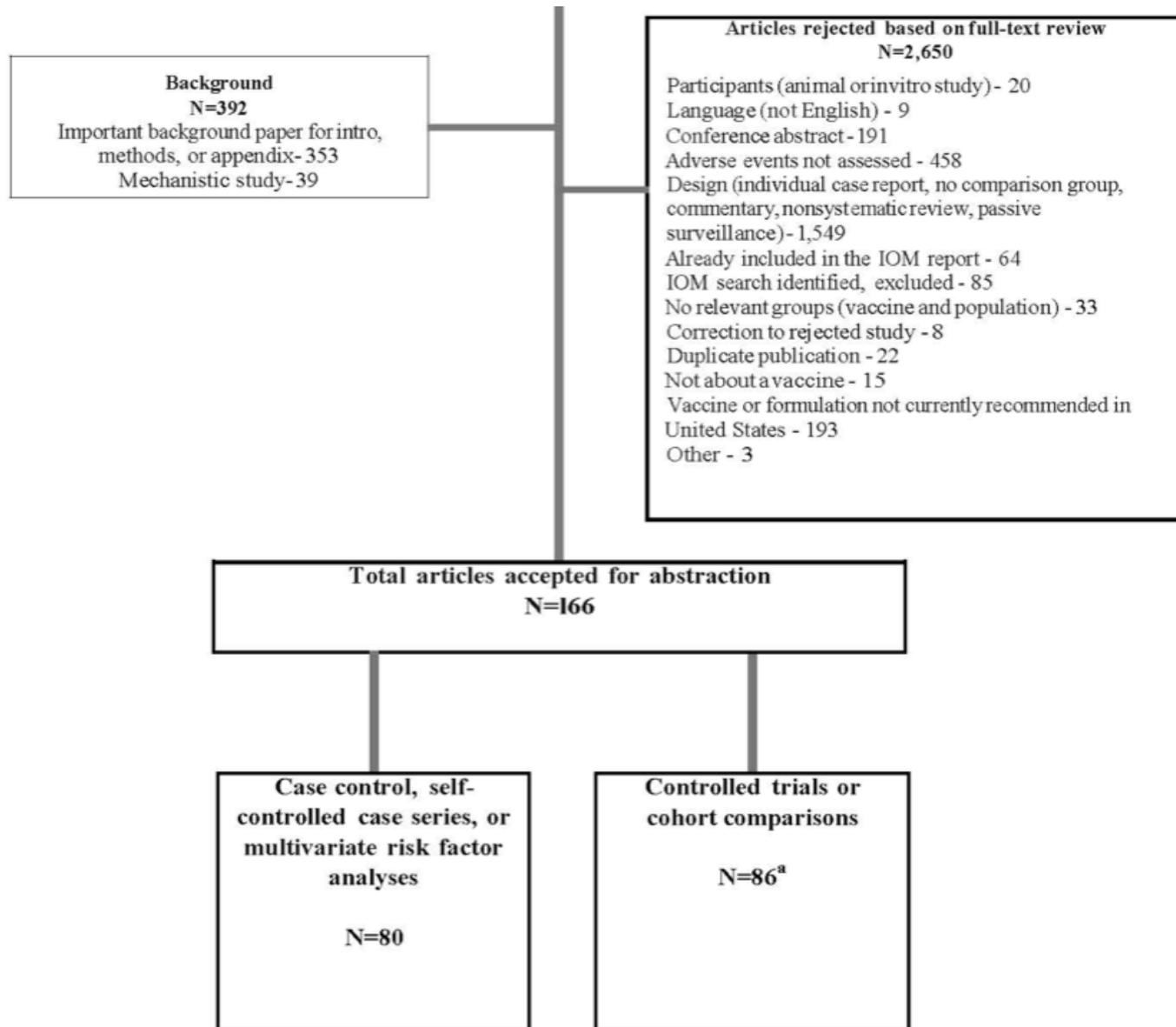
- Quality of study on adverse events:
McHarm instrument
 - This quality-assessment tool is intended for use in conjunction with standardized quality-assessment tools for design-specific internal validity issues
- Overall strength of evidence:
AHRQ guidance
 - Required domains: risk of bias, consistency, directness, and precision
 - Additional domains: dose response, plausible confounders that would decrease the observed effect, strength of association, and publication bias

- IOM “convincingly supports” = high strength of evidence
- IOM “favors acceptance” = “moderate” strength of evidence
- IOM “inadequate to accept or reject” = “insufficient”
- If new evidence identified, ratings could be adjusted up or down according to our assessment of the new studies.
- IOM “favors rejection” = moderate or high based on our review of IOM evidence plus any studies published later

Study/Literature Flow Diagram



Study/Literature Flow Diagram (cont.)



