Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Safety of Vaccines Used for Routine Immunization in the United States: An Update

Draft report available for public comment from October 26, 2020, to November 23, 2020.

Research Review Citation: Gidengil C, Goetz MB, Maglione M, Newberry SJ, Chen P, O'Hollaren K, Qureshi N, Scholl K, Ruelaz Maher A, Akinniranye O, Kim TM, Jimoh O, Xenakis L, Kong W, Xu Z, Hall O, Larkin J, Motala A, Hempel S. Safety of Vaccines Used for Routine Immunization in the United States: An Update. Comparative Effectiveness Review No. 244. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-2015-00010-I.) AHRQ Publication No. 21-EHC024. Rockville, MD: Agency for Healthcare Research and Quality; May 2021. DOI: 10.23970/AHRQEPCCER244. Posted final reports are located on the Effective Health Care Program search page.

Comments to Draft Report

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This document includes the responses by the authors of the report to comments that were submitted for this draft report. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Quality	Superior	Thank you
Peer Reviewer #3	Quality	Superior	Thank you
Peer Reviewer #4	Quality	Superior	Thank you
Peer Reviewer #5	Quality	Superior	Thank you
Peer Reviewer #6	Quality	Superior	Thank you
TEP #1	Quality	Superior	Thank you
TEP #2	Quality	Superior	Thank you
TEP #3	Quality	Superior	Thank you
TEP #4	Quality	Superior	Thank you
TEP #5	Quality	Fair	Thank you
TEP #6	Quality	Superior	Thank you
Peer Reviewer #1	General	Comments on “Safety of Vaccines Used for Routine Immunization in the United States: An Update”. First, I would like to congratulate the authors for their extensive and thorough work on this update for the safety of vaccines used for routine immunization in the United States. The update has addressed many important evidence gaps. From the statistical perspective, here are a few comments [see rows below]	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	1) While Hartung-Knapp-Sidik-Jonkman approach and its modification for random-effects meta-analysis is becoming advocated for general use for a meta-analysis (with few studies), there is a range of potential concerns (see Jackson et al.1). When the outcome is binary, the Hartung-Knapp-Sidik-Jonkman approach is a two-step approach. For example, when the effect measure of interests is RR, it first computes log(RR) and its standard error for each study; when there is zero cells, some continuity correction is implemented. Then it applies that the Hartung-Knapp-Sidik-Jonkman approach to combine log(RR) from all studies. Given that for many adverse events only a small number of studies was available, many studies reported zero events as many adverse events are rare, this approach is not optimal as it does not directly use binomial likelihood and need some ad hoc continuity corrections for zero cells. There is a wide range of literature available on meta-analysis with zero events, and none of them seems to be cited in the reference list.	We have specifically selected our approach to address the small number of studies. We also agree that the Hartung-Knapp-Sidik-Jonkman (HK) approach needs a modification to address the issues raised by Jackson et al. and have used a modification recently implemented in the metafor package in R. We have added a citation specific to zero events to address this comment and have added more details how we have addressed zero events.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	2) Following comments in 1), the authors might consider Bayesian hierarchical models (which can be easily implemented in BUGs or JAGS) or generalized linear mixed models, and use the exact binomial likelihood to model the data.	We believe that our approach is more suitable to the 400+ meta-analyses undertaken for this report. We do not believe that a different model will come to different conclusion, in particular given the rare nature of events and the often inadequate samples.
Peer Reviewer #1	General	3) For the outcomes with sufficient number of studies to perform meta-analysis, the authors might consider using forest and other plots to visually present the data and results	Thank you. We considered including forest plots, however because of the number of analyses (400+) and the length of this report (1200 pages) we have decided not to include them as we believe they are of limited value.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	4) In addition to RR, the authors may consider presenting the absolute risks (and risk differences) of adverse events for vaccinated versus not vaccinated. It may be more useful for decision making and for the general audience to understand the risks of adverse events.	While we generally agree, none of the new risk estimates in this report are statistically significant. Therefore, addition of absolute risks would provide information of limited value. In addition, for some risk estimates, the data is not reported in such a way that permits us to calculate the absolute risk. However, we do provide all rates of key adverse events in the Summary of Findings tables. We also provide the rates of key adverse events in the main text whenever the confidence intervals around the risk estimate were wide, as well as contextual information to help interpret the rates (e.g., were the events attributed to the vaccine or not).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General	This overview presents an enormous amount of information and reflects considerable work by the authors who should be recognized for their efforts. Two major comments: First, the paper discusses adverse events which is appropriate given the title. However, suggest more discussion of the enormous benefit of vaccines. Note that no vaccine is 100% safe. But the overwhelming benefit of vaccines far exceeds any risk. Risk is present with anything we do, from eating to crossing the road. The issue is relative risk.	We agree that the effectiveness of vaccines is an important counterpoint to the risk of vaccines, and that all decisions about vaccines must be made in the context of both the safety and effectiveness. However, the effectiveness of vaccines is beyond the scope of this review. In order to address and acknowledge this important point, we have added some text to the discussion, noting that the risks of rare adverse events should be weighed against the protective benefits that vaccines provide.
Peer Reviewer #2	General	Second, individual vaccines are discussed in separate sections throughout the text. It is difficult to address the issue of reported adverse events for an individual vaccine. Would an index be possible?	We have updated the Table of Contents to include sub-headings for each vaccine. In addition, the summary tables are also already organized by vaccine and provide an easy means of accessing findings by vaccine. Finally, we have reorganized some sub-sections to merge information about vaccines so that it is easier for the reader.
Peer Reviewer #2	General	This reference by Meissner, Plotkin addresses the issue “The facts about vaccine safety” Clin Inf Dis 2020 10.1093/cid/ciaa697. Other possible sites are Discussion on page 27.	We have added this reference to the portion of text where we highlight that effectiveness of vaccines must be weighed against risk in decision making.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	1. Thank you for this extensive and detailed work on such an important topic. In general, the report is carefully done, well-organized, and well-written. I have several general comments, followed by several more specific or detailed ones.	Thank you
Peer Reviewer #3	General	2. It is not always clear when the referenced data comes from pre-licensure vs. post-licensure data. Often the terms "RCT" or "trial" are used, and I suspect these were mainly pre-licensure. And a related but arguably more important point: whenever possible, please try to include what the comparator was for the RCTs whenever possible (seems present in most but not all references to RCT results).	We have reviewed the report to ensure that we use only the terms "RCT" or "trial" to be consistent. Most RCTs were conducted pre-licensure. We note the comparator in each study in the evidence tables in Appendix D. We have also ensured that we note the comparator in the main body of the report when it was an active comparator (e.g., a comparator vaccine).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	3. Each Key Question asked about the short-term and long-term safety. Yet almost all that followed (text and summary tables) did not make any reference or distinction regarding whether the adverse event under study was monitored over a shorter or longer interval. Organizationally, where would this best fit? One could consider adding a section ("short term vs. long term safety") to each major text section. Or adding a column to most evidence tables?	We collected all adverse events based on the longest follow-up available to ensure we captured as complete safety data as possible. The exact follow-up for each study is stated in the evidence tables in Appendix D. We now also note the proportion of the studies that provided short-term follow-up (42 days or less) in the beginning of the Results section. Finally, we have added a sentence to the Discussion acknowledging that the timing of events was not always optimally reported.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	4. Related to above, some adverse events (anaphylaxis) are much more important to study in the short term, others in the long term (multiple sclerosis), whereas others may be important in both time frames (myocardial infarctions?)	We agree that the timing of each adverse event relates to the vaccine and particular adverse event. We collected all adverse events based on the longest follow-up available to ensure we captured as complete safety data as possible. The adverse events were selected with the help of content experts, and were not distinguished by the timeframe in which they would be expected to occur. Had any of the associations been significant, we would have provided more detail in terms of the timing of the events, etc. However, such detail at a study level or even vaccine/adverse event level would make the report even more lengthy.
Peer Reviewer #3	General	5. Why is there a distinction made between “collected in” and “reported in” outcomes?	"Collected in" refers to which adverse events were planned to be collected, or were reported as having been collected by the authors. "Reported in" means that there was documentation of the presence or absence of the event. We have clarified this in the Methods section of the report (under Key Questions).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	6. I certainly appreciate the challenges in conveying the state of knowledge clearly and concisely. But I found phrases such as “low SoE for no evidence of increased risk” a bit problematic. It represents something of a triple negative. An alternative risk-first phrasing could be something like “no increase in risk detected (low strength of evidence)”	We appreciate this comment and acknowledge that this is a complex phrasing. However, we feel strongly that we should continue to use the accurate, conservative phrasing currently in the report. We have, however, clarified the usage of this phrasing in the report to ensure that the rationale for its use is clear (see the Note for each Table in the Executive Summary).
Peer Reviewer #3	General	7. Is it true that findings from an individual study would always be regarded as “insufficient evidence” of an adverse event, if no other studies were available or an individual study could not be combined with others into a meta-analysis (such as for MMRV vaccines and febrile seizure risk)?	We applied the outlined criteria to downgrade the strength of evidence also for single studies. Single studies were not considered insufficient evidence *per se*.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	8. The authors combined studies where comparators differed. While the approach may be justified, could the authors expand on their discussion of the limitations and strengths of this approach?	We have expanded on the limitations and strengths of this approach in the Discussion section. Specifically, we note that a comparison between a vaccine and an active comparator may underestimate rate of adverse effects relative to a comparison between that same vaccine and placebo. Given this, we clearly note when an active vaccine comparator was used throughout the text of this report. While our inclusive approach added to the complexity of the review, this approach has the benefit of capturing the fullest evidence base possible for the range of vaccines and potential harms.
Peer Reviewer #3	General	9. There is an important discussion of the limitations of self-controlled case series analyses (Page 132). Does the fact that results from self-controlled case series analyses cannot be combined with results from other study designs (RCT, cohort) lessen their contribution to the body of safety literature?	We do not believe that the inability to combine these results with other study designs lessens their contribution to the body of safety literature. Although we could not combine such events numerically, we still took all studies available into account when determining the strength of evidence of a finding.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	10. There is no discussion (pages 125-135) of the important distinction between short-term and long-term safety data. Understandably, more is known about short-term safety. However, vaccine-hesitant parents and adults are often more concerned about long-term safety, including risk of chronic disease.	We collected all adverse events based on the longest follow-up available to ensure we captured safety data as completely as possible, and in part to address concerns about long-term safety. In fact, the majority of studies had long-term follow-up (>42 days) for serious adverse events, with some following patients for years. The exact follow-up duration is stated in the evidence tables in Appendix D. We now also note the proportion of the studies that provided long-term (>42 versus short-term follow-up in the beginning of the Results section.
Peer Reviewer #4	General	Yes, this report is clinically meaningful. The target populations and audience are explicitly defined, and the key questions are appropriate and explicitly stated.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	General	The report is very thorough, providing useful information in multiple formats to relate to different audiences. Summaries are provided regularly and then followed by source data for those who want all of the details. The Evidence Summary provides a valuable overview of new information since the last report in 2014. At first, I was a bit overwhelmed by the size of the report and the level of detail included for the studies that were taken into consideration. If I were reading this for informational purposes, I think I would probably tackle it by vaccine and really dig in on the results. The organizational structure (by pathogen/vaccine) is particularly helpful for those looking for details on vaccines for a particular infectious disease.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	General	This report is significantly clinically meaningful and comprehensive. The target populations and audiences are defined and presented per each vaccine. However, since adolescents are explicitly mentioned it may be helpful to explicitly mention the age range of this designation. To adolescent health professionals adolescent healthcare includes young adults and generally extends from age 11 to age 24 or 26. Given my experience in vaccine schedules I understand that ACIP adult vaccination schedules are generally from age 19 and older while children and adolescents schedules are 18 years old and younger. I suspect some of the studies reviewed considered adults to be individuals 18 years of age and older. There could be some clarity around the distinctions between the consideration of adolescents and adults in this report and in the studies reviewed.	We agree that there is some variation in how "adults" are defined. As noted, ACIP considers adults to be those 19 and older, and children (including adolescents) to be 18 and younger. However, functionally in almost all reviewed studies, adults are considered those who are 18 and older. We have revised the methods to simplify the terminology and now make clear that the term "children" throughout the report includes adolescents as well.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	General	The key questions are explicitly stated and are appropriate. Answers are specifically given for each key question under the designated subsection. This review is not only important for its intended audience, but it can also be easily translated for a lay audience. This should be considered in dissemination strategies as there are growing concerns about vaccine safety among anti-vaxers and others concerned about COVID vaccination.	Thank you
TEP #1	General	This a nice review of the available evidence regarding vaccine safety. It is a clinically meaningful report that will be valuable to clinicians, researchers and healthcare organizations interested in vaccine safety. The key questions were appropriate and explicitly stated.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP #2	General	This is a comprehensive document providing updates to the safety of the range of vaccines for children, adults and pregnant woman. It serves as a critical reference document where information can easily be accessed in the summary tables providing the strength of the evidence each potential key adverse event. Its availability should be widely publicized with targeted communication to public health vaccination programs as well as clinicians.	Thank you
TEP #3	General	This is a comprehensive report that exhaustively and systematically reviews the evidence for possible associations between specific vaccines and specific adverse events. It will be of value to scientists, clinicians and policy makers who deal with vaccines in general and vaccine safety in particular. I have some specific comments in the attached pdf file.	Thank you
TEP #4	General	Excellent review that is clinically meaningful, thorough, thoughtful. KQ easily identified, appropriate, and explicitly stated. Target populations clearly identified.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP #5	General	Throughout the report, the term "no evidence of increased risk" is used. The report indicates that this phrase means that the "reviewed studies did not constitute evidence of an increased risk of the adverse event." This term could be misleading, as it could be interpreted in multiple ways. It is preferable to use a term or terms that better articulate that the weight of the evidence, based on the specific analyses that were conducted, did not definitively support an increased risk following vaccination.	Thank you for noting this. We carefully considered the most conservative and correct wording to express certainty in risk of an adverse event. The EPC Program's strength of assessment also uses this phrasing. As this phrasing is used throughout the EPC Program, we use it here for consistency'. However, to make the findings clearer to the reader, we have also added color-coded symbols to the tables summarizing findings to more easily identify where there were signals for increased risk versus no increased risk (or insufficient evidence to draw conclusions).
TEP #5	General	A clear and upfront explanation of the difference between insufficient evidence and the different grades of SoE is recommended, as it is not readily apparent from the descriptions of events assigned to either of these categories in the report. It is important that the terms used to inform results and conclusions accurately capture the nature of the analyses performed.	Thank you – we have added an explanation of the different grades of SoE to the Executive Summary.

