Vaccine 39 (2021) 3696–3716

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Safety of vaccines used for routine immunization in the United States: An updated systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 8 February 2021
Received in revised form 18 March 2021
Accepted 22 March 2021
Available online 25 May 2021

Keywords:
Vaccine safety
Meta-analysis
Systematic review
Childhood vaccines
Pregnancy

ABSTRACT

Background: Understanding the safety of vaccines is critical to inform decisions about vaccination. Our objective was to conduct a systematic review of the safety of vaccines recommended for children, adults, and pregnant women in the United States.
Methods: We searched the literature in November 2020 to update a 2014 Agency for Healthcare Research and Quality review by integrating newly available data. Studies of vaccines that used a comparator and reported the presence or absence of key adverse events were eligible. Adhering to Evidence-based Practice Center methodology, we assessed the strength of evidence (SoE) for all evidence statements. The systematic review is registered in PROSPERO (CRD42020180089).
Results: Of 56,603 reviewed citations, 338 studies reported in 518 publications met inclusion criteria. For children, SoE was high for no increased risk of autism following measles, mumps, and rubella (MMR) vaccine. SoE was high for increased risk of febrile seizures with MMR. There was no evidence of increased risk of intussusception with rotavirus vaccine at the latest follow-up (moderate SoE), nor of diabetes (high SoE). There was no evidence of increased risk or insufficient evidence for key adverse events for newer vaccines such as 9-valent human papillomavirus and meningococcal B vaccines. For adults, there was no evidence of increased risk (varied SoE) or insufficient evidence for key adverse events for the new adjuvanted inactivated influenza vaccine and recombinant adjuvanted zoster vaccine. We found no evidence of increased risk (varied SoE) for key adverse events among pregnant women following tetanus, diphtheria, and acellular pertussis vaccine, including stillbirth (moderate SoE).
Conclusions: Across a large body of research we found few associations of vaccines and serious key adverse events; however, rare events are challenging to study. Any adverse events should be weighed against the protective benefits that vaccines provide.

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https://doi.org/10.1016/j.vaccine.2021.03.079
0264-410X/

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1. Introduction

Vaccines are considered one of the greatest public health achievements and the effectiveness of vaccines in controlling the spread of and even eradicating many infectious diseases is widely acknowledged [1]. Although vaccination rates for children remain high, parents and caregivers still express worries about the safety of childhood vaccines [2–4]. Vaccination rates for adults lag well behind those for children [5]. Only about a third of pregnant women receive both tetanus, diphtheria, and acellular pertussis (Tdap) and influenza vaccines as indicated during their pregnancies [6], due in part to safety concerns [7].

Safety concerns about vaccines have persisted in spite of the rigorous, transparent processes that vaccines must undergo, overseen in the United States by the U.S. Food and Drug Administration (FDA) [8]. Once a vaccine is licensed and recommended for use following clinical trials, multiple systems are in place to ensure ongoing assessments of safety through Phase IV studies [9], including post-licensure safety surveillance [10] and the FDA's Post-Licensure Rapid Immunization Monitoring (PRISM) system [11–13]. Multiple databases contribute to surveillance, such as the Vaccine Adverse Event Reporting System (VAERS) [14], Vaccine Safety Datalink [15,16], and Clinical Immunization Safety Assessment project [17,18].

Reassurance of vaccine safety remains critical for population health in the context of an evolving vaccine landscape and notably the emergence of vaccines against the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2). The purpose of this systematic review was to assess the evidence regarding the safety of vaccines routinely recommended for adults, children, and pregnant women in the United States.

2. Methods

The evidence review assessed and examined adverse events potentially associated with vaccines to determine the safety of vaccines in adults, children, and pregnant women, following the Agency for Healthcare Research and Quality's Methods Guide for Effectiveness and Comparative Effectiveness Reviews [19] (full details can be found in the online Appendix). The list of included vaccines comprises those licensed by the FDA [20] and included in the CDC's immunization schedules as of November 2020 (Table 1) [21,22].

This update builds on a 2014 report on the safety of vaccines requested by AHRQ [23], supporting the Office of the Assistant Secretary of Health's Office of Infectious Disease and HIV/AIDS Policy (OASH/OIDP). The 2014 report built upon a 2011 Institute of Medicine (IOM) consensus report [24]; the prior 2014 report did not search for or include studies on vaccines that were covered in the IOM report and published prior to 2011. Similarly, in this update only for vaccines for which there were new indications (or for new vaccines) did we perform targeted searches for research published prior to 2014. The review is registered in PROSPERO (CRD42020180089) [25] the review protocol and 2021 report ares posted on AHRQ's Effective Health Care Programwebsite [26].

We searched MEDLINE (including TOXLINE), Embase, CINAHL, Cochrane CENTRAL, Web of Science, and Scopus, through November 2020 (see Appendix for full search strategy). We searched broadly and did not rely on filters for adverse events. Instead, all evaluations of vaccines were obtained and the full text screened for information on adverse events. We reference-mined existing systematic reviews and Advisory Committee on Immunization Practices statements; screened Clinicaltrials.gov; reviewed supplemental material from authors and industry submitted to AHRQ; and consulted with content experts. Experimental and observational studies with a concurrent or historic comparator that reported the presence or absence of adverse events (e.g., self-controlled studies such as those conducted by the Vaccine Safety Datalink [15]) met inclusion criteria. The update allowed for control groups receiving either no vaccine or standard of care (i.e., the previously available vaccine) as comparators. With the assistance of a technical expert panel–comprised of vaccine experts with particular clinical expertise in key populations (children, adults, older adults, and pregnant women), vaccine safety methodologists, and consumers–we determined a set of key adverse events *a priori* to allow an unbiased synthesis across studies.

Two trained reviewers (with Master's degrees and experience in systematic reviews) independently screened the citations and full text publications. Data were abstracted by an experienced subject matter expert with clinical and research expertise in vaccines (C. G.). For each key adverse event, we computed the relative risk (RR) and 95% confidence intervals (CI) of the adverse event among those who received the vaccine of interest compared to controls across all studies. We combined estimates across studies in random effects meta-analyses using Hartung-Knapp correction of standard errors where appropriate. For cases with zero events across studies, we added a constant to the empty cell to enable computation. We determined the most appropriate meta-analysis model (see Appendix), given that for many adverse events only a small number of studies were available, studies reported on rare events, and several studies reported zero events [27–29]. Where studies did not report sufficient detail and could not be combined into the meta-analysis, we reported the risk estimates provided by the authors.

