Evidence-based Practice Center Systematic Review Protocol

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

I. Background and Objectives for the Systematic Review

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 at an all-time 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 are 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 is occurring 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 vaccine during the second or third trimester of pregnancy to protect their newborns from pertussis.

Table 1. Vaccines routinely recommended for children and adolescents

Vaccine	Children
DTaP (diphtheria, tetanus, and acellular pertussis)	2 months – 6 years
Hepatitis A	12 months and older

Source: www.effectivehealthcare.ahrq.gov
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Hepatitis B	Birth and older
Hib (*Haemophilus influenzae* 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
PCV13 (pneumococcal conjugate vaccine)	6 weeks – 18 years
Pneumococcal polysaccharide vaccine	2 years and older
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	**Adults**
Hepatitis A	All adults at increased risk of hepatitis A infection
Hepatitis B	All unvaccinated adults at risk for hepatitis B infection and all adults 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

Source: www.effectivehealthcare.ahrq.gov
Published Online: October 22, 2012

Table 3. Vaccines routinely recommended for pregnant women

Vaccine	Pregnant women
Hepatitis B	Recommended in some circumstances
Influenza (inactivated)	All pregnant women after the first trimester
Td (tetanus, diphtheria)	Should be used if indicated
Tdap (tetanus, diphtheria, and acellular pertussis)	All pregnant women after the first trimester if indicated

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.[8] Vaccines are unique when compared with many other drugs and 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 that 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.[8] 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,[9] including postlicensure safety surveillance conducted by the FDA,[10] the Vaccine Adverse Event Reporting System (VAERS),[11] the Vaccine Safety Datalink,[12] and the Clinical Immunization Safety Assessment Network.[13]

Despite the stringent regulation and evaluation of vaccines, concerns about vaccine safety continue to persist for the lay public. Perhaps the most highly publicized safety concern of the last 2 decades has been the link between autism and the MMR vaccine, first reported in *The Lancet* by Dr. Andrew Wakefield.[14] Vaccination rates for measles, mumps, and rubella plummeted in the United Kingdom leading to measles outbreaks[15] and concern about vaccines and autism spread globally. In 2010, *The Lancet* fully retracted the 1998 publication,[16] 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.[17] 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) and children 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 AEs potentially associated with vaccines as opposed to the benefits, as all of these vaccines are already recommended. Our work will expand the consensus report *Adverse Effects of Vaccines: Evidence and Causality*, which was published by the Institute of Medicine (IOM) in 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 will build upon the IOM report in a number of important ways. In addition to those vaccines covered by the IOM report, our systematic review will also cover the pneumococcal, rotavirus, *Haemophilus influenzae* type b, inactivated poliovirus, and zoster vaccines. We will use the existing IOM bibliography as a springboard and will update the literature search with more recent studies and include original searches for the vaccines recommended for adults, children, and pregnant women that are not included in the IOM report. We provide an assessment of AEs for all vaccines and include searches for studies that address the severity of, relative risk for, and risk factors for each AE type. Appendix A contains an extensive list of potential AEs by vaccine; our methods are summarized below.

II. The Key Questions

Question 1

What is the evidence that vaccines included in the 2011 immunization schedule recommended for U.S. adults[18]* 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 is the proposed biological mechanism? (Answers to this question will be compiled in an appendix.)

4. 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)?

* Recommended adult vaccines: influenza, tetanus, diphtheria, and pertussis; varicella; human papillomavirus; zoster; measles, mumps, and rubella; pneumococcal (polysaccharide); meningococcal; hepatitis A; and hepatitis B.

Question 2

What is the evidence that vaccines included in the immunization schedules recommended for U.S. children and adolescents in 2011[19]* 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 is the proposed biological mechanism? (Answers to this question will be compiled in an appendix.)

4. 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)?

* Recommended child and adolescent vaccines: hepatitis B; rotavirus; diphtheria, tetanus, and pertussis; *H. influenza* type b; pneumococcal; inactivated poliovirus; influenza; measles, mumps, and rubella; varicella; hepatitis A; meningococcal; and human papillomavirus.

Question 3

What is the evidence that vaccines recommended for pregnant women[20]* 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 is the proposed biological mechanism? (Answers to this question will be compiled in an appendix.)