Commentator & Affiliation	Section	Comment	Response
TEP #5	General	This report leans heavily on the use of confidence intervals (CI) in the assessment of the study data. The report states that: “there remains insufficient evidence for some rare potential adverse events for which very large samples would be needed to estimate the risk or to definitively exclude a risk of such adverse events.” It would be helpful to clearly describe the limitations of the use of the CI to assess rare events in studies that are inadequately powered or designed to detect statistically significant differences and to describe how the analysis of “increased risk” may not be as useful for such events. The statistical significance of risk comparisons of rare events may be less relevant than an examination of the specific cases for causality.	We agree with this comment. We have added more context as appropriate for risk estimates with wide confidence intervals by including absolute rates of the rare adverse events in the studies in the main text and additional information to help interpret these rates (e.g., whether the event was attributed to the vaccine or not). Finally, we have also added some text to the Discussion around the use of CI and rare events.
TEP #5	General	Additionally, the methods used to combine studies and statistically analyze the results (such as the CI) are not clearly explicated in the report, and likely pose some methodologic limitations that should be clearly discussed, as this may impact the interpretation of this data in the context of the categories used.	The full methods can be found in Appendix A. We have also added some text to the discussion around the interpretation of CI for rare events.

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TEP #6	General	Would suggest adding information on SARS-CoV2 as this will likely be relevant to many readers. Recognize that the data is limited, but would acknowledge the vaccines and potentially share available information.	Thank you for this comment. The SARS-CoV2 vaccines in development and under consideration do not meet inclusion criteria as they are not currently routinely recommended. This has been clarified throughout the report (including in the Executive Summary).
Peer Reviewer #2	Preface	[Comment on "The list of Technical Experts who provided input to this report follows", P. iv] Comment: Page 4, lines 26 & 28 make same statement	We have deleted the duplicate statement.
Peer Reviewer #2	Abstract	[Comment on "A large body of evidence is available to evaluate adverse events following vaccination. Of 49,740 reviewed citations, 152 studies met inclusion criteria for this update at the time of the draft report adding to in the prior report for a total of 302 included studies reported in 461 publications." P.v) Comment: Page 5, line 35, 152 + 302 = 613, not 461, not clear what is added here.	The total number of included studies across both reports is 338; we have revised the text to make this clearer.
Peer Reviewer #6	Abstract	Structured abstract – line 43, Remove either after the word no. It should read "we found either no..", rather than "we found no either"…	We have corrected this wording.

Commentator & Affiliation	Section	Comment	Response
TEP #6	Evidence Summary	Main points ES-1: Could consider simplifying the language, content accurate	Thank you. We have reviewed the language to ensure that it is as simple as possible. There is a large amount of information to distill into a small number of bullet points. The content remains accurate however.
Peer Reviewer #2	Evidence Summary	[Comment on "The list of vaccines is based on the Centers for Disease Control and Prevention's (CDC) immunization schedules3, 4 and includes only those currently licensed for use in the United States by the FDA.", p. ES-2] Comment: Page 10, line 9, some vaccines licensed by FDA are not included in report, what you mean is vaccines licensed by FDA and recommended by CDC for routine use.	The reviewer is correct – we mean vaccines licensed by the FDA and recommended by the CDC for routine use. We have clarified this in the text.
Peer Reviewer #2	Evidence Summary	[Comment on "In total, 152 studies reported in 287 publications were included in this update at the time of the draft report (October 2020), adding to studies identified in the original 2014 AHRQ report on the topic for a total of 302 included studies reported in 461 publications. The 2014 report built on findings from a detailed IOM report on vaccine safety published in 2011", p. ES-2] Comment: Page 10, line 46, restatement of page 5, line 35, is that intended?	Yes, the restatement from the abstract in the methods of the ES was intended.