All studies that reported rates of adverse events that could be computed were combined in meta-analyses. When studies could not be combined statistically, we narratively synthesized the findings to inform the strength of evidence (SoE) assessment and ensure that all available evidence was considered. For the synthesis we determined whether there was evidence of an increased risk of adverse events relative to a control group. In addition to the relative effect, we also documented the actual incidences, sample sizes, and resulting rates of adverse events in the vaccinated and control groups for each individual study where available. We reviewed all instances where the vaccinated group had reported more instances of adverse events in detail. In the absence of evidence of an increased risk across studies, we also reviewed the risk reported in individual studies and documented the observed rates. For estimates that were imprecise–given the small number of reported events and the small number of samples from which conclusions for the true risk could be estimated–the narrative synthesis also reports observed rates to transparently document the available evidence.

We used McHarm [30] for critical appraisal of individual studies, rating studies that reported timing and severity and used standard, precise definitions of adverse events higher than studies that did not. The body of evidence was assessed based on AHRQ Evidence-based Practice Center grading [31]. We used four criteria

Table 1
Included vaccines, populations, and recent changes (within five years).

Vaccine (abbreviation; brand name)	Populations recommended for routine use	Recent changes to formulation, age indication, or dosing (within last five years)
9-valent human papillomavirus (HPV9; Gardasil 9®)	Adults, children	Gardasil 9 approval expanded to include use in women and men 27 through 45 years of age in 2018. Gardasil 9 approved as a two-dose series if first dose initiated 9–14 years of age (otherwise three-dose series as before) in 2016. Catch-up HPV vaccination recommended for all persons through age 26 years in 2019.
13-valent pneumococcal conjugate (PCV13; Prevnar 13®)	Adults, children	Age indications were expanded from younger than 18 years and older than 50 years to include adults aged 18–49 years in 2016.
23-valent pneumococcal polysaccharide (PPSV23; Pneumovax®)	Adults, children	None
Diphtheria, tetanus, and acellular pertussis (DTaP; Daptacel®, Infanrix®)	Children	None
Haemophilus influenzae type b (Hib; ActHIB®, Hiberix®, PedvaxHIB®)	Children	Hiberix approved in 2016 as a three-dose primary series at ages 2, 4, and 6 months (initially approved only as a booster dose for ages 15 months through 4 years).
Hepatitis A (HepA; Havrix®, Vaqta®)	Adults, children	None
Hepatitis B (HepB; Engerix-B®, Recombivax HB®, HEPLISAV-B®)	Adults, children, pregnant women (except for HEPLISAV-B, which is not recommended for children and pregnant women)	HEPLISAV-B approved in 2017.
Inactivated poliovirus (IPV; IPOL®)	Children	None
Influenza, inactivated (IIV; Afluria Quadrivalent®, Fluarix Quadrivalent®, Flucelvax Quadrivalent®, Flulaval Quadrivalent®, Fluzone High Dose Quadrivalent®, Fluzone Quadrivalent®)	Adults, children, pregnant women (except for Fluzone High Dose Quadrivalent, which is for adults aged 65 years and older)	Afluria Quadrivalent and Flucelvax Quadrivalent approved in 2016. Fluzone High Dose Quadrivalent approved in 2019. Flulaval Quadrivalent expanded use to 6 months of age and older in 2016. Afluria Quadrivalent and Fluarix Quadrivalent expanded use to 6 months of age and older in 2018. Fluzone Quadrivalent dose for children aged 6 through 35 months was updated to be either 0.25 mL or 0.5 mL in 2018. Changes to influenza strains for vaccine made annually.
Influenza, inactivated, adjuvanted (aIIV; Fluad®, Fluad Quadrivalent®)	Adults aged 65 years and older	Fluad approved in 2015; Fluad Quadrivalent approved in 2020. Changes to influenza strains for vaccine made annually.
Influenza, recombinant (RIV; Flublok Quadrivalent®)	Adults, pregnant women	Flublok Quadrivalent approved in 2017. Changes to influenza strains for vaccine made annually.
Influenza, live attenuated (LAIV; FluMist Quadrivalent®)	Adults (through 49 years of age), children	Changes to influenza strains for vaccine made annually.
Measles, mumps, rubella (MMR; M–M–R II®)	Adults, children	None
Serogroup A, C, W, and Y meningococcal (MenACWY-D, Menactra®; Men-ACWY-CRM, Menveo®; MenACWY-TT, MenQuadfi®)	Adults, children	MenQuadfi (MenACWY-TT) was approved in 2020.
Serogroup B meningococcal (MenB-FHbp, Trumenba®; MenB-4C, Bexsero®)	Adults, children	None.
Rotavirus (RV; Rotarix®, RotaTeq®)	Children	None
Tetanus, diphtheria, and acellular pertussis (Tdap; Adacel®, Boostrix®)	Children, adults, pregnant women	Adacel approved for repeat dose in people 10 through 64 years of age in 2019. ACIP recommendation updated to allow for use of Tdap or Td as decennial booster, wound prophylaxis, and catch up vaccination in 2020.
Tetanus, diphtheria (Td; TDVAX®, Tenivac®)	Adults	None
Varicella (VAR; Varivax®)	Children, adults	None
Zoster recombinant (RZV; Shingrix®)	Adults	Shingrix was approved in 2017. (Use of live zoster vaccine [Zostavax] was discontinued in November 2020.)

Abbreviations: aIIV—Adjuvanted inactivated influenza vaccine; DTaP— Diphtheria and tetanus toxoids and acellular pertussis vaccine; HepA—Hepatitis A vaccine; HepB—Hepatitis B vaccine; Hib— *Haemophilus influenzae* type b vaccine; HPV9—9-valent human papillomavirus vaccine; IIV—Inactivated influenza vaccine; IPV—Inactivated poliovirus vaccine; LAIV—Live attenuated influenza vaccine; MenACWY—Serogroups A, C, W, and Y meningococcal vaccine; MenB—Serogroup B meningococcal vaccine; MMR—Measles, mumps, and rubella vaccine; PCV13—13-valent pneumococcal conjugate vaccine; PPSV23—23-valent pneumococcal polysaccharide vaccine; RIV—Recombinant influenza vaccine; RV—Rotavirus vaccine; RZV—Recombinant zoster vaccine; Td—Tetanus and diphtheria toxoids; Tdap—Tetanus and diphtheria toxoids and acellular pertussis vaccine; VAR—Varicella vaccine.

to grade the SoE: (1) study limitations; (2) consistency; (3) precision; and (4) reporting bias. We differentiated *high*, *moderate*, *low*, and *insufficient* evidence to communicate the confidence for the findings across studies. *High* confidence indicates that the evidence reflects the true effect; further research is very unlikely to change our confidence in the estimate of effect. *Moderate* confidence indicates that the evidence reflects the true effect; further research may change our confidence in the estimate of effect and may change the estimate. *Low* confidence indicates 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* indicates that evidence either is unavailable or does not permit a conclusion.