Safety of Vaccines Results



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Adults

Vaccine	EPC Conclusions and Strength of Evidence
Tetanus, Diphtheria, and Acellular Pertussis (Tdap)	High: Association with anaphylaxis in patients allergic to ingredients of tetanus component
Hepatitis A Vaccine	Insufficient: Serious Adverse Events in long term (IOM, 2011)
Hepatitis B Vaccine	Insufficient: Serious Adverse Events in long term (IOM, 2011) Moderate: No association with MS onset or exacerbation (IOM, 2011) Moderate: Anaphylaxis in patients allergic to yeast

Adults (continued)

Vaccine	EPC Conclusions and Strength of Evidence
Influenza Vaccines	<p>High: Association with arthralgia, myalgia, malaise, fever, pain at injection site, anaphylaxis in allergic people</p> <p>High: No association with cardiovascular or cerebrovascular events in the elderly</p> <p>High: Association of H1N1 with Guillain-Barré Syndrome (GBS) (Salmon, 2013, meta-analysis)</p> <p>Moderate: No association with Serious Adverse Events in renal patients</p> <p>Insufficient: MS onset and exacerbation (IOM, 2011)</p>

Adults (continued)

Vaccine	EPC Conclusions and Strength of Evidence
MMR Vaccine	<p>Moderate: No association with Type 1 diabetes</p> <p>Moderate: Association with transient arthralgia in women</p> <p>Insufficient: MS onset, GBS, chronic arthralgia in women, and chronic arthritis and arthropathy in men (IOM, 2011)</p>
Pneumococcal Polysaccharide Vaccine	<p>High: No association with cardiovascular or cerebrovascular events in the elderly</p>
Zoster Vaccine	<p>Moderate: Association with injection site reactions, allergic reactions, cellulitis possibly related to allergy</p> <p>Insufficient: Serious Adverse Events</p>

Children and Adolescents

Vaccine	EPC Conclusions and Strength of Evidence
Diphtheria Toxoid, Tetanus Toxoid, and Acellular Pertussis-containing Vaccines	Moderate: No association with type 1 diabetes Insufficient: infantile spasms, seizures, cerebellar ataxia, autism , ADEM, transverse myelitis, MS relapse, serum sickness, immune thrombocytopenic purpura, and SIDS (IOM, 2011)
Hepatitis B Vaccine	Moderate: No association with MS (IOM, 2002; 2011) Insufficient: Food allergy Insufficient: Serious Adverse Events in long term (IOM, 2011)
Hib (Haemophilus influenzae type B) Vaccine	Moderate: No association with Serious Adverse Events in short term

Children and Adolescents (continued)

Vaccine	EPC Conclusions and Strength of Evidence
HPV Vaccine	<p>Moderate: No association with juvenile rheumatoid arthritis, type 1 diabetes, appendicitis, Guillain Barré Syndrome, seizures, stroke, syncope, venous thromboembolism</p> <p>Moderate: Association with anaphylaxis in patients with allergies; fever, headache, mild gastrointestinal AEs, skin infection</p> <p>High: Pain at injection site</p> <p>Insufficient: ADEM, transverse myelitis, neuromyelitis optica, MS, onset of Hashimoto's disease, chronic inflammatory demyelinating polyneuropathy, brachial neuritis, amyotrophic lateral sclerosis, transient arthralgia, pancreatitis, thromboembolic events, hypercoagulable states (IOM, 2011)</p>

Children and Adolescents (continued)