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Peer Reviewer #2	Evidence Summary	[Comment on "9-valent human papillomavirus (HPV9; Gardasil 9)", p. ES-4]: Comment: Page 12, line 10, two additional references Pediatrics 2019;144(6):e20191791 and Pediatrics 2019;144(4):2019808	Thank you for flagging these two studies. The first (Shimabukuro et al., Pediatrics, 2019) does not meet inclusion criteria as it uses VAERS (there is no comparator group). The second – assuming the reviewer meant 144(6) – is already included in the report (Donahue et al., Pediatrics, 2019).
Peer Reviewer #2	Evidence Summary	[Comment on "Moderate: Transient arthralgia in women)" p. ES-5] Comment: Page 13, line 51, evidence for transient arthralgia after rubella vaccine seems more than moderate.	This was taken directly from the published IOM report and prior AHRQ 2014 report, and as such we have not altered the rating of the strength of evidence (we found no new evidence related to the association).
Peer Reviewer #2	Evidence Summary	[Comment on "Insufficient: Acute disseminated encephalomyelitis; ataxia; Guillain-Barré syndrome; secondary transmission of live varicella virus; transvers myelitis), p. ES-8] Comment: Page 16, line 30, this is a killed vaccine so no risk of transmission, why mention the issue? Also, Zostavax is not available (I believe)	We have removed Zostavax from the report as it is no longer available.
TEP #3	Evidence Summary	[Comment in pdf file on"HPV2 and HPV4 no longer in use" Table ES2, p. ES-10]: Comment: in the United States	This is correct – the review covers only those vaccines in use in the United States (FDA approved and recommended by the CDC for routine immunization)

Commentator & Affiliation	Section	Comment	Response
TEP #3	Evidence Summary	[Comment in pdf file on "Low: No evidence of increased risk of anaphylaxis or systemic allergic reaction; asthma; autoimmune disease;cardiovascular events; death;febrile seizures; seizures for quadrivalent IIV", Table ES2, p. ES-11]: Comment: See McNeil for anaphylaxis. Not a comparative study, but anaphylaxis can be considered causal just on clinical evidence.	The McNeil study is out of scope for this review due to the lack of a comparator as noted; we did not include or review studies without a comparator. There may be associations that are clinically credible, but we do not comment on them in this report.
TEP #3	Evidence Summary	[Comment in pdf file on "Trivalent LAIV no longer in use", Table ES2, p. ES-11]: Studies of asthma exacerbation.	We did not identify any studies of quadrivalent LAIV and asthma exacerbation. Studies of trivalent LAIV and asthma exacerbation would be out of scope for this review as the vaccine is no longer in use.
Peer Reviewer #2	Evidence Summary	[Comment on "Moderate: Increased risk of febrile seizures based on IOM report (downgraded due to inconsistency, with one study in current report showing no evidence of increased risk)" p. ES-12] Comment: Page 20, line 26, most would not agree with moderate evidence of febrile seizure after MMR, as it is pretty well established.	We agree that this is well established clinically, but based on our review of the evidence, we have rated the association as being of moderate strength.

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TEP #3	Evidence Summary	[Comment in pdf file on "encephalitis/encephalopathy; Kawasaki disease; meningitis; multiple sclerosis; reproductive system events; transverse myelitis", Table ES2, p. ES-13]: Comment: GBS?	We did not identify any studies of GBS in the current review.
Peer Reviewer #2	Evidence Summary	[Comment on "Rotavirus (RV; Rotarix, RotaTeq)" p. ES-14] Comment: Page 22, line 35, rotavirus vaccine is associated with increased risk of intussusception.	Based on our review of the literature we found moderate strength of evidence for no increased risk of intussusception. The relative risk across all 19 RCTs for which we could combine data was 0.65 (95% CI 0.41, 1.05). Some, but not all, of the other studies that could not be combined showed an increased risk of intussusception. The basis of our strength of evidence rating takes all of these studies into account. This finding is consistent with the conclusions of a recent meta-analysis in JAMA.
TEP #3	Evidence Summary	[Comment in pdf file on "Low: No evidence of increased risk of acute disseminated encephalomyelitis, death", Table ES2, p. ES-16]: Comment: febrile seizures?	Since the prior AHRQ 2014 review, we identified three studies of MMR-V and febrile seizures with conflicting results, which constituted insufficient evidence.
Peer Reviewer #3	Introduction	Good	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Introduction	The introduction provides the needed background, delineates the changes made in vaccine use since the 2014 report, and clearly states the purpose and scope of the report.	Thank you
Peer Reviewer #5	Introduction	Strong introduction that does a good job of leading the reader to the detailed information in the paper. I am providing comments using page numbers at the top:	Thank you
Peer Reviewer #6	Introduction	The introduction is strong and provides the appropriate preface and foundation for the scientific information that is to follow. In the introduction an important broad overview of the success of vaccination is presented as well as an outline of the vaccine development and commercialization process. Vaccine safety and surveillance measures are also included as well as the purpose and scope of the systematic review.	Thank you
TEP #1	Introduction	The introduction is well-written and summarize the current literature and also points to the previous report.	Thank you
TEP #2	Introduction	Defines the purpose and scope of the review process.	Thank you
TEP #3	Introduction	The Introduction clearly lays out the purpose, background, need and intended uses of the report	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP #4	Introduction	Table 1 is very helpful to sort through vaccine changes since the last report. Clear explanation of the background and scope for this report. Good review of vaccine development and review process, as well as ongoing safety monitoring programs. It may be worthwhile to add a sentence that this report does not evaluate vaccine efficacy.	We have added a sentence clarifying that the report does not evaluate the effectiveness of vaccines.
Peer Reviewer #2	Introduction	[Comment on "As a result, vaccines have improved health outcomes and reduced mortality for adults, in addition to decreasing health care costs." P. 1) Comment: Page 28, line 16 should also state vaccines prevent an untold amount of suffering.	We have added a sentence to this effect.
Peer Reviewer #2	Introduction	[Comment on "The purpose of this report is to assess the evidence regarding the safety of vaccines routinely recommended for adults, children and adolescents, and pregnant women in the United States among by systematic review." P. 5] Comment: Page 32, line 15, first sentence does not make sense.	We have revised this sentence.
Peer Reviewer #5	Introduction	1) p. 28, lines 54-55. In 2014, the office was NVPO, not OIDP.	Thank you – we have changed this to reflect that it was NVPO at that time.
Peer Reviewer #5	Introduction	2) p. 28, line 55: "S" in AIDS should be capitalized.	We have corrected this.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Introduction	3) p. 32, line 18 “among by systematic review.” Does not fit with the rest of the sentence.	We have revised this sentence.
Peer Reviewer #5	Introduction	4) p. 32, line 19 “comprises those currently licensed for use by the FDA.” Language is misleading. It sounds like the FDA is the group using the vaccine rather than licensing it.	We have revised this sentence to read as follows: “comprises those currently licensed by the FDA”.
TEP #5	Introduction	See above for relevant comments.	No response needed.
Peer Reviewer #3	Methods	See below, comments which refer jointly to methods and results.	No response needed.
Peer Reviewer #4	Methods	The inclusion and exclusion criteria are clearly states and justifiable. The search strategies are explicitly stated and logical and include the grey literature. The definitions, outcome measures and statistical methods are appropriate. The analytic framework was presented and it made it clear that the fetus/infant was also a population of interest	Thank you
Peer Reviewer #5	Methods	The search strategies are well described and logical. The content and analyses of multiple studies are provided in an organized and easy-to-follow manner.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Methods	The inclusion and exclusion criteria are justifiable. The search strategies are explicitly stated and logical and include grey literature. The definitions, outcome measures and statistical methods are appropriate. The analytic framework was presented and it made it clear that the fetus/infant was also a population of interest. The inclusion of infants wasn't immediately obvious to me from reading the Evidence Summary. The authors also reviewed and included the studies from the previous report.	Thank you
TEP #1	Methods	The inclusion and exclusion criteria are justifiable but they were not clearly defined in the method. I could not say why one study on maternal Tdap and risk of ASD was included while the study on maternal influenza vaccine and ASD was not included. Maybe providing more explanation on exclusion criteria would help readers. The statistical method was appropriate.	The full methods can be found in Appendix A.

Commentator & Affiliation	Section	Comment	Response
TEP #2	Methods	The inclusion and exclusion criteria justifiable. The search strategies are explicitly stated and are logical. The definitions for the outcome measures appropriate. The statistical methods seem to be appropriate although this is not my area of expertise.	Thank you
TEP #3	Methods	All of the above criteria are met. The methods lean heavily on clinical trials, which is justifiable, but nonetheless leads to prioritizing studies of rather limited sample size for many of the rare adverse events evaluated.	Thank you. We included all studies that met inclusion criteria, which also included non-trial studies (e.g., self-controlled designs).
TEP #4	Methods	The key questions are clearly identified and are clinically relevant. The create an appropriate framework for the report. Target populations clearly identified.	Thank you
TEP #4	Methods	Inclusion and exclusion criteria are appropriate. I feel it would add clarity if the Table A.1 (eligibility criteria) was included in the document rather than as an appendix. It is a quick and easy to read summation of the eligibility criteria. This is often the first thing I look at with systematic reviews to determine if I would keep reading further.	We carefully considered this thoughtful comment within our team, but given the straightforward inclusion criteria and the existence of the table of included vaccines in the introduction, we did not add this table on top of the brief summary of inclusion/exclusion criteria.