Findings are reported below for the selected key adverse events (adverse events identified in the prior report that were not selected as key adverse events for this update are included in the Appen-

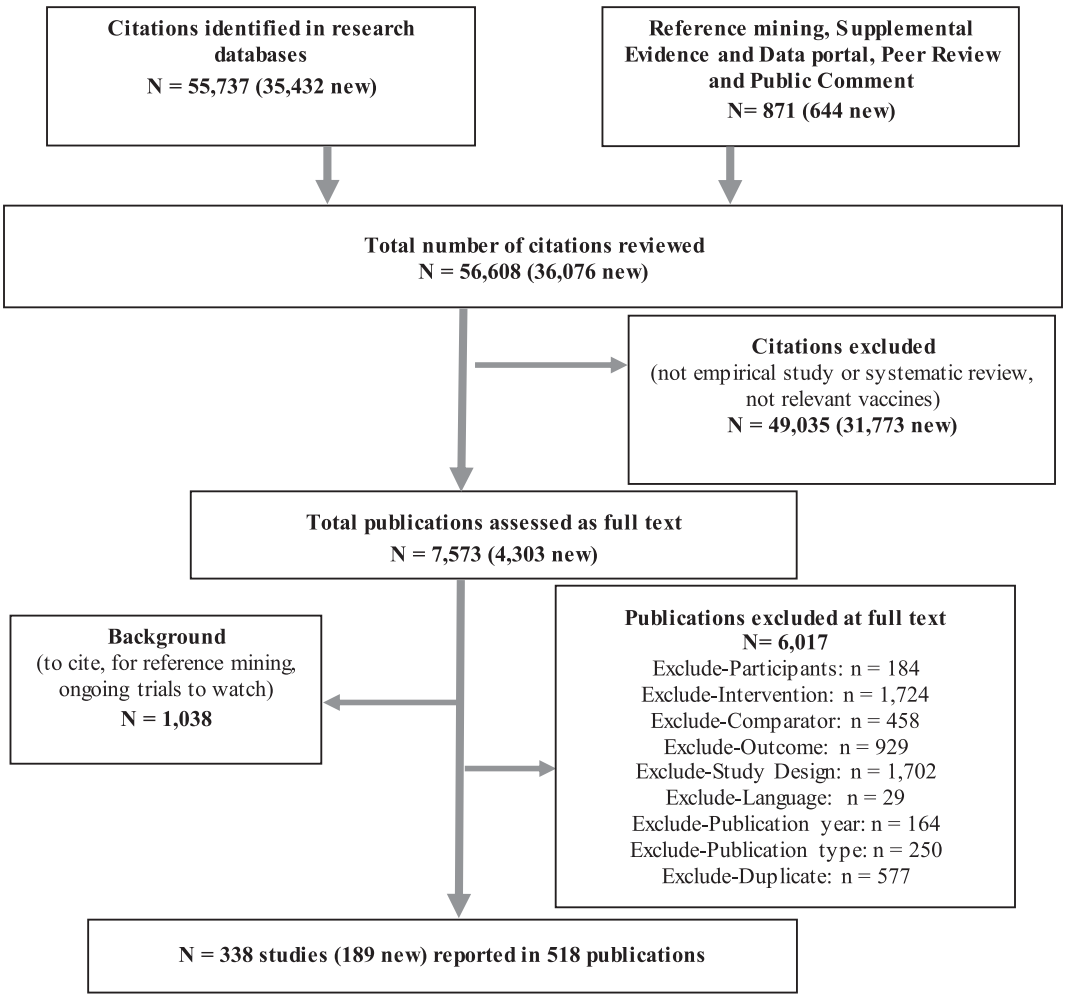

Fig. 1. Literature flow. Note: At the full text stage, publications could be excluded because of participants (animal or mechanistic/in vitro studies; populations for whom the vaccine is not approved or contraindicated); intervention (vaccines not on the US recommended schedules, including brands/formulations not available in the US or no longer used); comparator (no appropriate intervention comparator); outcome (reported effectiveness outcomes only); study design (no comparator at all, e.g., case studies); language (only reported in non-English publication); publication year (included in the 2011 IOM report or were published prior to IOM report for vaccines included in that report); and publication type (published in abbreviated form only; e.g., letters, conference abstracts).

dix). We report effect estimates (RR and 95% CI) that could be computed for findings of moderate or high SoE across studies; we also report findings that were of low SoE, but not the effect estimates.

3. Results

Of 56,603 reviewed citations, 189 new studies met inclusion criteria in this update for a total of 338 studies reported in 518 publications across the prior report and update (Fig. 1) [32–331,332,333,334,335,336,337,338,339,340,341,342,343,344,345,346,347,348,349,350,351,352,353,354,355,356,357,358,359,360,361,362,363,364,365,366,367,368,369,370,371,372,373,374,375,376,377,378,379,380,381,382,383,384,385,386,387,388,389,390,391,392,393,394,395,396,397,398,399,400,401,402,403,404,405,406,407,408,409,410,411,412,413,414,415,416,417,418,419,420,421,422,423,424,425,426,427,428,429,430,431,432,433,434,435,436,437,438,439,440,441,442,443,444,445,446,447,448,449,450,451,452,453,454,455,456,457,458,459,460,461,462,463,464,465,466,467,468,469,470,471,472,473,474,475,476,477,478,479,480,481,482,483,484,485,486,487,488,489,490,491,492,493,494,495,496,497,498,499,500,501,502,503,504,505,506,507,508,509,510,511,512,513,514,515,516,517,518,519,520,521,522,523,524,525,526,527,528,529,530,531,532,533,534,535,536,537,538,539,540,541,542,543,544,545,546,547]. Study designs included RCTs, cohort studies, pre-post designs, case-control designs, non-randomized controlled clinical trials, and self-controlled studies (either self-controlled risk interval or self-controlled case series analyses). Many studies followed patients for six months or longer, and some for up to 15 years to record emerging adverse events.

The methodological rigor and reporting of the adverse events over 15 assessed domains varied widely across studies (Appendix Table 1; Appendix Fig. 1). Most studies reported the timing and frequency of the adverse events assessment, but few reported the qualifications of the outcome assessors.

Full study characteristics can be found in Appendix Tables 2–4.

Safety of vaccines included in the routine immunization schedule in children

A summary of the strength of evidence for the findings can be found in Table 2 (all effect estimates and assessments of the quality of the evidence are in Appendix Table 5, followed by synthesis of the SoE across the prior report and update in Appendix Table 5a).

9-valent human papillomavirus vaccine. All but one study compared 9-valent human papillomavirus vaccine to 2- or 4-valent vaccines. We also reviewed studies that combined children

Table 2
Strength of Evidence (SoE) for safety of vaccines recommended in children.

