Evidence-based Practice Center Systematic Review Protocol

Project Title: ***Safety of Vaccines Used for Routine Immunization in the United States***

I. Background and Objectives for the Systematic Review

Vaccines are considered one of the greatest public health achievements of the 20th century and the effectiveness of vaccines in controlling the spread of and even eradicating a variety of infectious diseases is widely acknowledged.[1] This evidence review focuses solely on vaccine safety. Identifying both the frequency and severity of adverse events associated with vaccines and, when appropriate, the absence of adverse effects, is critically important. Assessment of vaccine safety depends on clinical trials conducted for vaccine approval, systematic post-marketing surveillance, and a nationwide reporting system documenting all negative outcomes, including rare events, that may have been associated with use of a vaccine.

Since the 2014 Agency for Healthcare Research and Quality (AHRQ) review of vaccine safety,[2] a number of new vaccines have been approved, and indications for a small number of existing vaccines have been revised. Several new influenza vaccines have been introduced, with many changes to population approvals for both new and older influenza vaccines.[3] For example, the 9-valent HPV vaccine (HPV-9) has replaced the 2- and 4-valent HPV vaccines, with indications that have steadily expanded to include men and women through 45 years of age.[4] Two new serogroup B meningococcal vaccines are available to high-risk populations and adolescents.[5] Some novel adjuvants are now in use, such as those for the new recombinant shingles vaccine Shingrix, which was approved in 2017.[6]

Thoughtful assessment and synthesis of the evidence related to the safety of vaccines in specific populations help support strategies to increase vaccination rates, including effective communication about vaccines. For each population—adults (including adults 65 years of age and older), children and adolescents, and pregnant women—several questions must be considered when evaluating short- and long-term adverse events of vaccines. The concept of 'safety' in medical literature is measured and described as the number, type, and severity of 'adverse events' reported by study participants. A systematic review will need to address a number of important questions. First, what adverse events can occur with individual and combination vaccines? Which effects are transient, and which ones pose a permanent heath risk? Also, what are the risks of specific adverse events, the frequency of events, and the certainty of the association? Clinicians, patients, and caregivers want information on the nature and the frequency of potential side effects to help them weigh the benefits of vaccines against potential risks. Also important to stakeholders is the severity of the adverse events, even when events are likely to be very rare. Finally, understanding the risk factors for a given event (e.g., age, sex, race/ethnicity,

medical comorbidity, concomitant medications, adjuvants, etc.) is important for policymakers and clinicians to potentially modify vaccine recommendations as needed.

Evidence review scope: The scope of this systematic review of the evidence is to assess the safety of vaccines in the immunization schedule recommended for children, adults, and pregnant women (see Appendix A for all vaccines within scope). The list of vaccines is based on the Centers for Disease Control and Prevention (CDC)'s immunization schedules,[7, 8] and includes only those currently licensed for use in the United States by the FDA.[9] The review will include individual as well as combination vaccines in use in the US.

Purpose of the Review: The purpose of this review commissioned by the Office of the Assistant Secretary of Health/Office of Infectious Disease & HIV/AIDS Policy (OASH/OIDP) is to assess the evidence regarding the safety of vaccines used for routine immunization in the United States among children, adults of all ages, and pregnant women by evaluating adverse events reported in the literature.

II. Key Questions

The systematic review will be guided by the following key questions (KQ) and subquestions:

KQ 1: What is the evidence that vaccines included in the immunization schedule recommended for adults in the United States (https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html) are safe in the short term (within 42 days following immunization) or long term (>42 days after immunization)?

- KQ 1a. What adverse events (AEs) are collected in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?
- KQ1b. What AEs are reported in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?
- KQ1c. What AEs are associated with these vaccines?
    1. For each AE associated with a particular vaccine, what is the average severity and frequency?
    2. For AEs without statistically significant associations with a particular vaccine, what is the range of possible effects?
    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 children and adolescents in the United States (https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html) are safe in the short term (within 42 days following immunization) or long term (>42 days after immunization)?

- KQ2a. What AEs are collected in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?

KQ2b. What AEs are reported in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?

KQ2c. What AEs are associated with these vaccines?

1. For each AE associated with a particular vaccine, what is the average severity and frequency?
2. For AEs without statistically significant associations with a particular vaccine, what is the range of possible effects?
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 in the United States are safe in the short term (within 42 days following immunization) or long term (>42 days after immunization) for both the woman and her fetus/infant?

KQ3a. What AEs are collected in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?

KQ3b. What AEs are reported in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?

KQ3c. What AEs are associated with these vaccines?

1. For each AE associated with a particular vaccine, what is the average severity and frequency?
2. For AEs without statistically significant associations with a particular vaccine, what is the range of possible effects?
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)?

KQ3d. 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 and frequency?
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)?