Commentator & Affiliation	Section	Comment	Response
TEP #4	Methods	Statistical methods appropriate. Including the evidence tables was extremely valuable, though I could not easily find the bias assessments for the included studies.	Thank you for noting this. A summary of the bias assessment is in Figure 6. Because we did an extensive risk of bias assessment, we also include documentation of each source of bias for each study in a separate table in Appendix C (Table C.5).
TEP #3	Methods	[Comment in pdf file on "KQ1a. What adverse events are collected in clinical studies (Phases I–IV) and in observational studies containing a control/comparison group?", p.6]: Comment: May miss important studies that employ a self-control design.	We included studies that employ a self-control design, and have clarified this in the Methods.
TEP #6	Methods	Key Question 2, p 7. Would clarify why we chose 42 rather than 30 days.	Because this report is an update of the prior AHRQ 2014 report, the key questions remained the same. In the prior report, 42 days was the cut-off between short- and long-term.
Peer Reviewer #2	Methods	[Comment on "We included trial records, even in the absence of a corresponding publication, from which we abstracted severe and serious adverse events, as well as deaths." P. 9] Comment: Page 36, line 42, how could you include vaccine trials that were not published? How did you identify them? Doesn't seem appropriate.	We included data from entries on clinicaltrials.gov, which contains data often prior to publication or that were not published in a journal (if published, we ensured that such results were only included once). We systematically searched trial registries for such data.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Methods	[Comment in pdf file on "We included comparisons to placebo, unvaccinated groups or pre-vaccination status as well as standard of care, i.e., studies testing a new vaccine compared to the previously available or closest vaccine formulation." P. 9]: Comment: How defined?	Thank you for noting this – we have added the definition of what we considered the closest vaccine formulation to Appendix A (Methods).
TEP #4	Methods	Page 32, Line 9: This sentence discusses evaluating risk factors for adverse events and includes race/ethnicity. As we work to move away from race based medicine, a brief recognition that race is not a risk factor (because it is not a biologically distinct entity) but rather racism and social determinants of health equity are a risk factor that may manifest as differences in outcomes based on race is warranted.	We have added some text to the Methods (under Analytic Framework) to acknowledge this very important point in the report, in part using the wording suggested.
TEP #6	Methods	Content of Figure 1, page 9, is accurate but the figure might be simplified for the reader.	Thank you – we have opted to leave this figure as is as it mirrors the figure in the prior review, and is part of the study protocol.
Peer Reviewer #6	Methods	Figure 2. The Literature flow diagram could be improved by adding the "N" and the relevant numerical value to the box with "reference mining, supplemental evidence and data portal, etc." The missing value could be determined by subtraction, but should be explicitly stated	We have added these numbers to the figure.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Methods	Figures 3 and 4 need headers on either the x axis and/or y axis	We have added these headers to the figures.
TEP #4	Methods	Table C.5 in the appendix C could use a legend explaining the rating system.	We have added this legend.
TEP #5	Methods	Appendix A was not included and thus the specific methods were not available for review.	The posted draft report contained all Appendices for review as a link on the last page of the report.
Peer Reviewer #3	Results	Specific comments (page numbers refer to page numbers at the bottom of page):	No response needed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	The amount of detail presented in the results section is appropriate for this type of report. It is clearly presented and is supplemented by a detailed Appendix. The characteristics of the studies are clearly defined by each vaccine in the text and tables. The key messages are explicit and applicable. It is also clear when there aren't any studies to evaluate an outcome. I am not aware of any studies that should have been included. The investigators did a comprehensive search to include additional studies from the first review. The information presented at times seems repetitive. One suggestion for consideration is to perhaps organize all of the information for each vaccine in its own section with subheadings for the adverse events that were collected, those that were reported, and those associated by number and severity, statistical significance, and risk factors. Rather than listing information for each of the vaccines under each of these sections. So that all of the information about a single vaccine I presented in one place.	We appreciate this suggestion and discussed it. Ultimately, we have opted to retain the structure so that it follows the Key Questions. We hope that the summary tables at the end of each section are helpful in this regard.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	The amount of detail presented in the results section is appropriate for this type of report. It is clearly written and presented and is supplemented by a detailed appendix. The study characteristics are very clearly defined by each vaccine in the text and tables. The key messages are explicitly and applicable. It is also clear when there weren't any studies to evaluate an outcome. I am not aware of any studies that should have been included that were excluded. The investigators did a comprehensive search to include a significant number of additional studies since the first review.	Thank you
TEP #1	Results	The amount of detail presented in the results was appropriate and the characteristics of the studies were described. Key messages were explicit. The investigators did not overlook any study and they were very thorough in the literature review.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP #2	Results	The detailed results are summarized in a table format which is very helpful, with only the "bottom line" presented in the text. It is particularly important that effect sizes and 95% confidence intervals have been reported. Characteristics of the studies are clearly described and key messages are explicitly stated and applicable to the safety issues addressed in this review. It does not appear that any studies have been overlooked and I don't see any studies that ought to have been excluded.	Thank you
TEP #3	Results	The amount of detail is extensive, but appropriate. The figures and tables are adequate. I think all relevant studies that met the inclusion criteria have been included.	Thank you
TEP #4	Results	Thank you for including the evidence to decision tables, such as Table 2.	Thank you
TEP #4	Results	The key messages are explicit and applicable, easily identifiable in the report.	Thank you
TEP #4	Results	The study characteristics are clearly described, though I have struggled to find the bias assessment	Thank you
TEP #4	Results	I did not identify any missing studies or incorrectly included studies	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP #4	Results	I felt the discussions of the studies were appropriate, relevant, and clearly outlined. I appreciated the discussion of where additional evidence was needed due to lack of evidence.	Thank you
TEP #4	Results	I appreciated that the key points section clearly identified when the strength of evidence was changed from the prior reports (for example: page 83, line 3).	Thank you
TEP #4	Results	The tables were clear and easy to read, added to the content well.	Thank you
TEP #3	Results: Description of Included Evidence	[Comment in pdf file on "The most frequent study designs identified in the update were randomized clinical trials (RCTs, n=91), followed by cohort studies (n=26), pre-post designs (n=12), case-control designs (n=9), and one non-randomized controlled clinical trial, along with 13 others that used selfcontrol methods (either self-controlled risk interval or self-controlled case series analyses; two of these used self-control methods in conjunction with a cohort design). Studies reported on a variety of datasets, ranging in size from fewer than 50 to millions of data points (Figure 3).", p. 13]: Comment: OK	No response needed.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results: KQ1	[Comment on p. 17] Comment: Page 44, line (no line # given) how about two adjuvanted vaccine at same visit, like influenza and haplisav.	If there was an appropriate comparator, we would include a study in which two adjuvanted vaccines were given at the same visit. However, we identified no such studies that met our inclusion criteria.
Peer Reviewer #3	Results: KQ1	11. Page 18: I would suggest separating the description of "hepatitis vaccines" into separate sections for hepatitis A vaccines and hepatitis B vaccines.	Given that there is a combined HepA-HepB vaccine, we have opted not to delete the Hepatitis vaccines section, but have instead added sub-headings. We have also added sub-headings to other sections that cover multiple vaccines within one category.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results: KQ1	12. In some of the references provided (ref 74, 88, 212, 213), it is not clear what documents are being referenced. Are these results reported in peer reviewed journals, or from the vaccine package inserts, or another source?	Thank you for this observation. In general, we include all results if published, including if they are published online as part of clinicaltrials.gov. Wherever possible, we cite the paper that is published from the trial. In some cases, no paper is published, as happened with reference 74, which is of one of the trials of HEPLISAV-B. The effectiveness results were published, as were safety results in a subset of adults with diabetes aged 60-70 years. However, the full safety results are available only in the clinical trial record, and this is what we used for data abstraction. Reference 88 is also a clinical trial record for HEPLISAV-B that was not published as a paper. Again, to present a complete picture of the safety of the vaccine we abstracted data directly from clinicaltrials.gov. References 212 and 213 are the trial records for other papers and are cited in the literature flow and are considered “multiple publications” (meaning they are reviewed, but when citing results relevant to the trial, we always cite the main paper if one was published).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	P. 24, Comment: PDF Document Page 51, Lines 16-17 – It states the "latter" had extremely wide confidence intervals, but the CI listed is 0.08 – 22.21. Why was this considered extremely wide? Most of the Cis in other studies noted to be wide ranged into the thousands.	We defined "extremely wide" confidence intervals as anything higher than 15. While some confidence intervals were even larger, we did not differentiate further than that.
Peer Reviewer #4	Results	Document Page 25, Line 41 – The sentence doesn't quite make sense. Maybe "A limited number of studies included listed adverse events stratified…".	We have revised this sentence as suggested.
Peer Reviewer #3	Results: KQ1	13. Page 27, Table 2: It is confusing (at least to me) to have zero studies listed in the third column, but then to present a risk estimate from a study in the fourth column.	Thank you for this observation – we have revised the column headers of the tables to make this clearer. The third column lists studies that contribute to the RR. The fourth column contains the RR, as well as other studies that were considered when grading the strength of evidence. If an RR could not be generated, then the fourth column would only list these other studies.
TEP #3	Results: KQ1	[Comment in pdf file on "One study found no increased risk (OR 0.4; CI 0.1, 1.9)" Table 2, p. 27: Comment: Not clear why one study is listed here but previous box lists no studies.	Thank you for this observation – we have expanded the footnote of the table to explain this further.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results: KQ1	14. Page 30: Wasn't there any clinical trial data for the safety of the combined hepatitis A-hepatitis B vaccine to report?	As this vaccine was released in 2001 and available both at the time of the prior AHRQ 2014 report and IOM report, we did not review literature outside of the updated search period for this report. There were no clinical trials for this vaccine since 2014.
TEP #3	Results: KQ1	[Comment in pdf file on "There was insufficient evidence for all outcomes of interest for HPV9 because no study that evaluated the vaccine in adults only met inclusion criteria (Table 3a). HPV9 was not available at the time of the prior 2014 report, thus there are no studies of HPV9 vaccine across both reports. Table 3a summarizes the findings across both reports." P. 32]: Comment: Substantial number of large studies on safety of HPV2 and HPV4 have been published since last report. Both vaccines are still used in much of the world. These studies provide important data on the safety of HPV vaccines, especially regarding neurologic and autoimmune outcomes and are of relevance to HPV9 safety in light of specific studies of this vaccine.	We acknowledge that such studies could be useful. This report focuses on vaccines currently in use in the United States. We have added the fact that this review is U.S.-focused to the Limitations in the Discussion section.
TEP #4	Results	Figure 6: Line 32, page 42: It is unclear to me what the "High risk" and "low risk" in the legend of the figure.	We have clarified that the "High risk" and "Low" risk are of bias in the legend.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Results: KQ1	[Comment in pdf file on "Encephalitis/encephalopathy – RR 1.00; CI 0.02, 50.18 (0/225 vs 0/225" Table 4, p. 33]: Comment: With zero cases in both groups, it seems that the RR should be undefined; not clear how a RR was calculated. Same comment for some of the outcomes below.	For consistency reasons, we have calculated the relative risk throughout; in order to calculate the confidence interval around the point estimate, a constant was added to the empty cells. Throughout, we mention in the text when no events occurred in the intervention and control group.
Peer Reviewer #5	Results	p. 36, lines 31-32: "Studies evaluating vaccines included in the CDC's routine immunization schedules recommended for adults, children and adolescents, and pregnant women." This isn't a full sentence. Is this meant to be a header or is something missing?	Thank you, we have revised the sentence.
Peer Reviewer #5	Results	p. 36, line 43: States "severe and serious adverse events". I think it is confusing to list these together since severity is part of a grading scale and serious is not.	We have revised the sentence.
Peer Reviewer #5	Results	p. 42, Table 6 is blurry and very difficult to read	The AHRQ copy editor will ensure that the tables are not blurry for the final posted report.
Peer Reviewer #5	Results	p. 42, line 51. Should say "only a few studies"	We have revised this as suggested.
Peer Reviewer #5	Results	p. 46, line 7. "More evidence on human papillomavirus vaccines are documented". Should be "is documented"	We have revised this as suggested.