   4. 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?

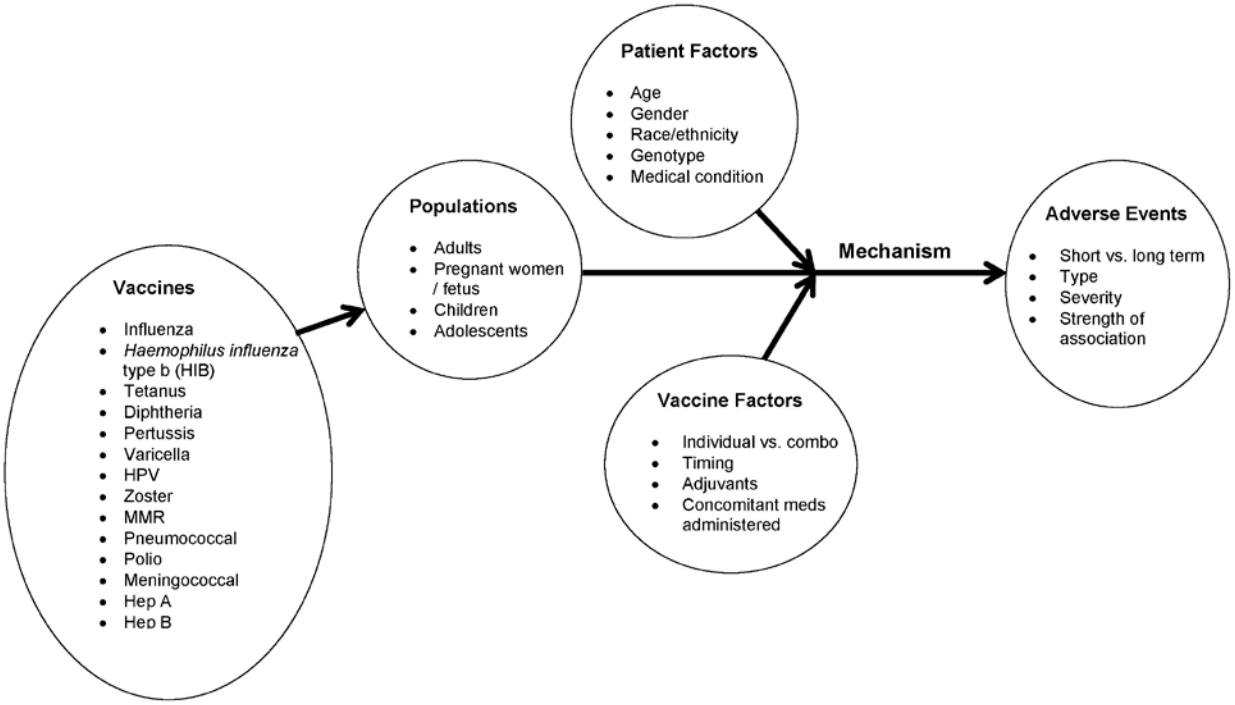
   3. For each AE associated with a particular vaccine, what is the proposed biological mechanism? (Answers to this question will be compiled in an appendix.)

4. 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)?

* Hepatitis B, if indicated; influenza; tetanus-diphtheria, if indicated; tetanus, diphtheria, and pertussis, in some situations as noted by the Advisory Committee on Immunization Practices (ACIP).

III. 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) in 2011 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 ACIP. Both patient factors (i.e., age and race) and vaccine factors (i.e., formulation, dosage, and timing) may be risk factors for potential AEs associated with vaccination.



Abbreviations: Hep A = hepatitis A; Hep B = hepatitis B; HPV = human papilloma virus; MMR = measles, mumps, and rubella

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

The following publication types / studies will be **excluded**:

- Letters
- Editorials
- Individual case reports
- Animal studies
- Mechanistic/in vitro (animal or human) studies; we will include an appendix summarizing potential biological mechanisms
- Studies of vaccines not on the recommended 2011 schedules, including brands/formulations not available in the United States
- Non–English-language studies
- Studies not reporting or mentioning AEs

The following types of studies will be **included**:

- All other studies that compare AEs between a vaccinated group and an unvaccinated control or comparison group
- Multivariate analysis for risk factors (no unvaccinated group necessary, but must control for multiple factors in a regression analysis)
- Vaccination with high-dose influenza vaccine versus another dose in elderly adults
- Vaccination of pregnant women versus a nonpregnant group
- Interdermal versus intramuscular administration of influenza vaccine
- Studies of vaccines that do not have an unvaccinated group for ethical reasons (i.e., testing a new product against the vaccination that is licensed/in use), such as:
  - Pneumococcal conjugate vaccine 13 (PCV13) versus pneumococcal conjugate vaccine 7 (PCV7)
  - Inactivated polio vaccine (IPV) versus oral polio vaccine (OPV)
  - Live attenuated influenza vaccine (LAIV) versus trivalent influenza vaccine (TIV)
  - Tetanus, diphtheria, and acellular pertussis (Tdap) versus tetanus and diphtheria (Td)
  - Meningococcal conjugate vaccine (MCV4) versus meningococcal polysaccharide vaccine 5 (MPS5)

There will be no limitations regarding publication date.

B. Development of the Search Strategy: Searching for the Evidence

Keyword Searches

Our search strategy will build upon the recent IOM report for the eight vaccines contained therein. Using the IOM keyword search strategy, we will update their searches on varicella, influenza, hepatitis A, hepatitis B, HPV, MMR, meningococcus, diphtheria, pertussis, and tetanus 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. Because our focus is on AEs in general, we will add more general AE keywords to the list of health terms such as "safe" or "safety" or "side effect" or "harm." We are not including minor AEs such as crying, fever, injection site tenderness, et cetera.

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

In addition to using broad terms such as "safety" to identify studies assessing AEs, we will use keyword search terms for specific AEs. Preliminary searches will be based on AEs reported in systems just as VCIP, VAERS, and the FDA's Mini-Sentinel Program. Input from the Technical Expert Panel (TEP) was used to identify additional AEs of interest. The detailed search strategy, as well as a list of potential AEs for each vaccine, is included as Appendix A.

Data Sources

The following databases will be used to conduct searches and 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 also will be used to identify studies. Relevant review articles will be mined for references.

Title/Abstract Screening

Two independent researchers will review the titles and abstracts. The union of their selections will be retrieved. Two independent reviewers will review the full text of study reports and meet to reach consensus regarding exclusion/inclusion. Disputes will be settled by the principal investigators.

Retrieval of Publications

We have access to a biomedical library, which gives us access to the majority of published articles. We also use a library ordering system called ILLiad, an online tool to place interlibrary loan and document requests, track their progress, and view order histories.

C. Data Abstraction and Data Management

Data will be entered in DistillerSR software (Evidence Partners Inc., Ottawa, Ontario, Canada),[21] which is designed specifically for systematic reviews and meta-analyses, and exported to SAS (SAS Institute Inc., Cary, NC) for analysis.

Based on our experience conducting systematic reviews of the evidence on other products, procedures, and medications, we have developed a structured approach to assessing AEs instead of relying on a random post-hoc grouping. We will use a tested and standardized form to extract AEs; two independent content experts will then determine the nature and the severity of the AE as part of the data extraction process. The identified harms will be characterized by using the Common Terminology Criteria for Adverse Events (CTCAE) classification system, and serious adverse events (SAE) will be defined and coded.

The CTCAE system employs a scale of severity where lower grades reflect lower severity. The following are included in the CTCAE guidelines as published by the U.S. Department of Health and Human Services:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

Grade 4: Life-threatening consequences; urgent intervention indicated

Grade 5: Death related to AE

D. Data Quality: Assessment of Methodological Risk of Bias of Individual Studies

Santaguida and colleagues (2008)[22] developed a quality-rating instrument 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 study specify who collected the harms data?
- Did the study specify the timing of harms?

- Was number of participants who withdrew or were lost to followup reported?