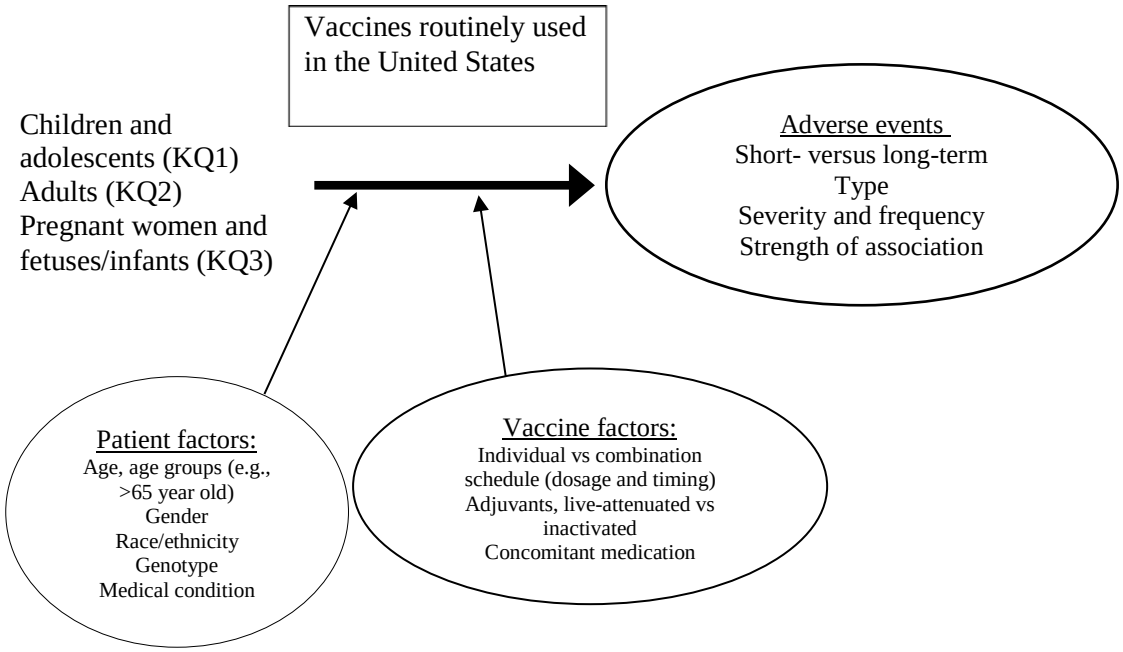
The evidence review will answer the review questions, summarizing the identified evidence across studies.

III. Analytic Framework

The analytic framework (see Figure 1) outlines the population, the interventions, and the outcomes that will be addressed in the evidence synthesis. This review is limited to a

safety assessment. The effectiveness of vaccines measured in intermediate and final health outcomes is outside the scope of this review.

Figure 1. Analytic framework for Safety of Vaccines Used for Routine Immunization in the United States*



*Current review is focused on safety of vaccines (adverse events) and will not be evaluating intermediate or final outcomes.

IV. Methods

The methods for this evidence review follow the Methods Guide for Evidence-based Practice Center (EPC) Program.[10] The evidence report will be based on a systematic review that is outlined in this protocol. Throughout the project, the evidence review team will be supported by a technical expert panel (TEP), a diverse panel of relevant stakeholders, including vaccine experts with clinical expertise in key populations (children, adults, older adults, and pregnant women), vaccine safety methodologists, and consumers. TEP members are not responsible for the content of the evidence report, but they provide the review team with important perspectives and advice on key components of the systematic review. The key questions, the protocol, and the draft report will be publicly posted on the AHRQ Effective Health Care website (https://effectivehealthcare.ahrq.gov/) to allow additional input.

Criteria for Inclusion/Exclusion of Studies in the Review: The eligibility criteria are described in a PICOTSSO (population, intervention, comparator, outcomes, timing, setting, study design, and other limiters) framework (Table 1):

Table 1: Eligibility criteria

Domain	Inclusion	Exclusion
Population	• Human participants of all ages for whom the vaccines are recommended in the United States	• Studies in animals or mechanistic/in vitro studies • Studies exclusively in populations for whom the vaccine is not approved or is contraindicated (see Tables A1a, A1b, A2 in Appendix A)
Interventions	**All KQs** • Individual vaccines included in the immunization schedule recommended for adults, children and adolescents, and pregnant women, as well as combination vaccines available in the United States (see Tables A2 and A3 in Appendix A) **Vaccines for adults (KQ1)** • Hepatitis A (HepA; Havrix, Vaqta); hepatitis B (HepB; Engerix-B, Recombivax HB, HEPLISAV-B); HepA-Hep B (Twinrix); Haemophilus influenzae type b (Hib; PedvaxHIB, ActHIB, Hiberix); human papillomavirus (HPV, HPV9; Gardasil 9); inactivated influenza (IIV; Afluria Quadrivalent, Flucelvax Quadrivalent, Fluarix Quadrivalent, Flulaval Quadrivalent, Fluzone High Dose, Fluzone Quadrivalent, Fluad); live attenuated influenza (LAIV; FluMist Quadrivalent); recombinant influenza (RIV; Flublok Quadrivalent); measles, mumps, rubella (MMR; M-M-R II); meningococcal (Menactra [MenACWY-D], Menveo [MenACWY-CRM]); Meningococcal B (MenB; Bexsero [MenB-4C], Trumenba [MenB-FHbp]); pneumococcal conjugate vaccine (PCV13; Prevnar 13); pneumococcal polysaccharide vaccine (PPSV23; Pneumovax); tetanus, diphtheria, & acellular pertussis (Tdap; Adacel, Boostrix); tetanus, diphtheria (Td; TDVAX, Tenivac); varicella (VAR; Varivax); zoster (recombinant, RZV; live, ZVL; Shingrix, Zostavax); **Children and Adolescents (KQ 2)** • Vaccines for children and adolescents will include diphtheria, tetanus, & acellular pertussis (DTaP; Daptacel, Infanrix); hepatitis A (HepA; Havrix, Vaqta); hepatitis B (HepB; Engerix-B, Recombivax HB); Haemophilus influenzae type b (Hib; PedvaxHIB, ActHIB, Hiberix); human papillomavirus (HPV, HPV9; Gardasil 9); inactivated polio vaccine (IPV; IPOL); inactivated influenza (IIV; Afluria Quadrivalent, Fluarix Quadrivalent, Flulaval Quadrivalent, Fluzone Quadrivalent, Flucelvax Quadrivalent); live attenuated influenza (LAIV; FluMist Quadrivalent); measles, mumps, rubella (MMR; M-M-R II); meningococcal (MenACWY-D, Men-ACWY-CRM; Menactra [MenACWY-D], Menveo [MenACWY-CRM]); meningococcal B (MenB; Bexsero [MenB-4C], Trumenba [MenB-FHbp]); pneumococcal conjugate vaccine (PCV13; Prevnar 13); pneumococcal polysaccharide vaccine (PPSV23; Pneumovax); rotavirus (RV; Rotarix, RotaTeq); tetanus, diphtheria, & acellular pertussis (Tdap; Adacel, Boostrix); varicella	• Studies of vaccines not on the United States recommended schedules, including brands/formulations not available in the United States, or no longer used