Commentator & Affiliation	Section	Comment	Response
TEP #4	Results	Page 50, line 31: KQ1c2: I found this section to be particularly useful and enlightening. Thank you for including it. It answered many of the questions I had developed while reading the earlier results for KQ1	Thank you
TEP #5	Results	Page 50 of 240, line 52: Would provide additional comment on imbalance in myocardial infarctions.	We have added additional detail about the imbalance in myocardial infarctions as suggested in both the Results and Discussion section.
TEP #5	Results	Page 51 of 240, line 11: Typo-"all risk estimated showing extremely [wide] confidence intervals.	Thank you, we have revised as suggested
TEP #5	Results	Page 52 of 240, lines 44-48: "Unsolicited adverse events were least common among people who are Black, most common among people who are Asian, more common among women compared to men, and very slightly more common among people aged 50 to 69 years than among those aged 70 years and older." It's not clear whether this reflects the make-up of clinical trial or that the events are proportionally lower in these populations.	We have revised this sentence for clarity.
Peer Reviewer #5	Results	p. 54-56, Table 2. It's difficult to determine which vaccine in the "Vaccine" column goes with the boxes to the right, especially when the table is several pages long.	Thank you – the AHRQ copy editor will address this comment when the tables are made 508-compliant.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Results	Page 55 of 240, lines 21-23: How can the RR for GBS be 0.67 when there were no events in the placebo group?	For consistency reasons, we have calculated the relative risk throughout; in order to calculate the confidence interval around the point estimate, a constant was added to the empty cells. Throughout, we mention in the text when no events occurred in the intervention and control group.
TEP #5	Results	The reference is unclear: "Corporation DT. Safety and Efficacy of HEPLISAV™ Hepatitis B Virus Vaccine Compared With Engerix-B® Vaccine. 2006."	We have corrected the citation
Peer Reviewer #4	Results	P. 56, Comment: PDF Document Page 83, Lines 14-15 – It says the assessment of moderate SoE for no risk of intussusception was downgraded from moderate in the previous report. Both say moderate. Also, I think there is a word missing form Line 14, it should say across studies.	We have clarified this wording and added the missing word.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Results	Page 56 of 240, lines 18-20: Table states no studies for optic neuritis, but then says “one study found no increased risk.” This occurs frequently in multiple tables. Would add a footnote to explain what is included in each column.	We have revised the column headers of the tables to make this clearer. The third column lists studies that contribute to the RR. The fourth column contains the RR, as well as other studies that were considered when grading the strength of evidence. If an RR could not be generated, then the fourth column would only list these other studies.
Peer Reviewer #3	Results: KQ2	15. Page 56: Combination vaccines, isn’t there data from clinical trials regarding the safety of the DTaP-HepB-IPV vaccine?	As this vaccine was released in 2002 and available both at the time of the prior AHRQ 2014 report and IOM report, we did not review literature outside of the updated search period for this report. There were no clinical trials for this vaccine since 2014. This is clarified in the Appendix Methods.
TEP #3	Results: KQ2	[Comment in pdf file on “Rotavirus vaccine: No evidence of increased risk of intussusception across (moderate SoE [downgraded from moderate from prior report when combining all available trials], p. 56]: typo	Thank you, we have revised the text.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results: KQ2	16. Page 56: Combination vaccines, my understanding is that the finding that MMRV vaccines can cause febrile seizures is based upon strong scientific evidence.	Thank you for noting this. Our assessment is based on the studies reviewed in the last report and the search update since the last report. We acknowledge in the discussion that CDC recommends guidance for parents around the decision to give MMR-V specifically because of the concern for febrile seizures.
Peer Reviewer #3	Results: KQ2	17. Page 58: For clarity, consider separating out the discussion of the safety of hepatitis A vaccines from that of hepatitis B vaccines.	We agree and have revised the documentation.
Peer Reviewer #5	Results	p. 59-65, Table 4. Same issue as Table 2. Some pages have no content in the "Vaccine" column. This may be fixed when the table is formatted for publication.	Yes, the copyeditor will revise the table and make tables 508 compliant.
Peer Reviewer #3	Results: KQ2	18. Page 60: What can be inferred from the safety of trivalent influenza vaccines to quadrivalent influenza vaccines, if everything else (all other vaccine constituents) remains the same? I'm not sure, but wanted to ask the question.	Trivalent influenza vaccines are no longer in use in the US (with the exception of Fluad at the time of this writing), and thus do not meet inclusion criteria for this report. We have expanded on the limitations associated with using active vaccine comparators in the Discussion section.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	P. 60, Comment: Document Page 87, under Adverse events reported for MMR in children, the first sentence of the 2nd paragraph refers to varicella vaccine rather than MMR. Not sure if this is an error typo or if the statement should be included under another heading.	We have corrected this wording.
Peer Reviewer #4	Results	P. 62, Comment: Document Page 89, Line 12 – The word event (e.g., serious adverse event) is missing. Also, Line 14, the word "as" should be "at" (Looking specifically at the newest…).	We have fixed this wording.
TEP #5	Results	Page 62 of 240, line 40: Typo- all instanced were judged…	We have fixed this typo.
TEP #3	Results: KQ2	[Comment in pdf file on "Across both reports, outcomes that were assessed in more than one study were asthma, cardiovascular events, death.." p. 63: vaccines.	We presume this refers to adding the word "vaccines" after "Studies assessed RotaTeq or Rotarix", and have revised the text accordingly.
Peer Reviewer #4	Results	P. 63, Comment: Document Page 90, Line 48 – I think the word analysis should be plural (two….analyses).	We have fixed this typo.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Results	Page 64 of 240, line 24-29: Report states: “events not vaccine-related per FDA review.” Would provide reference.	Thank you for noting the lack of a reference. We have removed the wording about FDA review of this event as it was not specifically commented on (we have retained the wording from the papers indicating that no serious adverse events, including myocardial infarction, were considered vaccine-related).
Peer Reviewer #3	Results: KQ2	19. Page 65: My understanding was that the risk of a febrile seizure following varicella vaccination was likely attributable to MMR vaccine given on the same day; can the authors disentangle the effect of varicella alone in the referenced manuscript (reference 110)?	Thank you for highlighting this. The authors of this paper believe that the risk observed after varicella vaccination is likely due to MMR being administered on the same day in most cases. We now note this in the results section as the effect cannot be disentangled.
Peer Reviewer #3	Results: KQ2	20. Page 66: Weren’t there pre-licensure clinical trials supporting the safety of DTaP-HepB-IPV vaccines? Similarly, weren’t there results from pre-licensure trials of DTaP-IPV-Hib?	As this vaccine was released in 2002 and 2003 respectively and available both at the time of the prior AHRQ 2014 report and IOM report, we did not review literature outside of the updated search period for this report. There were no clinical trials for this vaccine since 2014.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results: KQ2	21. Page 66: With respect to reference 111 (and this comment also applies to other safety studies cited in this review), my understanding is that risk interval designs produce results that have a strength of evidence and internal validity similar to that of other observational designs (such as case-control or cohort). The safety findings from reference 111 are described, but then excluded because "they were not assessed with a comparator." But my understanding is that a comparator is present, a different observation interval within the same individual.	In the instance of this particular study, there was no elevated risk detected but without any sort of comparator, including to an exposure window. Because of this, the authors did not further analyze these outcomes in the self-controlled risk interval design and there was no comparator. However, in general, studies of self-controlled design are included in our report, and the comparator is the different observation interval within the same individual. We cannot combine results from such designs into our RR analyses unless the study provides both a numerator of the subjects who experienced the adverse event and a denominator of subjects in each arm. In such studies, typically the denominator was person-days, which made it impossible to combine numerically. However, we still include these studies in our strength of evidence assessment.
Peer Reviewer #4	Results	P. 66, Comment: Document Page 93, Line 23 – I think the word "as" is missing (…such as an independent assessment…).	We have fixed this typo.
Peer Reviewer #4	Results	P. 67, Comment: Document Page 94, Lines 33-37 – The same statement appears to be repeated twice.	We have fixed this in the report.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Results: KQ2	[Comment in pdf file on "However, one study129 reported an increased risk of febrile ^ during the 7-10 days following MMR-V compared to MMR and varicella vaccine given separately (RR 1.98; CI 1.43, 2.73) but the study did not provide data that could be combined with the above trial for additional analyses." P. 69]: Comment: seizures	We have inserted the missing word "seizures".
Peer Reviewer #4	Results	P. 69, Comment: Document Page 96, Line 25 – The word "seizures" is missing after febrile.	We have inserted the missing word "seizures".
Peer Reviewer #4	Results	P. 70, Comment: Document Page 97, Line 47 – Remove the word "were".	We have revised as suggested.
Peer Reviewer #4	Results	P. 71, Comment: Document Page 98, Line 25 – The word "wide" is missing.	We have revised as suggested.
Peer Reviewer #4	Results	Organize all findings under one heading for each vaccines? Repetitive	Thank you for this suggestion. Given the required structure of the AHRQ EPC reports, we have retained the current structure to follow the Key Questions.
Peer Reviewer #5	Results	p. 73, line 3. "was evidence was graded". Delete first use of "was"	We have fixed this in the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results: KQ2	22. Page 81: Table 13a, the finding that hepatitis A vaccine was associated with ITP was based on one (or two?) exposed cases, I'm surprised that was considered moderate strength of evidence.	This finding is based entirely on the prior report, which used a combination of empirical studies and finding from the IOM report (which in turn reviewed epidemiologic and mechanistic evidence). We have added more context to help readers interpret the importance of this finding, as it was limited to children aged 7 to 17 years.
TEP #3	Results: KQ2	[Comment in pdf file on "However, all of the evidence review was for HPV2 and HPV4, which are no longer in use." P. 84]: Comment: Although no longer in use in the US HPV2 and HPV4 are widely used in other countries. Several large observational studies have been published since 2014, especially pertaining to autoimmune and neurological outcomes. These can help inform the safety evidence for HPV vaccines, including HPV9. See for example: Grimaldi-Bensouda L. J Autoimmun 2017 Sridhar G. Hum Vaccin Immunother 2017 Miranda S. Vaccine 2017 Hviid A. J Intern Med 2018 Andrews NJ. Vaccine 2017 Gee J. Vaccine 2017	These vaccines were outside the scope of the report as they are no longer in use in the US. We have added the text noting the restriction to current US recommended as a limitation to the Discussion.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Results	Page 86 of 240, line 15-21: It seems better to study pregnancy outcomes in the context of adult vaccinations, as the offspring did not technically receive the vaccine.	These studies were of adults and children together, and as noted in earlier in the report, we include such studies under KQ2 (vaccines in children). The subjects of interest are the people who received the vaccines (in this case children or adults in the study who became pregnant).
TEP #5	Results	Page 87 of 240, line 49-50: Typo- In one self-controlled case series of children who received varicella [this result is for MMR] vaccine, there was increased risk of seizures following vaccination at 12 to 15 months (IRR 2.65; CI 1.99, 3.55) as well as at 16 to 23 months (IRR 6.53; CI 3.15, 13.53) but did not provide sufficient detail for further analyses.	We have revised the text.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Results	Page 88 of 240, line 49-56: If there were no cases in either arm, how can the RR be 0.76? Also, that reference does not include asthma, diabetes, or seizures- can you identify the source of the numbers on those specific Aes? If it is from data on clinicaltrials,gov, would reference the website with a link.	For consistency reasons, we have calculated the relative risk throughout; in order to calculate the confidence interval around the point estimate, a constant was added to the empty cells. Throughout, we mention in the text when no events occurred in the intervention and control group. The source for the numbers for asthma, diabetes, and seizures do come from the entry on clinicaltrials.gov. The EPC's practice is to cite the main paper, but we always checked clinicaltrials.gov for additional data. The clinicaltrials.gov entry is referenced in the evidence tables.
TEP #5	Results	Page 90 of 240, line 21-23: You cite reference 50 for "Another pre-post study50 reported an age-adjusted risk estimate for Kawasaki disease of 1.07 (CI 0.70, 1.63) in a self-controlled case series and 0.97 (CI 0.79, 1.19) compared to an unvaccinated cohort." I think this is supposed to be reference 56.	Thank you for noting this. We have now ensured that we point to the correct reference.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results: KQ2	23. Page 91: It appears that the strength of evidence regarding MMR vaccine and febrile seizures was downgraded due to one study reporting no evidence of increased risk. Was that a study of febrile seizures 0-1 day following vaccination? If so, that doesn't refute a finding that MMR vaccine can cause febrile seizures 7-10 days following vaccination (because of timing of replication of a live virus vaccine).	We re-reviewed all evidence around MMR and febrile seizures. We considered this study to be insufficient evidence. This, along with insufficient evidence for increased risk of seizures based on studies added from our search update (presumed largely to be primarily febrile seizures), means that we no longer downgrade the finding from the prior 2014 report. The finding across both reports for the risk of MMR and febrile seizures is high SoE for increased risk.
TEP #5	Results	Page 98 of 240, line 25-26: Typo: with low precision given the extremely [wide] confidence intervals	We have fixed this typo.