E. Data Synthesis

Most of the outlined review questions will be answered by providing descriptive data (e.g., number of studies reporting AEs, type of AEs, etc.). We will create detailed evidence tables displaying critical data for each included study. Where appropriate, odds ratios of AEs for vaccination and comparison arms will be computed for each study and pooled across studies in a meta-analysis for a summary estimate. The absolute risk of serious adverse events (SAEs) will also be computed. Studies will be included for analysis if information about the total number of people in each group and the number of people with events in each group is available. For groups of events that appear in at least three trials, a meta-analysis can estimate the odds ratio and its 95-percent confidence interval. Since AEs are generally rare, conditional pooling using exact methods will provide a fixed effects estimate of the odds ratio. Analyses will be conducted with Stat Xact® Procs for SAS.[23]

Unless statistical power is adequate, subgroup analyses will be narrative in order to be able to make comparisons between study designs and other variables in the heterogeneous dataset. Further input about effect modifiers and pertinent subgroups has been discussed with a local content expert and the TEP. (See the comparisons listed under Criteria for Inclusion/Exclusion of Studies in the Review.)

Multiple publications of the same study will be noted but counted (and extracted, assessed for quality, and analyzed) as one study to ensure that the same participants do not enter the analyses multiple times. Multiple publications are defined by the investigated patients.

F. Assessing Strength of Evidence: Grading the Strength of Evidence for Individual Outcomes

We will assess the overall strength of evidence by using guidance suggested by AHRQ for its Effective Health Care Program.[24] This method is based loosely on one developed by the GRADE Working Group[25] 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; the additional domains

are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias.

G. Assessing Applicability

Applicability refers to the extent to which the effects observed in published studies are likely to reflect the expected results when a specific intervention (i.e., vaccination) is applied to the population of interest under "real-world" conditions. Relatively few clinical trials are designed with applicability in mind; furthermore, they sometimes report only a few of the factors needed to fully assess applicability. Thus, we are including observational studies that contain an unvaccinated control/comparison group such as population surveillance, retrospective and prospective cohorts, and analyses of administrative databases.

Defining the populations, interventions, timing, and outcomes (as described in the KQs and analytic framework) inevitably takes into account factors that may affect the applicability of studies. Reviewers will abstract this information and consider it in summarizing the applicability and limitations of the evidence. Evidence tables will clearly distinguish studies designed to assess effectiveness versus those designed specifically to assess safety. To make applicability information useful, the review will address how specific aspects of study design affected the final population and how greatly (and in which direction) it may differ from more representative populations in practice.

V. References

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VI. Definition of Terms

ADL = Activities of daily living
Adjuvant = A pharmacological agent added to a drug to affect the action of the drug's active ingredient
AE = Adverse event

CTCAE = Common Terminology Criteria for Adverse Events
Hib = *Haemophilus influenzae* type b
HPV = Human papillomavirus
MCV = Meningococcal conjugate vaccine
MMR = Measles, mumps, and rubella
SAE = Serious adverse event
Tdap = Tetanus, diphtheria, and acellular pertussis
VAERS = Vaccine Adverse Event Reporting System
VCIP = Vaccine Injury Compensation Program

VII. Summary of Protocol Amendments

Date	Section	Original Protocol	Revised Protocol	Rationale

VIII. Review of Key Questions

Not applicable.

IX. Key Informants

Not applicable.

X. Technical Experts

The Technical Expert Panel (TEP) is a multidisciplinary group of clinical, content, and methodological experts who provide input in further refining populations, interventions, comparisons, or outcomes, as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the Evidence-based Practice Center (EPC) to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published 3 months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

All project team members completed a conflict of interest disclosure form. No members reported any conflict of interest.

XIII. Role of the Funder

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Appendix A. Adverse events of interest, included in electronic search terms

Adverse event	Vaccine type
Acute disseminated encephalomyelitis	All vaccines on U.S. recommended schedule (heretoforth "All")
Afebrile seizures	All
Amyotrophic lateral sclerosis	HPV
Anaphylactic shock (anaphylaxis) or acute systemic allergic reaction	All
Anaphylactoid reactions	All
Angina	All
Angioedema	All
Ankylosing spondylitis	All
Arthritis/arthralgia	Varicella MMR Influenza HPV DT, TT, and aP
Asthma	Influenza
Ataxia	Varicella (as cerebellar ataxia) MMR DT,TT, aP
Atopic dermatitis	Below severity threshold
Autism	DT, TT, and aP MMR
Autoimmune hepatitis	Hepatitis A
Autoimmune thyroiditis (Hashimoto)	Hepatitis B (under "Autoimmune thyroid disease")
Bell's palsy	Varicella Influenza Hepatitis A DT, TT, and aP Meningococcal
Birth defects	All vaccines recommended during pregnancy
Brachial neuritis	MMR Influenza Hepatitis B HPV
Bronchospasm	Under asthma: Influenza