Domain	Inclusion	Exclusion
	(VAR; Varivax); DTaP-HepB-IPV (Pediarix); DTaP-IPV/Hib (Pentacel); DTaP-IPV (Kinrix, Quadracel); MMR-V (ProQuad); DTaP-IPV-Hib-HepB (Vaxelis) **Vaccines for pregnant women (KQ3)** • Hepatitis B (HepB; Engerix-B, Recombivax HB, HEPLISAV-B); inactivated influenza (IIV; Afluria Quadrivalent, Flucelvax Quadrivalent, Fluarix Quadrivalent, Flulaval Quadrivalent, Fluzone Quadrivalent); recombinant influenza (RIV; Flublok Quadrivalent); tetanus, diphtheria, & acellular pertussis (Tdap; Adacel, Boostrix)	
Comparators	• Active comparators (e.g., other vaccines or other vaccination schedules) and inactive comparators (e.g., no vaccine)	• Studies without intervention comparator
Outcomes	• Adverse events identified in participants, and, in the case of pregnant women, in their fetuses/infants (including the presence and the absence of harms, toxicities, transient side effects, and unintended adverse health effects)	• Studies reporting only on effectiveness outcomes
Timing	• Short term (within 30–42 days following immunization) as well as long term (>42 days after immunization) effects	• No exclusions apply
Setting(s)	• No restrictions with regard to settings	
Study design	• Controlled studies (randomized and non-randomized controlled clinical trials, cohort studies comparing two or more cohorts, case-control studies, self-controlled case series)	• Studies without comparator (e.g., case studies*)
Other limiters	• English language scientific journal publications and trial records with published results	• Studies published in abbreviated form only (e.g., letters, conference abstracts) • Studies reported only in non-English publications

*Case studies are outside the scope of the review because they do not include unvaccinated individuals for comparison.

Literature Search Strategies to Identify Studies to Answer the Key Questions: The literature searches build on the prior AHRQ report on vaccine safety, which itself built on a prior Institute of Medicine (now National Academy of Medicine) review of vaccine safety. Searches will be restricted by publication year only for vaccines and vaccine indications that have been covered previously. Appendix B outlines the changes.

Sources: We will search the research databases PubMed, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Scopus, and TOXLINE to identify controlled studies evaluating vaccines. PubMed indexes a wide-range of biomedical literature, EMBASE emphasizes pharmacological and European journals, CINAHL includes nursing literature, the Web of Science and Scopus index many technology journals, and TOXLINE indexes studies of adverse events associated with drugs and other chemicals. TOXLINE will be searched in early December 2019, before the database is integrated into PubMed. Clinicaltrials.gov will be searched for more information on published trials as well as results published in the trial record.

In addition, we will review Advisory Committee on Immunization Practices (ACIP) statements and the literature that is cited in the statements. We will also review vaccine

package inserts to identify relevant safety information. Although basic manufacturer safety warnings may not be based on data from comparative studies that can be used to determine the rates of adverse events, the report will summarize these safety warnings for completeness. We will reference-mine published systematic reviews[11-106] to ensure that all relevant studies have been identified, i.e., rather than summarizing the reviews, we will use them as sources to identify available research studies. Furthermore, the content experts on the TEP and experts serving as peer reviewers will be asked to help ensure that all relevant studies have been considered. Finally, a Supplemental Evidence And Data for Systematic review (SEADS) portal will be available and a Federal Register Notice will be posted for this review to ensure that all relevant evidence has been considered.

The draft search strategy for the databases is documented in Appendix B. The search strategies will be developed, executed, and documented by an experienced EPC librarian and peer-reviewed by an experienced methodologist. The literature search will be updated while the draft report is under peer review to ensure that the evidence included in the final report is up to date.

Screening Procedure: The citations will be screened by two independent literature reviewers. Citations deemed relevant by at least one reviewer will be obtained as full text. Full text articles and grey literature material will be screened by two independent reviewers against the explicit eligibility criteria. Any discrepancies will be discussed among the full review team.

Data Abstraction and Data Management: Data will be abstracted in an online data abstraction program for systematic reviews. The abstraction forms include detailed instructions, definitions, and descriptions of categories to guide reviewers and to avoid ambiguities. The data abstraction will be checked for accuracy and consistency across studies by an experienced literature reviewer. The progress will be monitored frequently, any questions will be discussed among the review team, and additional guidance will be added to the online forms as needed.

The data abstraction process will capture all information published about the study, including the trial record, study protocol, interim analyses, main analysis, or subgroup analyses. Multiple publications reporting on the same participant groups will be counted as single studies and will not enter the review analysis multiple times. Throughout the data abstraction process, publications reporting on the same participant group will be consolidated.

The data abstraction will include study-level variables that will be displayed in evidence tables and variables that will be used in the review analysis or critical appraisal of the study:

- Study ID
    - Author and publication year of the main publication, country, PubMed entry link, trial registration number, additional publications reporting on the study, type of publication (journal manuscript, trial record), study design (parallel RCT, cluster RCT, clinical trial, cohort study, case-control study), number of participants (study size indication), power calculation for non-

inferiority analysis, funding type (industry-funded, industry-funded but unrestricted grant, unclear, non-industry funding)

- Participant characteristics
    - Key question category (children, adults, pregnant women), age (mean, standard deviation [SD]), gender (% female), race/ethnicity, genotype information, underlying medical conditions, inclusion criteria, proportion of participants given the vaccine outside of recommended age range
- Intervention arms
    - Vaccine type, dose and schedule, formulation, individual or combination vaccine, mode of administration; adjuvants, co-interventions (e.g., medications (including other vaccines) administered concomitantly)
- Control and comparator arms
    - Type, description
- Outcomes
    - Method and type of collected safety information
- Results
    - Type of outcome, severity, and adverse event rates in intervention and the control arms

We will implement a transparent and comprehensive categorization system that allows the reader to understand the type and severity of the events. The categorization system will be based on the Common Terminology Criteria for Adverse Events (CTCAE) classification system [107] to structure the safety assessment. The current CTCAE system (version 5) differentiates 837 adverse events within 26 adverse event domains (see Appendix C).