Vaccine (abbreviation; brand name[s])	Synthesis of SoE* and findings for key adverse events
9-valent human papillomavirus (HPV9; Gardasil 9®)	Low: No evidence of increased risk of autoimmune disease, birth defects, death, reproductive system events, seizures, spontaneous abortion
13-valent pneumococcal conjugate (PCV13; Prevnar 13®)	Moderate: No evidence of increased risk of death Low: No evidence of increased risk of asthma, cardiovascular events, intussusception, meningitis, reproductive system events, seizures Low: Increased risk of febrile seizures
23-valent pneumococcal polysaccharide (PPSV23; Pneumovax®)	Insufficient evidence to draw conclusions about key adverse events
Diphtheria, tetanus, and acellular pertussis (DTaP; Daptacel®, Infanrix®)	Moderate: No evidence of increased risk of type 1 diabetes mellitus Low: No evidence of increased risk of asthma or death
Tetanus, diphtheria, and acellular pertussis (Tdap; Adacel®, Boostrix®)	ow: No evidence of increased risk of cardiovascular events, or death
Haemophilus influenzae type b (Hib; PedvaxHIB®, ActHIB®, Hiberix®)	Insufficient evidence to draw conclusions about key adverse events
Hepatitis A (HepA; Havrix®, Vaqta®)	Moderate: Increased risk of idiopathic thrombocytopenic purpura among children aged 7 to 17 years
Hepatitis B (HepB; Engerix-B®, Recombivax HB®)	Moderate: No evidence of increased risk of multiple sclerosis
Inactivated poliovirus (IPV; IPOL®)	Insufficient evidence to draw conclusions about key adverse events
Influenza, inactivated (IIV; Afluria Quadrivalent®, Fluarix Quadrivalent®, Flulaval Quadrivalent®, Fluzone Quadrivalent®, Flucelvax Quadrivalent®)	Moderate: No evidence of increased risk of death Low: No evidence of increased risk of anaphylaxis or systemic allergic reaction, asthma, autoimmune disease, cardiovascular events, febrile seizures, seizures
Influenza, live attenuated (LAIV; FluMist Quadrivalent®)	Low: No evidence of increased risk of death or seizures
Measles, mumps, and rubella (MMR; M−M−R II®)	High: No evidence of increased risk of autism High: Causal relationship with anaphylaxis in children with allergies based on mechanistic evidence; increased risk of febrile seizures Moderate: Increased risk of idiopathic thrombocytopenic purpura Low: No evidence of increased risk for asthma
Meningococcal, A, C, W, and Y (MenACWY; MenACWY-D [Menactra®], MenACWY-CRM [Menveo®], MenACWY-TT [MenQuadfi®])	Moderate: No evidence of increased risk of cardiovascular events, diabetes, febrile seizures, intussusception, idiopathic thrombocytopenic purpura, Kawasaki disease, seizures Moderate: Causal relationship with anaphylaxis in children with allergies based on mechanistic evidence Low: No evidence of increased risk of acute disseminated encephalomyelitis, anaphylaxis or systemic allergic reaction (among all children), asthma, autoimmune disease, death, encephalitis/encephalopathy, meningitis, multiple sclerosis, reproductive system events, transverse myelitis
Meningococcal B (MenB; MenB-4C [Bexsero®], MenB-FHbp [Trumenba®])	Moderate: No evidence of increased risk of anaphylaxis or systemic allergic reaction, reproductive system events Low: No evidence of increased risk of asthma, death, seizures
Rotavirus (RV; Rotarix®, RotaTeq®)	High: No evidence of increased risk of diabetes Moderate: No evidence of increased risk of intussusception (moderate SoE for increased risk from prior report was not confirmed when combining all available trials, though some observational studies showed increased risk). No evidence of increased risk of asthma, autoimmune disease, death, encephalitis/encephalopathy, febrile seizures, idiopathic thrombocytopenic purpura, seizures, stroke Low: No evidence of increased risk of anaphylaxis or systemic allergic reaction, autoimmune thyroiditis (Hashimoto's disease), Kawasaki disease, meningitis, reproductive system events
Varicella (VAR; Varivax®)	High: Causal relationship with anaphylaxis, as well as with herpes zoster, meningitis, and encephalitis as a result of vaccine strain viral reactivation based on mechanistic evidence Moderate: Increased risk of idiopathic thrombocytopenic purpura among children aged 11 to 17 years

*Please see Appendix Table 5a for a description of the SoE and findings from the prior 2014 report (including adverse events not examined as key adverse events in the update), the update, and the synthesis across the report and update (including for combination vaccines).

and adults. There was no evidence of increased risk of autoimmune disease, birth defects, death, reproductive system events, seizures, or spontaneous abortion (all low SoE).

13-valent pneumococcal vaccine. Risk estimates were based on comparisons of 13-valent pneumococcal vaccine to 7-valent pneumococcal vaccine, except for death. There was no evidence of increased risk of death (RR 2.02; CI 0.07, 59.88; risk estimate based on 1 study; moderate SoE assessed across all 5 available studies). The risk estimate was imprecise as the sample size was small with only one event (1/193 vs 0/195). There was also no evidence of increased risk of asthma, cardiovascular events, intussusception, meningitis, reproductive system events, or seizures (all low SoE). There was an increased risk of febrile seizures (low SoE). There was insufficient evidence for 23-valent pneumococcal polysaccharide vaccine for the outcomes of interest.

Diphtheria, tetanus, and acellular pertussis (DTaP) vaccine. There was no evidence of increased risk of type 1 diabetes mellitus for vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens (moderate SoE, effect estimate N/A). There was no evidence of increased risk of asthma or death (low SoE).

Tetanus, diphtheria, andacellular pertussis vaccine. There was no evidence of increased risk of type 1 diabetes mellitus for vaccines containing diphtheria toxoid, tetanus toxoid, and acellular pertussis antigens (moderate SoE, effect estimate N/A). There was no evidence of increased risk of cardiovascular events or death (low SoE).

Hepatitis A vaccine. There was an increased risk of idiopathic thrombocytopenic purpura among children aged 7 to 17 years (moderate SoE, effect estimate N/A).

Hepatitis B vaccine. There was no evidence of increased risk of multiple sclerosis (moderate SoE, effect estimate N/A).

Quadrivalent influenza vaccines (IIV). Quadrivalent IIV was compared to trivalent IIV in all but one of the studies that contributed to risk estimates (this study only contributed to the risk estimate for death). There was no evidence of increased risk of death (RR 1.08; CI 0.02, 53.95; estimate based on 1 study; moder-

Table 3
Strength of Evidence (SoE) for safety of vaccines recommended in adults.

