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

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<table>
<thead>
<tr>
<th>Name</th>
<th>Affiliation</th>
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| **Richard Beigi, M.D., M.Sc.** | Magee-Women’s Hospital
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# Peer Reviewers

<table>
<thead>
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<th>Name</th>
<th>Affiliation</th>
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<tbody>
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<td>Janet D. Cragan, M.D., M.P.H.</td>
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<tr>
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<td>Massachusetts General Hospital Boston, MA</td>
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Safety of Vaccines

Methods
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

- Titles identified from RAND library searches: N=20,239
- Titles identified from reference mining: N=224
- Hand search, Scientific Information Packets: N=4
- Titles identified from peer review and public comment: N=13

Total number of titles/abstracts identified for review: N=20,478

- Titles and abstracts excluded: N=17,270
  - No data (not on vaccines, no safety data, case report) - 16,888
  - Vaccine not on U.S. recommended list - 273
  - Other (not English language, animal study, etc.) - 104
  - Article could not be obtained - 5

Total titles identified for full-text review: N=3,210
Study/Literature Flow Diagram (cont.)

Background
N=392
Important background paper for intro, methods, or appendix - 353
Mechanistic study - 39

Articles rejected based on full-text review
N=2,650
- Participants (animal or in vitro study) - 20
- Language (not English) - 9
- Conference abstract - 191
- Adverse events not assessed - 458
- Design (individual case report, no comparison group, commentary, non-systematic review, passive surveillance) - 1,549
- Already included in the IOM report - 64
- IOM search identified, excluded - 85
- No relevant groups (vaccine and population) - 33
- Correction to rejected study - 8
- Duplicate publication - 22
- Not about a vaccine - 15
- Vaccine or formulation not currently recommended in United States - 193
- Other - 3

Total articles accepted for abstraction
N=166

Case control, self-controlled case series, or multivariate risk factor analyses
N=80

Controlled trials or cohort comparisons
N=86*
Safety of Vaccines

Results
## Adults

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>EPC Conclusions and Strength of Evidence</th>
</tr>
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<tbody>
<tr>
<td><strong>Tetanus, Diptheria, and Acellular Pertussis (Tdap)</strong></td>
<td>High: Association with anaphylaxis in patients allergic to ingredients of tetanus component</td>
</tr>
<tr>
<td><strong>Hepatitis A Vaccine</strong></td>
<td>Insufficient: Serious Adverse Events in long term (IOM, 2011)</td>
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<tr>
<td><strong>Hepatitis B Vaccine</strong></td>
<td>Insufficient: Serious Adverse Events in long term (IOM, 2011)</td>
</tr>
<tr>
<td></td>
<td>Moderate: No association with MS onset or exacerbation (IOM, 2011)</td>
</tr>
<tr>
<td></td>
<td>Moderate: Anaphylaxis in patients allergic to yeast</td>
</tr>
<tr>
<td>Vaccine</td>
<td>EPC Conclusions and Strength of Evidence</td>
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<tr>
<td>Influenza Vaccines</td>
<td>High: Association with arthralgia, myalgia, malaise, fever, pain at injection site, anaphylaxis in allergic people</td>
</tr>
<tr>
<td></td>
<td>High: No association with cardiovascular or cerebrovascular events in the elderly</td>
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<tr>
<td></td>
<td>High: Association of H1N1 with Guillain-Barré Syndrome (GBS) (Salmon, 2013, meta-analysis)</td>
</tr>
<tr>
<td></td>
<td>Moderate: No association with Serious Adverse Events in renal patients</td>
</tr>
<tr>
<td></td>
<td>Insufficient: MS onset and exacerbation (IOM, 2011)</td>
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Adults (continued)
## Adults (continued)

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

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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>EPC Conclusions and Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated Polio Vaccine</td>
<td>Insufficient: Food allergy</td>
</tr>
<tr>
<td>Influenza Vaccines</td>
<td>Moderate: Association with mild gastrointestinal disorders, febrile seizures</td>
</tr>
<tr>
<td></td>
<td>Low: No association with Serious Adverse Events in the short term in children with cancer or who have received organ transplants</td>
</tr>
<tr>
<td></td>
<td>Low: Association with influenza-like symptoms</td>
</tr>
<tr>
<td></td>
<td>Insufficient: Asthma exacerbation (with live vaccine), seizures, ADEM, transverse myelitis</td>
</tr>
<tr>
<td>Vaccine</td>
<td>EPC Conclusions and Strength of Evidence</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
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</tbody>
</table>
| Measles-Mumps-Rubella Vaccine   | High: No association with autism spectrum disorder  
High: Association with febrile seizures, anaphylaxis in children with allergies  
Moderate: Association with transient arthralgia  
Moderate: Association with thrombocytopenic purpura  
Insufficient: Encephalitis, encephalopathy, afebrile seizures, meningitis, cerebellar ataxia, acute disseminated encephalomyelitis, transverse myelitis, optic neuritis, neuromyelitis optica, MS onset, and chronic arthropathy (IOM, 2011) |
<table>
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<tr>
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<tr>
<td>Meningococcal Vaccines</td>
<td>Moderate: Association with anaphylaxis in children with allergies &lt;br&gt; Insufficient: encephalitis, encephalopathy, ADEM, transverse myelitis, MS, Guillain Barré Syndrome, CIDP, chronic headache (IOM report)</td>
</tr>
<tr>
<td>Pneumococcal Conjugate</td>
<td>Moderate: Febrile seizures</td>
</tr>
<tr>
<td>Rotavirus Vaccines: RotaTeq, Rotarix</td>
<td>Moderate: Association with intussusception</td>
</tr>
<tr>
<td>Combination Vaccines or Multiple vaccines</td>
<td>Moderate: Association of DTaP-IPV-Hib with febrile seizures &lt;br&gt; High: No association of childhood leukemia with MMR, DTaP, Td, Hib, Hepatitis B, and polio vaccines &lt;br&gt; Moderate: Association of Hepatitis A, MMR, and varicella vaccine with purpura</td>
</tr>
</tbody>
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### Children and Adolescents (continued)

<table>
<thead>
<tr>
<th>Vaccine</th>
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</tr>
</thead>
</table>
| Varicella Vaccine | High: Anaphylaxis; disseminated Oka VZV with possible sequelae in immuno-compromised individuals (IOM, 2011)  
Insufficient: Seizures, ADEM, transverse myelitis, Guillain-Barré Syndrome, small fiber neuropathy, onset or exacerbation of arthropyathy, thrombocytopenia (IOM, 2011) |
## Pregnant Women

<table>
<thead>
<tr>
<th>Vaccine</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Influenza Vaccines</td>
<td>Moderate: No association with Serious Adverse Events</td>
</tr>
</tbody>
</table>
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
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.