Each specific adverse event will be graded for severity on a five-point scale, with grade 1 being *mild* and grade 5 being *death due to the event*. Rather than relying on the author's interpretation of outcomes, we will apply the categorization and CTCAE system consistently to all included studies and rate the adverse event severity accordingly.

We will apply the system to all assessed adverse events, thereby systematically identifying evidence of the presence as well as the absence of specific adverse events. Events that were assessed in research studies but that did not occur will also be abstracted and entered in the analyses. Data will be abstracted for both the intervention and control groups. Study results will be converted to rates and proportions to facilitate comparisons among studies.

Assessment of Methodological Risk of Bias of Individual Studies: All included studies will be assessed for key sources of bias that may have influenced the reported results. The assessments will be undertaken by one reviewer; a second reviewer will check the assessment for accuracy and consistency across studies. We will use the McHarm scale, a tool for structured critical appraisal of adverse event data reported in research studies, for the assessment. Adverse event assessment and reporting are often lacking in rigor; thus, we will apply critical appraisal criteria assessing two main domains:[108, 109]

- Data collection of adverse events
- Reporting of adverse events

The appraisal of the data collection method will evaluate the rigor of the adverse event assessment (e.g., use of a scale or checklist) and whether adverse event data were

collected actively (e.g., all participants were asked about the occurrence of specific harms) or passively (e.g., participants might have reported events at their discretion, but without structured assessment or specific prompts).

The reporting appraisal will assess whether adverse events, including serious adverse events, were defined by the study authors. In addition, we will review whether the authors specified the number of participants affected by each type of adverse event (the number of adverse events per group is a problematic measure because some patients experience multiple events).

Data Synthesis: The results will be documented in a structured synthesis, supported by tables and figures. The included studies will be broadly characterized based on study characteristics, participant details, intervention categories, identified comparator, and outcome categories employed in the published studies. Study details and results of all included studies for vaccines of interest will be documented in evidence tables to provide a concise overview. Summary tables will synthesize evidence across studies.

We will report the relative frequency and severity of the adverse events and the strength of evidence for the presence or absence of specific adverse events. The synthesis will report how many studies have assessed an adverse event to answer KQ1a, KQ2a, and KQ3a. We will document how many times the event occurred in the study samples to address KQ1b, KQ2b, and KQ3b, i.e., to determine whether a specific adverse event is associated with a vaccine. The review will include only studies that report on a control group or comparator not exposed to the vaccine (or time when an individual was not exposure to a vaccine, in the case of self-controlled case series), on a different vaccine schedule, or exposed to a different formulation. Rates of adverse events in the intervention group will be compared to those in an appropriate control group that ideally differs only in the exposure to the vaccine. We will calculate the relative risk for the adverse events for all studies by comparing the intervention and control group rates. We will include all active surveillance studies that use regression to control for confounders and test multiple relationships simultaneously. We refer to these as multivariate risk factor analyses. Data sources may include medical records, health insurance claims, and government registries. Where possible, we will combine study results in meta-analyses, aggregating data across studies. Meta-analyses will use random effects models with Knapp-Hartung corrections using the metafor package in R.[110] We will report the point estimate, the 95 percent confidence interval, and the statistical significance of the summary estimate. We will summarize the absolute rate of adverse events as well as the relative risk, to facilitate the interpretation of the results.

In addition to documenting the types of adverse events, we will characterize the severity and frequency of the events associated with the vaccines. To address the sub-questions KQ1c1, KQ2c1, and KQ3c1, we will use the CTCAE rating system to document the average severity of the specific adverse events reported in existing studies. KQ1c2, KQ2c2, and KQ3c2 will document the range of possible effects based on the confidence interval surrounding the point estimate across studies. To answer the key question KQ1c3, KQ2c3, and KQ3c3, we will explore potential risk factors for adverse events in meta-regressions and subgroups. Meta-regressions will add patient variables (age, gender, race/ethnicity, genotype, underlying medical conditions) and intervention variables

(individual vs combination vaccines, schedule of administration, adjuvants, and medication administered concomitantly) of interest to the meta-analysis model. The analyses will explore whether patient or vaccine characteristics are systematically associated with observed adverse events. In addition to the key subgroups of adults, children and adolescents, and pregnant women, an additional pre-specified subgroup are adults over the age of 65 years (KQ1c1). Furthermore, we will differentiate live-attenuated and inactive vaccines.

Grading the Strength of Evidence for Major Comparisons and Outcomes: We will review the quality of evidence across studies for key adverse events, and the report will communicate the strength of evidence clearly using the approach below.