Vaccine (abbreviation; brand name[s])	Synthesis of SoE and findings for key adverse events
9-valent human papillomavirus (HPV9; Gardasil 9®)	Insufficient evidence to draw conclusions; see Table 2 for studies that combined children and adults
13-valent pneumococcal conjugate (PCV13; Prevnar 13®)	Moderate: No evidence of increased risk of cardiovascular events, herpes zoster, myocardial infarction, reproductive system events, stroke Low: No evidence of increased risk of acute disseminated encephalomyelitis, anaphylaxis or systemic allergic reaction, asthma, autoimmune disease, death, encephalitis/encephalopathy, herpes zoster, idiopathic thrombocytopenic purpura, meningitis, seizures
23-valent pneumococcal polysaccharide (PPSV23; Pneumovax®)	High: No evidence of increased risk of cardiovascular or cerebrovascular events in adults aged 65 years and older Moderate: No evidence of increased risk of death
Hepatitis A (HepA; Havrix®, Vaqta®)	Insufficient evidence to draw conclusions about key adverse events
Hepatitis B (HepB; Engerix-B®, Recombivax HB®, HEPLISAV-B®)	Moderate: No evidence of increased risk of multiple sclerosis (for hepatitis B vaccines except HEPLISAV-B, for which there was insufficient evidence) Moderate: No evidence of increased risk of diabetes (across all hepatitis B vaccines) Moderate: Causal relationship with anaphylaxis in patients allergic to yeast based on mechanistic evidence (for hepatitis B vaccines except HEPLISAV-B, for which there were no studies) Low: No evidence of increased risk of asthma, autoimmune disease, cardiovascular events, death, herpes zoster, reproductive system events; stroke for HEPLISAV-B
Influenza, inactivated (IIV; Afluria Quadrivalent®, Flucelvax Quadrivalent®, Fluarix Quadrivalent®, Flulaval Quadrivalent®, Fluzone High Dose Quadrivalent®, Fluzone Quadrivalent®)	Low: No evidence of increased risk of asthma, cardiovascular events, death, myocardial infarction, reproductive system events, seizures, stroke
Influenza, inactivated, adjuvanted (aIIV; Fluad®, Fluad Quadrivalent®)	Moderate: No evidence of increased risk of cardiovascular events or stroke Low: No evidence of increased risk of asthma, autoimmune disease, death, encephalitis/encephalopathy, Guillain-Barré syndrome, idiopathic thrombocytopenic purpura, myocardial infarction, seizures
Influenza, recombinant (RIV; Flublok Quadrivalent®)	Low: No evidence of increased risk of cardiovascular events, death, encephalitis/encephalopathy, myocardial infarction, reproductive system events, stroke
Influenza, live attenuated (LAIV; FluMist Quadrivalent®)	Insufficient evidence to draw conclusions about key adverse events
Measles, mumps, and rubella (MMR; M−M−R II®)	Moderate: No evidence of increased risk of type 1 diabetes mellitus
Meningococcal A, C, W, and Y (MenACWY; MenACWY-D [Menactra®], MenACWY-CRM [Menveo®], MenACWY-TT [MenQuadfi®])	Moderate: No evidence of increased risk of death Low: No evidence of increased risk of cardiovascular events, myocardial infarction, stroke
Meningococcal B (MenB; MenB-4C [Bexsero®],MenB-FHbp [Trumenba®])	Insufficient evidence to draw conclusions about key adverse events; see Table 2 for studies that combined children and adults
Tetanus, diphtheria, and acellular pertussis (Tdap; Adacel®, Boostrix®) and tetanus and diphtheria (Td; TDVAX, Tenivac®)	High: Causal relationship with anaphylaxis to tetanus toxoid based on mechanistic evidence
Varicella (VAR; Varivax®)	Insufficient evidence to draw conclusions about key adverse events
Zoster recombinant (RZV; Shingrix®)	High: No evidence of increased risk of herpes zoster Moderate: No evidence of increased risk of amyotrophic lateral sclerosis, anaphylaxis or systemic allergic reaction, asthma, cardiovascular events, death, diabetes, encephalitis/encephalopathy, Guillain-Barré syndrome, idiopathic thrombocytopenic purpura, meningitis, myocardial infarction, reproductive system events, seizures, stroke Low: No evidence of increased risk of acute disseminated encephalomyelitis, angioedema, ataxia, autoimmune disease, autoimmune thyroiditis (Hashimoto's disease)

*Please see Appendix Table 6a for a description of the SoE and findings from the prior 2014 report (including adverse events not examined as key adverse events in the update), the update, and the synthesis across the report and update (including for combination vaccines).

ate SoE across 6 studies). The risk estimate was imprecise because it was based on one small study with no deaths (0/99 vs 0/107). There was no evidence of increased risk of anaphylaxis or systemic allergic reaction, asthma, autoimmune disease, cardiovascular events, febrile seizures, or seizures (low SoE).

Quadrivalent live attenuated influenza vaccine (LAIV) was compared to placebo or no vaccine in some studies, or another influenza vaccine (trivalent LAIV or IIV) in other studies. There was no evidence of increased risk of death (when compared to trivalent LAIV) or seizures (when compared to placebo or no vaccine) (low SoE).

Measles, mumps, and rubella vaccine. There was no evidence of an association with autism (RR 0.60; CI 0.09, 4.12; based on 2 studies; high SoE across prior 2014 report and update). There was a causal relationship with anaphylaxis in children with allergies (based on mechanistic evidence from the IOM report [24]; high SoE), as well as an increased risk of febrile seizures (high SoE), and idiopathic thrombocytopenic purpura (moderate SoE) (effect estimates N/A). There was no evidence of increased risk of asthma (low SoE).

Serogroup A, C, W, and Y meningococcal vaccines. Some studies of serogroup A, C, W, and Y meningococcal vaccines used another meningococcal vaccine as an active comparator, while others used a non-active comparator (placebo or a base treatment received by both intervention and control groups). All estimates below are based on studies of children with a non-active comparator, but studies where an active comparator was used as well as studies of both children and adults also contribute to the SoE. There was no evidence of increased risk of cardiovascular events (RR 0.34; CI 0.02, 5.46; based on 1 study; moderate SoE across 3 studies), febrile seizures (RR 0.51; CI 0.18, 1.44; based on 1 study; moderate SoE across 4 studies), intussusception (RR 0.46; CI 0.10, 2.03; 1 study; moderate SoE), idiopathic thrombocytopenic purpura (RR 0.17; CI 0.01, 5.09; based on 1 study; moderate SoE across

Table 4
Strength of Evidence (SoE) for safety of vaccines recommended in pregnant women.

Vaccine (abbreviation; brand name [s])	Synthesis of SOE* and findings for key adverse events
Hepatitis B (HepB; Engerix-B®, Recombivax HB®)	Insufficient evidence to draw conclusions about key adverse events
Influenza, inactivated (IIV; Afluria Quadrivalent®, Flucelvax Quadrivalent®, Fluarix Quadrivalent®, Flulaval Quadrivalent®, Fluzone Quadrivalent®); Influenza, recombinant (RIV; Flublok Quadrivalent®)	Insufficient evidence to draw conclusions about key adverse events
Tetanus, diphtheria, and acellular pertussis (Tdap; Adacel®, Boostrix®)	Moderate: No evidence of increased risk of maternal cardiovascular events, maternal death, maternal diabetes, eclampsia/pre-eclampsia, preterm labor, maternal reproductive system events, stillbirth, cardiovascular events in infants, death in infants, encephalitis/encephalopathy in infants, seizures in infants Low: No evidence of increased risk of maternal encephalitis/ encephalopathy, autism in infants, birth defects in infants, febrile seizures in infants

*Please see Appendix Table 7a for a description of the SoE and findings from the prior 2014 report, the update, and the synthesis across the report and update.

