Billing Code: 4160-90-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Healthcare Research and Quality

Supplemental Evidence and Data Request on Safety of Vaccines Used for Routine Immunization in the United States

AGENCY: Agency for Healthcare Research and Quality (AHRQ), HHS.

ACTION: Request for Supplemental Evidence and Data Submissions

SUMMARY: The Agency for Healthcare Research and Quality (AHRQ) is seeking scientific information submissions from the public. Scientific information is being solicited to inform our review on *Safety of Vaccines Used for Routine Immunization in the United States,* which is currently being conducted by the AHRQ's Evidence-based Practice Centers (EPC) Program. Access to published and unpublished pertinent scientific information will improve the quality of this review.

DATES: *Submission Deadline* on or before 30 days after the date of this publication in the Federal Register.

ADDRESSES:

E-mail submissions: epc@ahrq.hhs.gov

Print submissions:

Mailing Address:

Center for Evidence and Practice Improvement

Agency for Healthcare Research and Quality

ATTN: EPC SEADs Coordinator

5600 Fishers Lane

Mail Stop 06E53A

Rockville, MD 20857

Shipping Address (FedEx, UPS, etc.):

Center for Evidence and Practice Improvement

Agency for Healthcare Research and Quality

ATTN: EPC SEADs Coordinator

5600 Fishers Lane

Mail Stop 06E77D

Rockville, MD 20857

FOR FURTHER INFORMATION CONTACT:

Jenae Benns, Telephone: 301-427-1496 or Email: epc@ahrq.hhs.gov.

SUPPLEMENTARY INFORMATION:

The Agency for Healthcare Research and Quality has commissioned the Evidence-based Practice Centers (EPC) Program to complete a review of the evidence for Safety of Vaccines Used for Routine Immunization in the United States. AHRQ is conducting this systematic review pursuant to Section 902(a) of the Public Health Service Act, 42 U.S.C. 299a(a).

The EPC Program is dedicated to identifying as many studies as possible that are relevant to the questions for each of its reviews. In order to do so, we are supplementing the usual manual and electronic database searches of the literature by requesting information from the public (e.g., details of studies conducted). We are looking for studies that report on *Safety of Vaccines Used for*

Routine Immunization in the United States, including those that describe adverse events. The entire research protocol is available online at: https://effectivehealthcare.ahrq.gov/products/safety-vaccines/protocol

This is to notify the public that the EPC Program would find the following information on *Safety of Vaccines Used for Routine Immunization in the United States* helpful:

- A list of completed studies that your organization has sponsored for this indication. In the list, please *indicate whether results are available on ClinicalTrials.gov along with the ClinicalTrials.gov trial number*.
    - *For completed studies that do not have results on ClinicalTrials.gov*, a summary, including the following elements: study number, study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, primary and secondary outcomes, baseline characteristics, number of patients screened /eligible /enrolled /lost to follow-up /withdrawn /analyzed, effectiveness/efficacy, and safety results.
- *A list of ongoing studies that your organization has sponsored for this indication*. In the list, please provide the ClinicalTrials.gov trial number or, if the trial is not registered, the protocol for the study including a study number, the study period, design, methodology, indication and diagnosis, proper use instructions, inclusion and exclusion criteria, and primary and secondary outcomes.

- Description of whether the above studies constitute *ALL Phase II and above clinical trials* sponsored by your organization for this indication and an index outlining the relevant information in each submitted file.

Your contribution is very beneficial to the Program. Materials submitted must be publicly available or able to be made public. Materials that are considered confidential; marketing materials; study types not included in the review; or information on indications not included in the review cannot be used by the EPC Program. This is a voluntary request for information, and all costs for complying with this request must be borne by the submitter.

The draft of this review will be posted on AHRQ's EPC Program website and available for public comment for a period of 4 weeks. If you would like to be notified when the draft is posted, please sign up for the e-mail list at: https://www.effectivehealthcare.ahrq.gov/email-updates.

The systematic review will answer the following questions. This information is provided as background. AHRQ is not requesting that the public provide answers to these questions.

Key Questions (KQ)

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)?

PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, Settings)

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
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 **Vaccines for adults (KQ1)**	• Studies of vaccines not on the United States recommended schedules, including brands/formulations not available in

Domain	Inclusion	Exclusion
	• 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	the United States, or no longer used

Domain	Inclusion	Exclusion
	(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	

Domain	Inclusion	Exclusion
	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 (VAR; Varivax); DTaP-HepB-IPV (Pediarix); DTaP-IPV/Hib (Pentacel); DTaP-IPV (Kinrix, Quadracel); MMR-V (ProQuad); DTaP-IPV-Hib-HepB (Vaxelis)	

Domain	Inclusion	Exclusion
	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	• Studies reporting only on effectiveness outcomes

Domain	Inclusion	Exclusion
	adverse health effects)	
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.

Dated: April 15, 2020.

Virginia Mackay-Smith,

Associate Director, Office of the Director, AHRQ.

[FR Doc. 2020-08331 Filed: 4/17/2020 8:45 am; Publication Date: 4/20/2020]