Commentator & Affiliation	Section	Comment	Response
TEP #6	Results	P98 Would check search on association between PCV-13 and febrile seizures. Some papers suggest an association but not consistent with table that notes: “Moderate SoE for no evidence of increased risk”	Thank you for noting this. In our update search we identified one new study that suggested an increased risk of febrile seizures (Baker, M. A., et al. The risk of febrile seizures following influenza and 13-valent pneumococcal conjugate vaccines. *Vaccine* 2020. 38:2166-2171). The other studies already identified in the current report do not suggest an increased risk of febrile seizures. We have expanded our discussion of PCV13 and febrile seizures in the text. In addition, we re-reviewed all evidence and downgraded the strength of evidence from moderate to low SoE of increased risk (rather than moderate SoE of no increased risk). Thus, across the prior report and this update, there is low SoE of increased risk of febrile seizures following PCV13.
Peer Reviewer #5	Results	p. 99, line 48. I don’t understand this sentence: “A number of other studies examined risk factors for effects of other vaccines.”	We have revised this sentence to be clearer.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results: KQ2	24. Page 102: I would recommend not combining the study regarding safety of rotavirus vaccine in premature infants (reference 66 I believe) with other studies with respect to cardiovascular events. Bradycardia in a premature infant is fundamentally different from other types of cardiovascular events (in fact, it is more a neurologic than a cardiovascular event in pathophysiology, I believe).	Thank you for this comment – for now we will keep it with cardiovascular events, but we have now added text to interpret it for the reader both directly in the table, as well as in the main Results text. This is text is intended to ensure that it is clear there is heterogeneity in the events reported, and that the effect estimate is driven by the study. We also note that bradycardia is likely more neurologic in nature than strictly cardiovascular.
TEP #5	Results	Page 102 of 240, Table 11: Multiple rows with 0 studies but then studies are described in the adjacent column.	We have revised the column headers of the tables to make this clearer. The third column lists studies that contribute to the RR. The fourth column contains the RR, as well as other studies that were considered when grading the strength of evidence. If an RR could not be generated, then the fourth column would only list these other studies.
Peer Reviewer #5	Results	p. 110 Table 14. Is there a reason why “pre-term labor” and “spontaneous abortion” are included in the section for vaccines in children? Are these pregnant teens?	Yes – these are studies of children, or children and adults, where the subject became pregnant.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Results: KQ2	25. Page 113: I disagree with the assessment there is "insufficient evidence" to conclude MMRV can cause febrile seizures.	Thank you for noting this. Our assessment is based on the studies reviewed in the last report and the search update since the last report. We acknowledge in the discussion that CDC recommends guidance for parents around the decision to give MMR-V specifically because of the concern for febrile seizures.
TEP #5	Results	Page 113 of 240, Table 16: For autism, Kawasaki disease, seizures (non-febrile), and cardiovascular events, Greenberg 2014 (102) is cited, but there is no mention of autism in the study report or supplemental information. Would verify source.	The data for autism comes from the clinical trial record for NCT01240746; this trial is the basis of the paper.
TEP #3	Results: KQ3	[Comment in pdf file on "Another was material seizures, with an RR of 2.07 (CI 0.12, 32.41), due to seizures occurring in one subject in each of the intervention and control groups." P. 117]: Comment: maternal?	We have fixed this error (should read "maternal").
Peer Reviewer #4	Results	P. 126, Comment: Document Page 153, Line 33 – The word "new" should be removed.	We have revised the text.
Peer Reviewer #5	Results	p. 145, line 53. "results was not statistically significant". Should be "results were..."	We have changed the wording as suggested.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Results	Page 145 of 240, lines 16-25: Early Tdap was associated with significantly increased risk of premature rupture of membranes (aRR 1.08; CI 1.02, 1.15), but optimally timed Tdap was not (aRR 1.03; CI 1.00, 1.06). Optimally timed Tdap was associated with significantly lower risk of preeclampsia/eclampsia (aHR 0.96: 0.94, 0.99), but early Tdap was not (aHR 1.05; CI 0.99, 1.12). Overall, early administration of Tdap was safe except for the slightly increased risk of premature rupture of membranes. However, it is possible that the study failed to adjust for all residual confounding, and that receipt of the Tdap vaccine prior to the recommended timing might have been a proxy for atypical care or anticipated premature birth. The study provides an aHR which is slightly different than what is in the paper. It's unclear why this finding, which is a very small difference, results in a statement of "safe except for." Is there something particular about this finding that is concerning? The biologically plausible mechanism whereby temporal distance is more associated with a mechanical rupture of membranes than temporal proximity is unclear.	We have revised the text to avoid the use of the wording "safe except for", and also expanded the discussion in this portion of the report to note that the biological plausibility of this mechanism (and particularly the temporal aspect) is unclear.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Results	Page 146 of 240, lines 15-20: You don't describe the vaccine you are talking about (TdaP based on the references)	Thank you – we have revised the text to clarify that we are discussing Tdap.
TEP #5	Results	Page 148 of 240, Table 23: How is the RR 1.52 for maternal deaths when none were reported in the treatment group?	We have added more detail to this effect in the text (no deaths occurred in the intervention groups but one death occurred in the control group and the RR was inflated due to an imbalance in the sample sizes after adding a constant for computational purposes).
Peer Reviewer #5	Results	p. 156, line 43, "no difference were seen" should be "no differences were seen"	We have changed the wording as suggested.
TEP #5	Results	Page 156 of 240, lines 10-11: "As noted above for rotavirus vaccine, risk among special populations such as extremely low-birth-weight infants may warrant further study." However, there is no discussion of ELBW in the rotavirus section.	We have removed the beginning of this sentence as it is correct that we do not discuss ELBW in the rotavirus section.