3 studies), Kawasaki disease (RR 1.37; CI 0.15, 12.22; based on 1 study; moderate SoE across 2 studies), or seizures (RR 1.51; CI 0.05, 44.86; based on 1 study; moderate SoE across 7 studies).

There was no evidence of increased risk of diabetes (RR 1.32; CI 0.00, 21861366; based on 2 studies; moderate SoE across 6 studies) but the risk estimate was imprecise due to small samples and few or no cases in the vaccinated and unvaccinated groups (1/396 vs 0/397; 0/392 vs 0/296).

There was also no evidence of increased risk of acute disseminated encephalomyelitis, asthma, autoimmune disease, death, encephalitis/encephalopathy, meningitis, multiple sclerosis, reproductive system events, or transverse myelitis (low SoE). There was a causal relationship with anaphylaxis in children with allergies (based on mechanistic evidence from the IOM report [24]; moderate SoE, effect estimate N/A), but there was no evidence of increased risk among all children (low SoE).

Serogroup B meningococcal vaccine. There was no evidence of increased risk of anaphylaxis or systemic allergic reaction (RR 0.56; CI 0.00, 34735108; 2 studies; moderate SoE), but the risk estimate was imprecise due to no cases in the vaccinated and unvaccinated groups (0/198 vs 0/121; 0/992 vs 0/501). There was no evidence of increased risk of reproductive system events (RR 0.89; CI 0.01, 65.20; 3 studies; moderate SoE); again, the risk estimate was imprecise, in this case due to small samples and few or no cases in the vaccinated and unvaccinated groups (1/198 vs 0/121; 1/174 vs 0/99; 0/374 vs 1/378). There was no evidence of increased risk of asthma, death, or seizures (low SoE).

Rotavirus vaccine. We found no evidence of increased risk of intussusception across all studies that could be combined for an estimate (RR 0.65; CI 0.41, 1.05; based on 19 studies; moderate SoE across 43 studies), though some observational studies indicated increased risk, particularly around the first dose. There was no evidence of increased risk of asthma (RR 1.33; CI 0.65, 2.72; 5 studies; moderate SoE), autoimmune disease (RR 0.65; CI 0.16, 2.67; 2 studies; moderate SoE), death (RR 1.05; CI 0.82, 1.35; based on 14 studies; moderate SoE across 15 studies), diabetes (RR 0.74; CI 0.45, 1.22; based on 3 studies; high SoE across 4 studies), febrile seizures (RR 0.82; CI 0.33, 2.05; based on 7 studies; moderate SoE across 9 studies), or seizures (RR 1.02; CI 0.25, 4.16; based on 5 studies; moderate SoE across 8 studies).

There was no evidence of increased risk of encephalitis/encephalopathy (RR 0.67; CI 0.00, 85995; based on 2 studies; moderate SoE across 4 studies), but the risk estimate was imprecise due to few or no cases in the vaccinated and unvaccinated groups (1/1647 vs 2/1641; 1/34904 vs 1/34862). There was no evidence of increased risk of idiopathic thrombocytopenic purpura (RR 0.64; CI 0.00, 1778394; 2 studies; moderate SoE); again, the risk estimate was imprecise due to there being few or no cases in the vaccinated and unvaccinated groups (1/34904 vs 0/34862; 0/4359 vs 2/4328). There was no evidence of increased risk of stroke (RR 1.32; CI 0.00, 1459247; 2 studies; moderate SoE). The risk estimate is imprecise given the small number of studies and studies reporting few or no cases in the vaccinated and unvaccinated groups (1/34904 vs 0/34862; 1/1666 vs 1/1667).

There was no evidence of increased risk of anaphylaxis or systemic allergic reaction, autoimmune thyroiditis (Hashimoto's disease), Kawasaki disease, meningitis, or reproductive system events (all low SoE).

Varicella vaccine. There was a causal relationship with anaphylaxis, as well as with herpes zoster, meningitis, and encephalitis as a result of vaccine strain viral reactivation (all based on mechanistic evidence from the IOM report [24]; high SoE, effect estimates N/A). There was increased risk of idiopathic thrombocytopenic purpura (among children aged 11–17 years; moderate SoE, effect estimate N/A). ***Haemophilus influenzae* type b vaccine, inactivated poliovirus vaccine.** Evidence was insufficient to draw conclusions about key adverse events.

3.1. Safety of vaccines included in the routine immunization schedule in adults

A summary of the strength of evidence for the findings can be found in Table 3 (all effect estimates and assessments of the quality of the evidence are in Appendix Table 6, followed by synthesis of the SoE in Appendix Table 6a).

13-valent pneumococcal conjugate vaccine. Some studies of 13-valent pneumococcal conjugate vaccine used another pneumococcal vaccine as an active comparator, while others used a non-active comparator (placebo or a base treatment received by both intervention and control groups). All risk estimates below are based on studies with a non-active comparator, but studies where an active comparator was used also contribute to the SoE. There was no evidence of increased risk of cardiovascular events (RR 0.97; CI 0.58, 1.64; based on 4 studies; moderate SoE across 6 studies), myocardial infarction (RR 1.76; CI 0.42, 7.39; based on 4 studies; moderate SoE across 6 studies), or reproductive system events (RR 0.59; CI 0.01, 42.46; based on 3 studies; moderate SoE across 5 studies).

There was no evidence of increased risk of herpes zoster (RR 1.49; CI 0.00, 24855526; 2 studies; moderate SoE). The risk estimate was imprecise as only two studies reported on the outcome with few or no cases occurring in the vaccinated and unvaccinated groups (0/576 vs 0/575; 1/42237 vs 0/42255). There was also no evidence of increased risk of stroke (RR 1.12; CI 0.00, 451; 2 studies; moderate SoE); the risk estimate was imprecise due to no events in one study (0/551 vs 0/560), and a large sample size with a small number of events in the other (9/42237 vs 8/42255).

We found no evidence of increased risk of acute disseminated encephalomyelitis, anaphylaxis or systemic allergic reactions, asthma, autoimmune disease, death, encephalitis/encephalopathy, idiopathic thrombocytopenic purpura, meningitis, or seizures (low SoE).

23-valent pneumococcal polysaccharide vaccine. We found no evidence of increased risk of death (RR 0.62; CI 0.16, 2.44; based on 4 studies; moderate SoE across 7 studies). We also found high SoE for no evidence of increased risk of cardiovascular events (RR 0.46; CI 0.27, 0.76; based on 4 studies; high SoE across 8 studies) or cerebrovascular events (effect estimate N/A) in people aged 65 years and older.