Source: www.effectivehealthcare.ahrq.gov
Published Online: October 22, 2012

Adverse event	Vaccine type
Cellulitis at injection site	Below severity threshold
Constipation	Below severity threshold
Crohn's disease	MMR
Death	All
Diarrhea	Below severity threshold
Eclampsia and pre-eclampsia	All vaccines recommended during pregnancy
Encephalitis/encephalopathy	Encephalitis: Varicella MMR Influenza Hepatitis B DT, TT, and aP Rotavirus Meningococcal Encephalopathy: Varicella MMR Influenza Hepatitis B DT, TT, and aP Meningococcal
Febrile seizures	DTaP MMR Influenza Polio Pneumococcal Rotavirus Tdap Varicella
Fever	Below severity threshold
Fibromyalgia	All
Fisher's syndrome	All
Gastrointestinal bleeding	Rotavirus
Guillain-Barre syndrome	All
Headache	Below severity threshold
Henoch-Schonlein purpura	Meningococcal
Herpes zoster	Zoster
Idiopathic thrombocytopenic purpura	All
Injection site infections	Below severity threshold
Intussusception	Rotavirus

Source: www.effectivehealthcare.ahrq.gov
Published Online: October 22, 2012

Adverse event	Vaccine type
Ischemic heart disease	All
Kawasaki disease	Rotavirus
Malaise/Fatigue	Below severity threshold
Meningitis/encephalitis	Meningitis: Varicella MMR DT, TT, and aP Rotavirus Encephalitis: Varicella MMR Influenza Hepatitis B DT, TT, and aP Rotavirus Meningococcal
Multiple sclerosis	MMR Influenza Hepatitis A Hepatitis B HPV DT, TT, and aP Meningococcal
Myocardial infarction	All
Myocarditis and pericarditis	DT, TT, and aP Rotavirus
Myoclonus	Included only as “Opsoclonus myoclonus Syndrome” for DT, TT, aP, and MMR
Narcolepsy	All except rotavirus
Nausea	Below severity threshold
Necrosis at injection site	Local reaction – not included
Oculorespiratory syndrome	Influenza
Optic neuritis	MMR Influenza Hepatitis B DT, TT, aP
Pain	Below severity threshold – local reaction
Pancreatitis	HPV

Source: www.effectivehealthcare.ahrq.gov
Published Online: October 22, 2012

Adverse event	Vaccine type
Polyarteritis nodosa	All
Polymyalgia rheumatica	All
Preterm labor	All vaccines recommended during pregnancy
Rash	Below severity threshold
Reiter's syndrome	Hepatitis B (under "Reactive arthritis" which is synonymous, and also would be covered by "arthritis/arthralgia" for some vaccines)
Rheumatoid arthritis and juvenile rheumatoid arthritis	All
Secondary transmission of live varicella virus	Varicella, zoster
Seizures	Varicella, MMR, influenza, hepatitis B, DT, TT, aP, meningococcal, rotavirus, pneumococcal
Sepsis	Rotavirus (as Gram-negative sepsis)
Serum sickness	All
Somnolence	Below severity threshold
Spontaneous abortion	All vaccines recommended during pregnancy
Stillbirth	All vaccines recommended during pregnancy
Stroke	All
Syncope (vasovagal)	HPV
Systemic allergic reaction	All
Systemic lupus erythematosus	All
Thrombocytopenia (including ITP)	Immune thrombocytopenia purpura: DT, TT, and aP MMR Thrombocytopenia: Meningococcal Pneumococcal Hib Polio Varicella
Tics	All
Transverse myelitis	All
Type 1 diabetes	All
Ulcerative colitis	MMR
Urticaria	DT, TT, and aP (as chronic urticaria)
Uveitis	All

Source: www.effectivehealthcare.ahrq.gov
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Adverse event	Vaccine type
Vasculitis	All
Venous thromboembolism	All
Vomiting	Below severity threshold