Commentator & Affiliation	Section	Comment	Response
TEP #5	Results	Page 156 of 240, lines 5-10: Cites reference 82 and states: One pre-post study of extremely low birth-weight infants comparing risk periods before and after different vaccines found an increased risk of sepsis and need for respiratory support after DTaP, IPV, Hib, Hep B, DTaP-IPV-Hib combination vaccine, and DTaP-HPV-Hep B combination vaccine, and increased risk of intubation after DTaP, IPV, Hib, and DTaP-HPV-Hep B combination vaccine. However, this reference addressed the increased risk of sepsis evaluations, not sepsis.	Thank you for noting this – we agree that this reference addressed sepsis evaluations, and we have revised the wording throughout to reflect this.
TEP #5	Results	Page 162 of 240, lines 10-13: Would verify these studies evaluated sepsis and not sepsis evaluations.	Thank you for noting this. Both studies were of sepsis evaluations - we have revised the text to note that these were sepsis evaluations, not episodes of sepsis.
Peer Reviewer #3	Discussion/Conclusion	As noted in my general comments, the discussion is good, but there are several points the authors could consider adding or expanding.	Thank you. We have responded to those specific comments.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Discussion/Conclusion	The implications of the findings are clearly stated. The strengths and limitations of the review and of the evidence base are presented clearly. I am not aware of any omitted studies. The future research section is clear and easily understood, but the section might be titled to more explicitly as something like “Areas of Future Research” or “Research Gaps”, rather than “Implications for Clinical Practice, Education, Research, or Health Policy” which seems a little broader than what the section conveys.	The heading for this section is standard for all AHRQ EPC reports, thus we have left it as is.
Peer Reviewer #5	Discussion/Conclusions	The discussion of the strengths and limitations of the research was well written and clear. The findings in relation to the decisional dilemmas section helped to define the changes since the last report and what might be of most interest to people who follow this area of research. There were several suggestions for areas where more research would be particularly beneficial.	Thank you
Peer Reviewer #6	Discussion/Conclusion	The implications of the major findings are clearly stated in the body of the document as well as the abstract and evidence summary. Additional findings about safety data on infants could be added to the abstract and evidence summary.	Given that the abstract and executive summary are already at or above the word limit, we have not added more text.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Discussion/Conclusion	The limitations of studies and the review are described adequately, however the population was studied in aggregate and there were few details on subgroup analyses. This was a limitation of the studies in the review. There were some inferences made by race and ethnicity. It may be helpful to add a sentence or two about race as a social construct that may more related to social determinants of health. Another limitation that could have been discussed in more detail is that all immunizations may not have been captured particularly if they occurred outside of the medical home and/or if the state doesn't have a vaccine registry. Of note statewide registries for adults are much less common than they are for children. Adults are also more likely to get their vaccines at alternate places such as at their workplace or at pharmacies.	Thank you – we have added some text to the Discussion about capturing all immunizations and thus adverse events.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Discussion/Conclusion	I do not recognize the omission of any important literature. The future research section is clear and easily translated into new research. This may be out of the scope for this project, however, some mention of the future of vaccination research related to perceived safety issues could be increasing due to vaccine hesitancy, the impact of a COVID vaccine, and prevailing health inequities.	We thank the reviewer for this comment, and have added some text to the discussion on the impact of COVID-19 vaccine and other new vaccine technologies, as well as ensuring that vaccine safety is viewed through the lens of health equity.
Peer Reviewer #6	Discussion/Conclusion	The report's conclusions are relevant to policy and practice decisions. While the conclusions of this report on the overall and specific safety of vaccines used for routine immunizations in the U.S. are the same as previous reports, that vaccines are safe, the new information on new studies and new vaccines developed since the last report is a significant new contribution.	Thank you
TEP #1	Discussion/Conclusion	Yes, the implications of the major findings are clearly stated and the review identified limitations in the current knowledge and identify areas for further investigations. I don't think the review omitted any important literature.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP #2	Discussion/Conclusion	The implications of the major findings clearly stated and the limitations of the review are well described adequately. A key point is that safety evaluations include rare events but in some cases, there is not enough evidence to associate or refute them as being related to a particular vaccine. It does not appear that any important literature has been overlooked. There is no section describing as how these finding could be translated into new research. It is suggested that this type of review be extended to safety considerations in the 65 and older population where adverse events are more likely to affect the performance of activities of daily living.	Thank you for this suggestion. We have added this point to the Implications for Clinical Practice, Education, Research, or Health Policy section.
TEP #3	Discussion/Conclusion	The implications, including the limitations, are well considered and clearly state. The future research section is clear and reasonable.	Thank you
TEP #5	Discussion/Conclusions	See relevant comments above.	No response needed.
Peer Reviewer #2	Discussion/Conclusion: Vaccines for adults	[Comment on "Many are indicated primarily or exclusively for older adults, who may be at increased risk for adverse events from vaccines." P. 125] Comment: Page 152, line 27, what increased risk from vaccines?	We have deleted this wording given the ambiguity.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Discussion/Conclusion	[Comment in pdf file on "Based on both reports consistently showing lower risk of autism, taken together with the findings from the prior 2014 report the SoE remains high for no evidence of increased risk of autism following MMR." P. 127]: Comment: I believe both studies examined risk among children with older siblings with autism.	This is correct, and we have revised the text to reflect that both studies comment on the risk among children with siblings with autism.
Peer Reviewer #2	Discussion/Conclusion: HPV9	[Comment on "While the higher rate of spontaneous abortion in the intervention group is still consistent with the background rate of the event,951 further surveillance of this specific outcome may be helpful." P. 128] Comment: Page 155, line 37, should note, HPV vaccine is not indicated if pregnant.	We have noted this as suggested earlier in the paragraph.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Discussion/Conclusion: HPV9	[Comment in pdf file on "However, one analysis of long-term follow-up data from Black adolescents and adults (aged 16-24 years) enrolled in two trials of HPV4 showed a possible increased risk of miscarriage of pregnancies within 4 years of vaccination; however this formulation of the vaccine is no longer in use. The current report examines studies of HPV9 only, as this is the currently available vaccine, and raises no new concerns around the safety of HPV9." P. 128]: Comment: See previous comment about updating the evidence with more recent studies of HPV4 and HPV2 safety.	These vaccines were outside the scope of the report as they are no longer in use in the US. We have added the text noting the restriction to current US recommended as a limitation to the Discussion.
TEP #3	Discussion/Conclusion: Vaccines for pregnant women	[Comment in pdf file on "For this update, we identified no studies in pregnant women that assessed the effects of hepatitis B vaccines, IIV or RIV, which is an area that could be targeted for further research." P. 129]: Comment: Specify IIV4.	We have clarified this as suggested.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Discussion/Conclusion	P. 130, Comment: Document Page 157, Line 27 – You did not really define safety anywhere in the document. I think what you mean is that you included all reported adverse events regardless of whether they were attributed to the vaccine. Suggest rewording to remove mention of the definition of safety.	We define safety in the Introduction to the report ("The concept of "safety" in medical literature is measured and described as the number, type, and severity of adverse events reported by study participants.)
Peer Reviewer #4	Discussion/Conclusion	P. 130, Comment: Document Page 157, Line 32 – The last word "we" should be capitalized	We have made this change.
Peer Reviewer #3	Results: Strengths and Limitations	26. Page 130: A good summary of the strengths and limitations, thanks!	Thank you
TEP #3	Discussion/Conclusion: Strength of the evidence base	[Comment in pdf file on "In the United States, the CDC's Vaccine Safety Datalink (VSD) uses data obtained through such systems at nine large health care organizations, enabling high-quality studies using methodologies such as self-controlled risk intervals analyses" p. 132] Comment: Currently 8	We have changed the wording as suggested.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Discussion/Conclusion: Applicability	[Comment on "Most vaccine interventions were tested either against placebo, against the next best vaccine (e.g., MenACWY-TT versus MenACWY-CRM), or against the vaccine the newer formulation was replacing (e.g., HPV9 versus HPV4)." P. 133] Comment: Page 160, line 42, instead of next best vaccine suggest "closest comparator".	We have changed the wording as suggested.
Peer Reviewer #2	Discussion/Conclusion: Implications for Clinical Practice, Education, Research, or Health Policy	[Comment on "It is important to note that this report is not intended to provide direct guidance to health care providers, but rather to assess the current state of knowledge about vaccine safety and to identify research gaps for future exploration." P. 134] Comment: Page 161, line 24, there has no mention of biological plausibility. In view of huge number of vaccines administered daily, any event will occur by chance after a vaccine. There should be some consideration of plausibility. For example, mention of rotavirus vaccine and need for respiratory support is not biologically plausible.	We agree that events can occur by change after a vaccine, which is why we focused on studies with a comparator group. In addition, we also conferred with our technical expert panel to ensure that we chose a relevant and plausible set of key adverse events *a priori* to allow us to synthesize findings across studies. We also provide context and interpretation where appropriate for findings.