Hepatitis B vaccine. For HEPLISAV-B (which was compared to previously available hepatitis B vaccines), there was no evidence of increased risk for asthma, autoimmune disease, cardiovascular events, death, herpes zoster, reproductive system events, or stroke (low SoE). For all hepatitis B vaccines, there was no evidence of increased risk of diabetes (RR 0.61; CI 0.55, 0.67; based on 1 study comparing hepatitis B vaccines to no vaccine; moderate SoE across 3 studies). For hepatitis B vaccines (not including HEPLISAV-B, for which there was insufficient evidence), there was no increased risk of multiple sclerosis, but there was a causal relationship with anaphylaxis in patients allergic to yeast based on mechanistic evidence from the IOM report [24] (both moderate SoE, effect estimates N/A).

Influenza vaccines (IIV). Influenza vaccines were compared to an active comparator (either trivalent influenza vaccine or another influenza vaccine). For quadrivalent IIV, we identified no evidence of increased risk of asthma, cardiovascular events, death, myocardial infarction, reproductive system events, seizures, or stroke (low SoE). For adjuvanted IIV (either trivalent or quadrivalent), there was no evidence of cardiovascular events (RR 0.47; CI 0.00, 81.39) or stroke (RR 1.18; CI 0.00, 33607) (both estimates based on 2 studies; moderate SoE across 3 studies). The risk estimate was imprecise as only two studies of differing sample sizes reported on the outcome with few cases occurring in the vaccinated and comparator groups for cardiovascular events (1/888 vs 3/888, 8/3545 vs 16/3537) and for stroke (0/888 vs 1/888, 3/3545 vs 2/3537). There was no evidence of increased risk of asthma, autoimmune disease, death, encephalitis/encephalopathy, Guillain-Barré syndrome, idiopathic thrombocytopenic purpura, myocardial infarction, or seizures (low SoE). For quadrivalent recombinant influenza vaccine, there was no evidence of increased risk of cardiovascular events, death, encephalitis/encephalopathy, myocardial infarction, reproductive system events, or stroke (low SoE). There was insufficient evidence for conclusions about increased risk of key adverse events for quadrivalent live attenuated influenza vaccine.

Measles, mumps, rubella vaccine. There was no evidence of increased risk of type 1 diabetes mellitus (moderate SoE, effect estimate N/A).

Serogroups A, C, W and Y meningococcal vaccines. Some studies of serogroup A, C, W, and Y meningococcal vaccines used another meningococcal vaccine as an active comparator, while others used a non-active comparator (placebo or a base treatment received by both intervention and control groups); all risk estimates below are based on studies with a non-active comparator, but studies where an active comparator was used also contribute to the SoE. There was no evidence of increased risk of death (RR 0.99; CI 0.00, 60563320; based on 2 studies; moderate SoE across 4 studies). The risk estimate was imprecise due to two small studies with no events (00/99 vs 0/100; 0/85 vs 0/84). There was no evidence of increased risk of cardiovascular events, myocardial infarction, or stroke (all low SoE).

Tetanus, diphtheria, and acellular pertussis and tetanus and diphtheria vaccines. There was a causal relationship with anaphylaxis to tetanus toxoid (based on mechanistic evidence from the IOM report [24]; high SoE, effect estimate N/A).

Recombinant zoster vaccine. We found moderate SoE of no evidence of increased risk of cardiovascular events (RR 0.89; CI 0.66, 1.21; 3 studies), death (RR 0.93; CI 0.78, 1.11; 4 studies), myocardial infarction (RR 0.89; CI 0.38, 2.05; 3 studies), or reproductive system events (RR 1.04; CI 0.03, 37.17; 2 studies).

For all other adverse events for which there was moderate SoE, the confidence intervals were wide because the risk estimate was based on two studies with few or no events occurring in the vaccinated and non-vaccinated groups: amyotrophic lateral sclerosis (RR 2.60; CI 0.00, 571537; 2/6950 vs 0/6950, 2/7695 vs 1/7710), anaphylaxis or systemic allergic reaction (RR 1.32; CI 0.00, 1463200; 1/6950 vs 1/6950, 1/7695 vs 0/7710), asthma (RR 0.90; CI 0.00, 493; 2/6950 vs 4/6950, 6/7695 vs 5/7710), diabetes (RR 1.00; CI 0.00, 606; 5/6950 vs 6/6950, 3/7695 vs 2/7710), encephalitis/encephalopathy (RR 0.50; CI 0.00, 2867570; 0/6950 vs 1/6950, 0/7695 vs 1/7710), Guillain-Barré syndrome (RR 0.67; CI 0.00, 86459; 1/6950 vs 2/6950, 1/7695 vs 1/7710), idiopathic thrombocytopenic purpura (RR 2.65; CI 0.00, 530690; 1/6950 vs 0/6950, 3/7695 vs 1/7710), meningitis (RR 0.50; CI 0.00, 2867570; 0/6950 vs 1/6950, 0/7695 vs 1/7710), seizures (RR 1.34; CI 0.00, 13492; 2/6950 vs 0/6950, 3/7695 vs 3/7710), or stroke (RR 1.44; CI 0.03, 71.52; 7/6950 vs 6/6950, 19/7695 vs 12/7710).

We found no evidence of increased risk of herpes zoster (RR 0.09; CI 0.02, 0.30; 5 studies; high SoE). There was no evidence of increased risk of acute disseminated encephalomyelitis, angioedema, ataxia, autoimmune disease, or autoimmune thyroiditis (low SoE).

9-valent human papillomavirus vaccine, hepatitis A vaccine, serogroup B meningococcal vaccine, and varicella vaccine. Evidence was insufficient to draw conclusions about key adverse events based on studies of adults only.

Safety of vaccines included in the routine immunization schedule in pregnant women (both for the woman and her fetus)

A summary of the strength of evidence for the findings is in Table 4 (all effect estimates and assessments of the quality of the evidence are in Appendix Table 7, followed by synthesis of the SoE in Appendix Table 7a).

We found insufficient evidence to draw conclusions about key adverse events for hepatitis B vaccine, quadrivalent inactivated influenza vaccines, or quadrivalent recombinant influenza vaccine in pregnant women.

All studies of Tdap compared to either placebo or base treatment also received by the control groups, except for one study that compared Tdap and Td. There was no evidence of increased risk for maternal cardiovascular events (RR 0.86; CI 0.41, 1.84; 6 studies), maternal death (RR 1.52; CI 0.07, 32.25; 4 studies), maternal diabetes (RR 0.98; CI 0.88, 1.10; 4 studies), eclampsia/pre-eclampsia (RR 0.96; CI 0.92, 1.01; 6 studies), preterm labor/delivery (RR 0.62; CI 0.46, 0.82; 10 studies), maternal reproductive system events (RR 0.52; CI 0.05, 5.91; 3 studies), stillbirth (RR 0.44; CI 0.11, 1.80; 6 studies), cardiovascular events in infants (RR 0.77; CI 0.50, 1.20; 4 studies), death in infants (RR 0.15; CI 0.00, 8.88; 3 studies), encephalitis/encephalopathy in infants (RR 1.23; CI 0.60, 2.54; 4 studies), or seizures in infants (RR 1.02; CI 0.76, 1.35; 3 studies) (all moderate SoE). There was also no evidence of increased risk of maternal encephalitis/encephalopathy, autism in infants, birth defects in infants, or febrile seizures in infants (low SoE).