For each key question, we selected key adverse events that will be documented in summary of findings tables. While the evidence tables can report all outcomes addressed in the individual studies, the strength of evidence assessment will use *a priori* defined outcomes to evaluate the safety of the vaccines across studies. These major outcomes were identified with the help of the TEP and content expert input, informed by published literature:

- Key outcomes for KQ 1 (adults): Acute disseminated encephalomyelitis, anaphylaxis or systemic allergic reaction, angioedema, death, Guillain-Barre syndrome (Miller Fisher syndrome), cardiovascular events (myocardial infarction, cardiac disorders, major vascular event, angina), seizures, stroke, transverse myelitis, diabetes
- Key outcomes for KQ 2 (children and adolescents): Acute disseminated encephalomyelitis, anaphylaxis or systemic allergic reaction, angioedema, death, Guillain-Barre syndrome (Miller Fisher syndrome), idiopathic thrombocytopenic purpura, cardiovascular events, seizures, stroke, transverse myelitis, diabetes
- Key outcomes for KQ 3 (pregnant women): Birth defects, death, eclampsia (pre-eclampsia), preterm labor, spontaneous abortion, stillbirth

In addition, for specific vaccines, additional key outcomes were determined. These include encephalitis (encephalopathy) and brachial neuritis for DTaP, Tdap and Td vaccines. Furthermore, autoimmune disease (autoimmune thyroiditis, Hashimoto), encephalitis (encephalopathy), multiple sclerosis, myocardial infarction, optic neuritis for Hepatitis B vaccines will be included. For HPV vaccines, amyotrophic lateral sclerosis, multiple sclerosis, and reproduction issues were selected. For all influenza vaccines, asthma will be assessed. For meningococcal vaccines the summary will address encephalitis (encephalopathy) and multiple sclerosis. For MMR vaccines, we will document autism, encephalitis (encephalopathy), immune thrombocytopenia purpura, meningitis, and multiple sclerosis incidence. For rotavirus vaccines, febrile seizures, intussusception, and Kawasaki disease will be specifically addressed. Finally, for varicella and zoster vaccines, we will assess the presence and absence of adverse events for ataxia, encephalitis (encephalopathy), Guillain-Barre syndrome, herpes zoster, meningitis, secondary transmission of live varicella virus, and stroke.

The summary of findings tables will document the results across studies for key outcomes as well as the quality of the evidence and our confidence in the effect estimates. The summary will be organized by key question, vaccine, and outcomes. The strength of evidence assessment will use the AHRQ EPC program strength of evidence assessment categories, taking the following domains into account:

- Study limitations
- Directness
- Consistency
- Precision
- Reporting bias

Study limitations (e.g., risk of bias in included studies) will be judged as low, medium, or high, and will focus on the assessment format as well as the rigor of reporting or identification. *Directness* differentiates between direct, i.e. head-to-head, comparisons (e.g., comparing two vaccination schedules) and indirect evidence derived from comparisons across studies (e.g., meta-regressions to assess the effect of combination versus individual vaccines). The domain *consistency* differentiates among consistent and inconsistent findings across studies, and assigns "unknown" in the case of a result that is based on a single study whose findings have not been replicated yet. We will review how consistently studies report the presence or the absence of specific effects that have been assessed. *Precision* is scored as either precise or imprecise, where precise indicates that the result reflects a clinically unambiguous conclusion. Precision is operationalized as the confidence interval surrounding the point estimate. The domain *reporting bias* differentiates between suspected bias (e.g., there is indication of publication bias, selective outcome reporting, or selective reporting of the analysis) and undetected bias (no bias indicated). We do not expect substantial reporting bias given that the decision to publish will have likely been driven by the effectiveness outcomes and not necessarily the outcomes of interest for this review (i.e., adverse events), but we will assess publication bias using standard tools (e.g., Begg and Egger tests) for the key outcomes, given that some studies may concentrate on serious adverse events only. The strength of evidence domains are compatible with the GRADE group's criteria to downgrade the quality of evidence.

Each evidence statement will be assessed with these criteria to determine the overall strength of evidence. The strength of evidence assessment will differentiate the following levels:

- High = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Medium = 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 = Evidence either is unavailable or does not permit a conclusion.

The categories communicate the confidence in the summary estimates for the findings across studies. The evidence statements will be drafted by one literature reviewer and discussed among the team to ensure quality control and consistency of interpretation.

Assessing Applicability: Applicability refers to the extent to which the effects observed in published studies are likely to reflect the expected results when the 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;[111] 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, self-controlled case series, retrospective and prospective cohorts, and analyses of administrative databases. Defining the populations, interventions, timing, and outcomes (as described in the key questions 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 from 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) that final population may differ from more representative populations in practice.

Throughout, we will also assess the likelihood of association of reported adverse events with the vaccine based on mechanism and biological plausibility, to provide the reader with additional, contextual information.

V. References

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VI. Definitions of Terms and Abbreviations

ACIP	Advisory Committee on Immunization Practices
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
CDC	Centers for Disease Control and Prevention
CTCAE	Common Terminology Criteria for Adverse Events classification system
DtaP	Diphtheria, tetanus, & acellular pertussis
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HepA	Hepatitis A
HepB	Hepatitis B
Hib	*Haemophilus influenzae* type b
HPV	Human papillomavirus
IIV	Inactivated influenza vaccine
IPV	Inactivated polio vaccine
KQ	Key Question
LAIV	Live attenuated influenza vaccine
MenACWY	Meningococcal conjugate vaccine, serogroups A, C, W, Y
MenB	Meningococcal B vaccine
MMR	Measles, mumps rubella
OIDP	Office of Infectious Disease & HIV/AIDS Policy
PCV13	Pneumococcal conjugate vaccine
PPSV2	Pneumococcal polysaccharide vaccine
RIV	Recombinant influenza vaccine
RV	Rotavirus vaccine
RZV	Zoster vaccine, recombinant
Td	Tetanus, diphtheria
Tdap	Tetanus, diphtheria, & acellular pertussis
TEP	Technical expert panel
VAR	Varicella vaccine
ZVL	Zoster vaccine, live

VII. Summary of Protocol Amendments

If the protocol needs to be amended, the EPC will give the date of each amendment, describe the change, and give the rationale in this section.

X. Technical Experts

Technical Experts constitute a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify particular studies or databases to search. The TEP is selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that fosters a thoughtful, relevant systematic review. Therefore, study

questions, design, and methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind; neither do they contribute to the writing of the report. They do not review the report, except as given the opportunity to do so through the peer or public review mechanism.