Vaccine	EPC Conclusions and Strength of Evidence
Inactivated Polio Vaccine	Insufficient: Food allergy
Influenza Vaccines	Moderate: Association with mild gastrointestinal disorders, febrile seizures Low: No association with Serious Adverse Events in the short term in children with cancer or who have received organ transplants Low: Association with influenza-like symptoms Insufficient: Asthma exacerbation (with live vaccine), seizures, ADEM, transverse myelitis

Children and Adolescents (continued)

Vaccine	EPC Conclusions and Strength of Evidence
Measles-Mumps-Rubella Vaccine	<p>High: No association with autism spectrum disorder</p> <p>High: Association with febrile seizures, anaphylaxis in children with allergies</p> <p>Moderate: Association with transient arthralgia</p> <p>Moderate: Association with thrombocytopenic purpura</p> <p>Insufficient: Encephalitis, encephalopathy, afebrile seizures, meningitis, cerebellar ataxia, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, neuromyelitis optica, MS onset, and chronic arthropathy (IOM, 2011)</p>

Children and Adolescents (continued)

Vaccine	EPC Conclusions and Strength of Evidence
Meningococcal Vaccines	Moderate: Association with anaphylaxis in children with allergies Insufficient: encephalitis, encephalopathy, ADEM, transverse myelitis, MS, Guillain Barré Syndrome, CIDP, chronic headache (IOM report)
Pneumococcal Conjugate	Moderate: Febrile seizures
Rotavirus Vaccines: RotaTeq, Rotarix	Moderate: Association with intussusception
Combination Vaccines or Multiple vaccines	Moderate: Association of DTaP-IPV-Hib with febrile seizures High: No association of childhood leukemia with MMR, DTaP, Td, Hib, Hepatitis B, and polio vaccines Moderate: Association of Hepatitis A, MMR, and varicella vaccine with purpura

Children and Adolescents (continued)

Vaccine	EPC Conclusions and Strength of Evidence
Varicella Vaccine	<p>High: Anaphylaxis; disseminated Oka VZV with possible sequelae in immunocompromised individuals (IOM, 2011)</p> <p>Insufficient: Seizures, ADEM, transverse myelitis, Guillain-Barré Syndrome, small fiber neuropathy, onset or exacerbation of arthropathy, thrombocytopenia (IOM, 2011)</p>

Pregnant Women

Vaccine	EPC Conclusions and Strength of Evidence
Influenza Vaccines	Moderate: No association with Serious Adverse Events

Safety of Vaccines

Limitations



Limitations

- Only two manufacturers responded to requests for scientific information
- Some RCTs report broad categories rather than specific AEs
- Most RCTs and post-marketing studies did not rate the severity of AEs or provide enough info for us to rate

Limitations (continued)

- Some epi studies used self-report of AEs, not medical records
- Some potential differences between those who get vaccinated and those who do not may not be captured
- Self-controlled case series do not control for time-related factors, just characteristics that do not change over time (gender, ethnicity). This is important in studies of very young children

Limitations (continued)

- Some post-licensure studies include many brands and formulations, do not stratify results (influenza studies)

Safety of Vaccines

Research Gaps



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Research Gaps – Adults

- Guillain Barré Syndrome: Risk factors are unclear. H1N1 vaccine associated with just 1.6 excess cases per million vaccinated; investigating risk factors will be difficult.
- IOM found evidence inadequate to accept or reject a causal relationship regarding MS and vaccines against Hepatitis A, Hepatitis B, and MMR. We identified no additional studies.

Research Gaps – Children and Adolescents

- Febrile seizures are associated with MMR, influenza, and pneumococcal conjugate vaccines. Younger age associated with increased risk in several studies; other patient risk factors are not clear.
- Rotarix and RotaTeq associated with intussusception in the short term following vaccination in U.S. children; patient risk factors not reported

Research Gaps – Children and Adolescents

- According to IOM, 2011, evidence is insufficient regarding vaccines such as DTaP, meningococcal vaccine, and varicella vaccine and ADEM, MS, GBS, and transverse myelitis.

Research Gaps – Pregnant Women

- Tdap vaccine was beyond the scope of our report. 2013 recommendation is for every pregnancy. Passive surveillance systems should be monitored for AEs, especially in women with multiple pregnancies over a few years.
- Not all AEs are immediately apparent at birth, so newborns should be sufficiently monitored. Large study samples are critical given the relative rarity of some birth defects.



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