4. Discussion

We assessed the evidence for the safety of vaccines currently used for routine immunization in the United States among children, adults, and pregnant women. We conducted extensive literature searches, screened 56,603 citations, and abstracted 338 studies reported in 518 publications.

Overall, our evidence review found vaccines to be safe across populations with serious adverse events being rare, consistent

with other recent systematic reviews of vaccine safety [548]. For adults, there was no evidence of increased risk (varied SoE) or insufficient evidence for key adverse events for newer vaccines such as adjuvanted inactivated influenza vaccine and recombinant adjuvanted zoster vaccine. We found no evidence of increased risk among pregnant women following Tdap, including for stillbirth (moderate SoE).

For children, across all studies SoE was high for no increased risk of autism following measles, mumps, and rubella (MMR) vaccine. SoE was high for increased risk of febrile seizures with MMR. There was no evidence of increased risk (varied SoE) or insufficient evidence for key adverse events for newer vaccines such as 9-valent human papillomavirus and meningococcal B vaccines. We found high SoE for no increased risk of diabetes following rotavirus vaccine, and moderate SoE for no increased risk of other adverse events, such as autoimmune disease and idiopathic thrombocytopenic purpura. We also found no evidence of increased risk of intussusception following rotavirus vaccine at the latest time of follow-up across studies that could be pooled, consistent with a recent meta-analysis [549]. However, there were mixed findings across other studies, which included pre-post studies, cohort studies, and self-controlled case series, particularly related to the risk following the first dose. While intussusception is a known possible side effect of rotavirus vaccination (listed in the package inserts for both vaccines and also in the Vaccine Injury Table as a condition covered under the National Vaccine Injury Compensation Program) [550] the finding that there is no increased risk with the longest-term follow-up from clinical trials is noteworthy.

Our study had some limitations. While our literature search procedures were extensive, some unpublished data may not have been identified, although we mitigated this by searching trial registries. The importance of trial registries has increased dramatically since reporting of results has become mandatory. Clinicaltrials.gov is set up to capture results that can be used in systematic reviews and meta-analyses, including data on severe adverse events, serious adverse events, and mortality. In general, the harms data in Clinicaltrials.gov have been found to be more complete than in the corresponding publications, [551,552] although we note that the database tends to better capture the presence of reported adverse events than the absence of such events.

However, trials often have insufficient sample sizes to identify rare adverse events and may not follow participants long enough to identify long-term sequelae; even in studies with generous follow-up times, timing of events is not always optimally reported. Indeed, many of the harms we assessed as key adverse events (e.g., acute disseminated encephalomyelitis, Guillain-Barré syndrome, transverse myelitis, anaphylaxis) are quite rare and the number of studies that reported on the events for a vaccine was often small. As a result, despite our extensive searches for data that could be combined across studies, our confidence intervals are often wide and the SoE often low or insufficient. Given the limitations of controlled trials, we included post-marketing surveillance and self-controlled analyses (if they met inclusion criteria) when grading the SoE. For example, in the United States the CDC's Vaccine Safety Datalink uses data obtained from eight large health care organizations, enabling studies that may be particularly useful for identifying safety signals and/or investigating concerns for rare serious adverse events. Such innovative methodologic approaches have improved the analysis of rare adverse events, particularly in the post-marketing phase.

We also may have missed studies due to the challenging nature of assessing harms (as contrasted with assessing effectiveness); however, we screened the full text of all identified vaccine intervention studies, and our search terms did not include safety terms in order not to miss relevant data. Wherever possible, we used data that could be combined in meta-analyses to estimate the relative risk based on all available research studies. When we could not combine data in pooled estimates, we integrated findings (including from the prior 2014 report) in a narrative synthesis to inform the SoE.

This review excluded studies of vaccines not currently in use in the United States and cannot make evidence statements for other vaccine schedules. We also excluded non-English language studies. Although we considered only vaccines approved for use in the United States, it is possible relevant epidemiological studies have been published in non-English journals.

Careful consideration should be given to research gaps, including where the evidence was insufficient to assess the potential associations between some vaccines and particular adverse events and/or where confidence intervals around risk estimates were extremely wide. However, when deciding whether studies are warranted, important factors to consider include the severity and frequency of the adverse event being studied and the challenges of conducting sufficiently powered studies when investigating rare events. Given the rare nature of some of the serious adverse events of interest, ongoing studies of large populations and post-marketing surveillance of vaccines after FDA licensure as noted earlier are needed to identify uncommon adverse events. Future vaccine research will also need to take into account the expanding landscape of new vaccines and vaccine technologies, in particular the new COVID-19 vaccines [553].

5. Conclusion

Across a large body of research, we found few instances in which vaccines are associated with serious adverse events; however, potential risks for rare adverse events should be weighed carefully against the protective benefits that those vaccines provide.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors gratefully acknowledge the following individuals for their contributions to this project: Kim Wittenberg, Stephanie Chang, Christine Chang, Thomas Acciani, David Kim, Kara Elam, Tammy Beckham, Mark Helfand, and Ethan Balk for helpful comments; Jeremy Miles for statistical consultation; Peggy Chen, Alicia Ruelaz Maher, Kelsey O'Hollaren, Nabeel Qureshi, Keller Scholl, Olamigoke Akinniranye, Tim M. Kim, Oluwafemi Jimoh, Lea Xenakis, Weilong (David) Kong, Zichun Xu, and Sangita Baxi for research assistance; and Judy Bearer for administrative assistance.

In addition, the authors would like to thank the Technical Expert Panel while acknowledging that the study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts. The list of technical experts who provided input for the AHRQ report are as follows: Meghan Baker, Richard Beigi, Sarah Coles, Frank Destefano, Kristen Feemster, Janet McElhaney, LaShawn McIver, Rebecca Reindel, Patricia A. Stinchfield, Melinda Wharton, Thomas Yoshikawa, and Ousseny Zerbo. The authors also sought additional peer review for the AHRQ report and would like to thank the following individuals: Haitao Chu, Tamera Coyne-Beasley, Janet Cragan, Matthew Daley, Cody Meissner, and Barbara Mulach.

Funding source

This project was funded under Contract No. HHSA290201600010I from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services (HHS). The funder had no role in the design, interpretation of results, nor the decision to submit this manuscript. The authors of this manuscript are responsible for its content. Statements in the manuscript do not necessarily represent the official views of or imply endorsement by AHRQ or HHS.

Author contributions

All authors attest that they meet the ICMJE criteria for authorship.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.03.079.

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