Members of the TEP must disclose any financial conflicts of interest greater than $5,000 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 AHRQ 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. The EPC considers all peer review comments on the draft report in preparing the final report. Peer reviewers do not participate in writing or editing of the final report or other products. The final report does not necessarily represent the views of individual reviewers.

The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after publication of the evidence report.

Potential peer reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Invited peer reviewers with any financial conflict of interest greater than $5,000 will be disqualified from peer review. Peer reviewers who disclose potential business or professional conflicts of interest can submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

None of the team members have any conflicts of interest to declare. EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Direct financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify an EPC core team investigator.

XIII. Role of the Funder

This project was commissioned and executed under Contract No. 290-2015-00009-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The AHRQ Task Order Officer reviewed the EPC response to contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A. Recommended Immunizations

Table A1a. Recommended individual vaccines for children and adolescents in the US, 2019

Vaccine	Brand name(s)	Recommendation
Diphtheria, tetanus, & acellular pertussis (DTaP)	Daptacel Infanrix	6 weeks through 6 years; routine
Hepatitis A (HepA)	Havrix Vaqta	12 months and older; routine
Hepatitis B (HepB)	Engerix-B Recombivax HB	All ages; routine
Haemophilus influenzae type b (Hib)	PedvaxHIB ActHIB Hiberix	2 months through 5 years (PedvaxHIB, ActHIB) 6 weeks through 4 years (Hiberix); routine
Human papillomavirus (HPV; also called HPV9)	Gardasil 9	9 through 45 years; routine
Inactivated polio vaccine (IPV)	IPOL	6 weeks and older; routine
Influenza, inactivated (IIV)	Afluria Quadrivalent Fluarix Quadrivalent Flulaval Quadrivalent Fluzone Quadrivalent Flucelvax Quadrivalent	6 months and older (Afluria Quadrivalent, Fluarix Quadrivalent, Flulaval Quadrivalent, Fluzone Quadrivalent) 4 years and older (Flucelvax Quadrivalent)
Influenza, live attenuated (LAIV)	FluMist Quadrivalent	2 through 49 years; IIV or LAIV
Measles, mumps, rubella (MMR)	M-M-R II	12 months and older for routine vaccination
Meningococcal (MenACWY-D, Men-ACWY-CRM)	Menactra (MenACWY-D) Menveo (MenACWY-CRM)	9 months through 55 years (Menactra); routine 2 months through 55 years (Menveo); routine
Meningococcal B (MenB)	Bexsero (MenB-4C) Trumenba (MenB-FHbp)	10 through 25 years; shared clinical decision making, unless in a high-risk group in which case routine
Pneumococcal conjugate vaccine (PCV13)	Prevnar 13	6 weeks and older; routine
Pneumococcal polysaccharide vaccine (PPSV23)	Pneumovax	2 years and older; high-risk groups

Rotavirus (RV)	Rotarix RotaTeq	6 through 24 weeks (Rotarix); routine 6 through 32 weeks (RotaTeq); routine
Tetanus, diphtheria, & acellular pertussis (Tdap)	Adacel Boostrix	10 through 64 years (Adacel); routine 10 years and older (Boostrix); routine; both can be used as young as 7 years for catch up
Varicella (VAR)	Varivax	12 months and older; routine

Notes: The table is based on the following sources:

- https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
- https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states

The age-range in the recommendation column reflects the FDA-approved indications and the current CDC guidance.

Table A1b. Combination vaccines for children and adolescents in use in the United States, 2019

Vaccine	Brand name(s)	Age range
DTaP-HepB-IPV	Pediarix	6 weeks through 6 years
DTaP-IPV/Hib	Pentacel	6 weeks through 4 years
DTaP-IPV	Kinrix Quadracel	4 years through 6 years
MMR-V	ProQuad	12 months through 12 years
DTaP-IPV-Hib-HepB	Vaxelis*	6 weeks through 4 years

Note: The table is based on the following sources:

- https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
- https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states

The age-range reflects the FDA-approved indications and the current CDC guidance.
* Noted on FDA website but not CDC website as combination vaccine currently in use.

Table A2a. Recommended individual vaccines for adults in the US, 2019

Vaccine	Brand name(s)	Recommendation
Hepatitis A (HepA)	Havrix Vaqta	12 months and older; if at risk
Hepatitis B (HepB)	Engerix-B Recombivax HB HEPLISAV-B	All ages (Engerix-B, Recombivax-B)

		18 years and older (HEPLISAV-B); if at risk
Haemophilus influenzae type b (Hib)	PedvaxHIB ActHIB Hiberix	2 months through 5 years (PedvaxHIB, ActHIB); if at risk 6 weeks through 4 years (Hiberix); if at risk
Human papillomavirus (HPV; also called HPV9)	Gardasil 9	9 through 45 years; through 26 years
Influenza, inactivated (IIV)	Afluria Quadrivalent Flucelvax Quadrivalent Fluarix Quadrivalent Flulaval Quadrivalent Fluzone High Dose Fluzone Quadrivalent Fluad	6 months and older (Afluria Quadrivalent, Fluarix Quadrivalent, Flulaval Quadrivalent, Fluzone Quadrivalent) 4 years and older (Flucelvax Quadrivalent) 65 years and older (Fluzone High Dose, Fluad) IIV, LAIV or RIV
Influenza, live attenuated (LAIV)	FluMist Quadrivalent	2 through 49 years; IIV, LAIV or RIV
Influenza, recombinant (RIV)	Flublok Quadrivalent	18 years and older; IIV, LAIV or RIV
Measles, mumps, rubella (MMR)	M-M-R II	12 months and older for routine vaccination; if no evidence of immunity
Meningococcal (MenACWY-D, Men-ACWY-CRM)	Menactra (MenACWY-D) Menveo (MenACWY-CRM)	9 months through 55 years (MenACWY-D); if at risk 2 months through 55 years (MenACWY-CRM); if at risk
Meningococcal B (MenB)	Bexsero (MenB-4C) Trumenba (MenB-FHbp)	10 through 25 years; if at risk
Pneumococcal conjugate vaccine (PCV13)	Prevnar 13	6 weeks and older; routine
Pneumococcal polysaccharide vaccine (PPSV23)	Pneumovax	2 years and older; routine
Tetanus, diphtheria, & acellular pertussis (Tdap)	Adacel Boostrix	10 through 64 years (Adacel) 10 years and older (Boostrix) Tdap or Td; both can be used as young as 7 years for catch up

Tetanus, diphtheria (Td)	TDVAX Tenivac	7 years and older; Tdap or Tb
Varicella (VAR)	Varivax	12 months and older; if no evidence of immunity
Zoster (recombinant, RZV; or live, ZVL)	Shingrix Zostavax	50 years and older; routine

Note: The table is based on the following sources:

- https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
- https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states

The age-range in the recommendation column reflects the FDA-approved indications and the current CDC guidance.

Table A2b. Combination vaccines for adults in use in the US, 2019

Vaccine	Brand name(s)	Age range
HepA-HepB	Twinrix	18 years and older

Note: The table is based on the following sources:

- https://www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html
- https://www.cdc.gov/vaccines/schedules/hcp/imz/adult.html
- https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states

The age-range reflects the FDA-approved indications and the current CDC guidance.

Table A3. Recommended Immunizations for pregnant women in the US, 2019

Vaccine	Brand name(s)	Recommendation
Hepatitis B (HepB)	Engerix-B Recombivax HB	Recommended in some circumstances*
Influenza, inactivated (IIV)	Afluria Quadrivalent Flucelvax Quadrivalent Fluarix Quadrivalent Flulaval Quadrivalent Fluzone Quadrivalent	Recommended (any influenza vaccine that is IIV or RIV)
Influenza, recombinant (RIV)	Flublok Quadrivalent	Recommended (any influenza vaccine that is IIV or RIV)
Tetanus, diphtheria, & acellular pertussis (Tdap)	Adacel Boostrix	Recommended

Note: * Hepatitis B vaccines will be included in this report because they were included in the prior report. The table includes only those vaccines recommended per CDC and not those that may be used if otherwise indicated (or for which there is a recommendation to base decisions on risk versus benefit). The table is based on the following sources:

- https://www.cdc.gov/vaccines/pregnancy/hcp-toolkit/guidelines.html
- https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states

Appendix B. Search strategy

The search strategy builds on the prior AHRQ review on the topic. For the prior AHRQ review, databases were searched from inception through August 2013 for the vaccines not covered by the IOM report; for the other vaccines, the searches dated from a year before the IOM report (i.e., 2010) through August 2013. The table documents changes since the last review.

Table A4. Vaccines of interest, relevant populations, and major changes since last review

Vaccine	Populations	Major changes since last review
Diphtheria, tetanus, & acellular pertussis (DTaP)	Children	None
Hepatitis A (HepA)	Children, adults	None
Hepatitis B (HepB)	Children, adults, pregnant women	New formulations (Heplisav-B approved 2017)
Haemophilus influenzae type b (Hib)	Children	New formulations (Hiberix approved 2016)
Human papillomavirus (HPV; also called HPV9)	Children, adults	New vaccine since last review (Gardasil 9 approved 2014; since then age indications expanded)
Inactivated polio vaccine (IPV)	Children, adults	None
Influenza, inactivated (IIV)	Children, adults, pregnant women	New formulations; age indications for some formulations expanded (e.g., FluZone Quadrivalent in age 6-36 months)
Influenza, live attenuated (LAIV)	Children, adults	New formulations
Influenza, recombinant (RIV)	Adults, pregnant women	New since last review
Measles, mumps, rubella (MMR)	Children, adults	None
Meningococcal (MenACWY-D, Men-ACWY-CRM)	Children, adults	None
Meningococcal B (MenB)	Children, adults	New vaccine since last review (approved Trumenba in 2014, Bexsero in 2015)
Pneumococcal conjugate vaccine (PCV13)	Children, adults	New age indications since last review (expanded to include adults 18-49 years; previously <18 years as well as 50 years and older)

Pneumococcal polysaccharide vaccine (PPSV23)	Children, adults	None
Rotavirus (RV)	Children	None
Tetanus, diphtheria, & acellular pertussis (Tdap)	Children, adults, pregnant women	New dosing (2nd dose in people 10-64 years of age); age indication expanded to 10 years old (Adacel)
Tetanus, diphtheria (Td)	Adults	None
Varicella (VAR)	Children, adults	None
Zoster (recombinant, RZV; or live, ZVL)	Adults	New vaccine (Shingrix approved 2017)
DTaP-HepB-IPV	Children	None
DTaP-IPV/Hib	Children	None
DTaP-IPV	Children	New formulation (Quadracel)
MMR-V	Children	None
DTaP-IPV-Hib-HepB	Children	New since last review
HepA-HepB	Adults	None

Database search

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to January 03, 2020>
Search Strategy:
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1 (((diphtheria tetanus acellular pertussis or tetanus diphtheria acellular pertussis or tetanus toxoid or dt or td or tt or diphtheria tetanus or tetanus diphtheria or whooping cough or (tetanus and diphtheria)) and (vaccin* or immuniz* or immunis*)) or (dtap or tdap)).mp. or diphtheria-tetanus-acellular pertussis vaccines/ or diphtheria pertussis tetanus vaccine/ or tetanus toxoid/ or diphtheria-tetanus vaccine/ or ((diphtheria/ or Whooping Cough/ or tetanus/) and (vaccination/ or vaccines/)) or (adacel or boostrix or infanrix or daptacel or pediarix or kinrix or quadracel or vaxelis or pentacle or tdvax or tenivac).mp. (21900)

2 ((hepatitis a or HepA or hep a) and (vaccin* or immuniz* or immunis*)).mp. or hepatitis a vaccines/ or ((hepatitis a/ or hepatitis a virus, human/) and (vaccination/ or vaccines/)) or (havrix or vaqta or twinrix).mp. (6090)

3 ((hepatitis b or HepB or hep b) and (vaccin* or immuniz* or immunis*)).mp. or hepatitis b vaccines/ or ((hepatitis b virus/ or hepatitis b/) and (vaccination/ or vaccines/)) or (engerix-b or engerix b or recombivax hb or recombivax-hb or heplisav-b or heplisav b or twinrix or pediarix or vaxelis).mp. (20411)

4 ((haemophilus b or haemophilus type b or haemophilus influenzae type b or hib) and (vaccin* or immuniz* or immunis*)).mp. or (Haemophilus influenzae type b/ and (vaccination/ or vaccines/)) or haemophilus vaccines/ or haemophilus influenza type b

polysaccharide vaccine-tetanus toxin conjugate.mp. or (pedvaxhib or acthib or hiberix or vaxelis).mp. (4769)
5 ((papillomaviridae or papillomavirus or hpv or hpv9) and (vaccin* or immuniz* or immunis*)).mp. or papillomavirus vaccines/ or ((papillomaviridae/ or papillomavirus infections/) and (vaccination/ or vaccines/)) or (Gardasil 9 or Gardasil-9).mp. (13839)
6 (polio* and (vaccine* or immuniz* or immunis*)).mp. or poliovirus vaccine, inactivated/ or (Poliomyelitis/ and (vaccination/ or vaccines/)) or (ipol or pentacel or kinrix or quadracel or vaxelis).mp. (12987)
7 ((influenza or flu or RIV or laiv or iiv or ipv) and (vaccin* or immuniz* or immunis*)).mp. or influenza vaccines/ or (influenza, human/ and (vaccination/ or vaccines/)) or (fluad or afluria or flucelvax or flulaval or flumist or fluarix or fluvirin or agriflu or fluzone or flublok).mp. (39690)
8 ((measles or mumps or rubella or mmr) and (vaccin* or immuniz* or immunis*)).mp. or measles mumps rubella vaccine/ or measles vaccine/ or mumps vaccine/ or rubella vaccine/ or ((measles/ or mumps/ or rubella/) and (vaccination/ or vaccines/)) or (mmr 2 or mmr II or m-m-r II or mmr v or proquad).mp. (19928)
9 (mening* and (vaccin* or immuniz* or immunis*)).mp. or meningococcal vaccines/ or (exp meningitis/ and
(vaccination/ or vaccines/)) or (menACWY-D or menACWY-CRM or menB or menactra or menveo or bexsero or trumenba).mp.
(12262)
10 ((pneumonia* or pneumococ*) and (vaccin* or immuniz* or immunis*)).mp. or pneumococcal vaccines/ or (pneumonia/ and (vaccination/ or vaccines/)) or (prevnar 13 or prevnar-13 or pneumovax or ppsv23 or pcv13).mp. (20949)
11 ((rotavirus or rv) and (vaccin* or immuniz* or immunis*)).mp. or (rotavirus/ and (vaccination/ or vaccines/)) or rotavirus vaccines/ or (rotarix or rotateq).mp. (5866)
12 ((chicken pox or chickenpox or varicella) and (vaccin* or immuniz* or immunis*)).mp. or exp chickenpox vaccine/ or (chickenpox/ and (vaccines/ or vaccination/)) or varivax.mp. (5653)
13 ((zoster or shingles or rzv or zvl) and (vaccin* or immuniz* or immunis*)).mp. or (exp herpes zoster/ and (vaccines/ or vaccination/)) or (shingrix or zostavax).mp. (3770)
14 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 (152174)

15 ("clinical trial" or "clinical trial, phase i" or "clinical trial, phase ii" or clinical trial, phase iii or
clinical trial, phase iv or controlled clinical trial or "multicenter study" or "randomized controlled trial").pt. or double-blind method/ or clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or early termination of clinical trials as topic/ or multicenter studies as topic/ or ((randomi?ed adj7 trial*) or (controlled adj3 trial*) or (clinical adj2 trial*) or ((single or doubl* or tripl* or treb*) and (blind* or mask*))).ti,ab,kw. or ("4 arm" or "four arm").ti,ab,kw. (1590656)
16 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/ or cohort.ti,ab. or longitudinal.ti,ab. or prospective.ti,ab. or retrospective.ti,ab. (2546908)

17 15 or 16 (3704287)
18 14 and 17 (28488)
19 limit 18 to yr="2013 -Current" (10671)
20 (study protocol or trial protocol or review protocol).ti. (11564)
21 19 not 20 (10631)
22 exp animals/ not humans.sh. (4660545)
23 21 not 22 (10457)
24 review.pt. (2596771)
25 23 not 24 (9418)

Removed internal duplicates = 9366

Appendix C. Common Terminology Criteria for Adverse Events classification system (CTCAE) adverse event domains

- Blood and lymphatic system
- Cardiac disorders
- Congenital, familial and genetic disorders
- Ear and labyrinth disorders
- Endocrine disorders
- Eye disorders
- Gastrointestinal disorders
- General disorders and administration site conditions
- Hepatobiliary disorders
- Immune system disorders
- Infections and infestations
- Injury, poisoning and procedural complications
- Investigations
- Metabolism and nutrition disorders
- Musculoskeletal and connective tissue disorders
- Neoplasms benign, malignant and unspecified (incl. cysts and polyps)
- Nervous system disorders
- Pregnancy, puerperium and perinatal conditions
- Psychiatric disorders
- Renal and urinary disorders
- Reproductive system and breast disorders
- Respiratory, thoracic and mediastinal disorders
- Skin and subcutaneous tissue disorders
- Social circumstances
- Surgical and medical procedures
- Vascular disorders