Commentator & Affiliation	Section	Comment	Response
TEP #3	Discussion/Conclusion: Implications for Clinical Practice, Education, Research, or Health Policy	[Comment in pdf file on "While studies of Tdap in pregnancy have greatly increased, epidemiological studies should track and report any adverse events in pregnant women or their offspring after influenza and HepB vaccine as well" p. 135] Comment: There have been many studies following H1N1 and IIV3.	Neither H1N1 nor IIV3 are reviewed in this report as they are no longer in use. We have clarified our statement by adding the word "quadrivalent" prior to influenza".
TEP #6	Discussion/Conclusion	P 135 would consider emphasizing need for post-market surveillance considering rare nature of many of the adverse events. Future research is easily translated into new research.	We highlight the need for post-marketing surveillance in the Discussion section, and have added some wording to emphasize this further (in the paragraph immediately prior to the Conclusion).
TEP #4	Discussion/Conclusion	Page 155, Line 12-15: This sentence read as confusing for me. The results suggested insufficient evidence of increased risk of febrile seizure with MMR-V. The Sentence "...The CDC recommends that providers who offer the combination MMR-V vaccine clearly communicate to parents and caregivers this increased risk," suggests that the increased risk is known. While I understand that it is the CDC recommendation, perhaps reword to make clear that this area is still under investigation.	We have reworded this sentence to indicate that the level of risk is uncertain.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Discussion/Conclusion: Limitations of the review	[Comment on "Although we were considering only vaccines approved for use in the United States, it is possible relevant epidemiological studies have been published in non-English journals.", p. 131] Comment: Page 158, line 5, is this referring to studies done in US but written in another language	This refers to studies performed outside of the US on a vaccine approved for routine use in the US, that are in another language.
TEP #4	Discussion/Conclusions	Page 160, Line 34: Would recommend removing the term "pregnant women" throughout the report and replacing with "pregnant persons" or "pregnant individuals." Gender is a spectrum and individuals who identify as men may have a uterus and choose to reproduce or may become pregnant. Please use gender inclusive language throughout the report.	Thank you for this suggested wording. Given the wording of the Key Questions (which refer to pregnant women), and the fact that all studies of pregnant women did not distinguish between gender and sex (all were either 100% women or 100% female), we have retained this wording. However, we have added some text to the Methods explaining the rationale and acknowledging that individuals who identify as other genders may become pregnant.
Peer Reviewer #3	Clarity and Usability	As noted above, low SoE of no evidence of increased risk is not the most clear phrasing!	We appreciate this comment and acknowledge that this is a complex phrasing. However, we feel strongly that we should continue to use the conservative and correct phrasing currently in the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Clarity and Usability	I found some of the information presented a bit repetitive. Perhaps consider organizing all of the information for each vaccine in its own section with subheadings for the adverse events that were collected, those that were reported, and those associated by number and severity, statistical significance, and risk factors. So that all of the information about a single vaccine I presented in one place and doesn't have to be repeated in another section.	We appreciate this suggestion but have opted to retain the current structure given that it follows the Key Questions. We hope that the summary tables with color-coded symbols and text for each vaccine will be helpful to the reader.
Peer Reviewer #5	Clarity and Usability	While I think the information here is very valuable, it is difficult to read through all of the data and statistics, especially because of the length of the report. The way the report is organized, a reader can go through particular infectious diseases in detail rather than reading the report from start to finish and expecting to stay focused on all of the data for all vaccines at once.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP #2	Clarity and Usability	The tables are very helpful. This is a lengthy report but it is well indexed to assist the reader in identifying the specific sections of interest. The results and conclusions are very helpful. The reader can easily find these and then go to the tables if additional details are needed.	Thank you
TEP #6	Clarity and Usability	Could consider a concise summary statement at the end of each section.	AHRQ EPC reports use key points and an executive summary. We provide brief tables and statements after each vaccine.
Public Reviewer #1, Anonymous	Evidence summary	Well-written.	Thank you

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	Evidence summary	Knowing one of the aims is assist a broad base of decision makers related to vaccine use, more clarification is needed in the grading of the strength of the body of evidence as it relates to decisions making. For example, in many examples in the documents it is stated: No evidence of risk but is also associated with low SoE. The level of certainty is not there to support strength of association based on SoE for the patient/HCP to make a decision. More information on the process of how decisions are informed specifically when evidence of risk does not seem to match SoE. Example: No evidence of an increased risk of death (low SoE).	This report reviews the evidence and provides a level of the strength of evidence for each findings. The strength of evidence communicates our confidence in the findings, and we have clarified this in the Executive Summary and Methods sections of the report. However, linking the strength of evidence to decision making is out of scope for this report.
Public Reviewer #1, Anonymous	Methods	Appropriate.	Thank you
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	Results	Please improve the readability on Figure 6, page 15.	We have improved the readability, and the AHRQ copy editor will also ensure that it is readable.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	Results	We appreciate the key points throughout the document.	Thank you
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	Results	On page 84, Table 14a, Safety of HPV9 in Children: findings in table note [and] quot;High: Pain at injection site [and] quot;. Pain is not mentioned in current report findings or synthesis. We would suggest including pain on report findings or synthesis.	We pre-specified key adverse events of interest with our technical expert panel. As with our last report, with their input we did not report on pain (or other non-serious or non-severe outcomes such as fever, redness, swelling). In the evidence tables, we do report on pain and other symptoms if rated as severe.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	Results	On page 115: [and] quot;Studies collected adverse events for pregnant women and their infants... [and] quot;. We suggest including the term fetus here. Additionally, various terms are used when reporting infant outcomes, including infant, neonate, and neonatal. Consistency in terms is suggested	We have added the term "fetus" here as suggested. We have also reviewed the report to ensure we are consistent in our use of the terms infant, neonatal, and neonate.
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	Results	Define [and] quot;peri- and post-partum [and] quot; for the reader to have an understanding of the time frame.	We have removed the terms peri- and post-partum in making other revisions.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	Results	On page 117, 8th line from the bottom – should this read maternal seizures versus the [and] quot;material seizures [and] quot; that is in the present version?	This was a typo and we have revised.
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	Results	On page 117, 4th line from the bottom reads [and] quot;Given the absence of deaths in the intervention group, this finding is not only statistically insignificant, but also of no concern at this time. [and] quot; While we appreciate the strength of statistical significance, we suggest edits to this sentence as every maternal death is of concern.	We have removed this sentence.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	Discussion	We would suggest addressing including the process of how patient/HCP reach a decision. We would also suggest demonstrating an increase in strength of association based on SoE, and including more information on how this informs decisions when the evidence of risk does not match SoE.	We have added more information on the difference between strength of evidence and evidence of increased risk of adverse events. Addressing the process of how patients and healthcare providers make a decision is out of scope for this report.
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	References	Please include the recent report from the Maternal Immunization Task Force (2020)	Thank you – we have added this reference.
Public Reviewer #1, Anonymous	General	Comprehensive and useful report. Would be curious to know if there were any data on the safety of Heplisav if inadvertently administered to a pregnant woman, although I realize that may be beyond the scope of the report since Heplisav is not recommended for use during pregnancy.	Thank you for your interest in this report. Examining the safety of HEPLISAV-B® in pregnant women would be beyond the scope of the report. Based on our inclusion/exclusion criteria, such a study would not have be included for review.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	General	Thank you for providing an in-depth report.	Thank you

Public Reviewer #3, Lewis Hsu, University of Illinois at Chicago	General	I am a practicing clinician and also deeply engaged with community-based organizations for people with sickle cell disease and other blood disorders. I applaud this systematic review, BUT .... I fear that this well-done systematic review paper will be a mere academic exercise with no practical impact. These messages about low rates of adverse events and a significant benefit of routine immunizations are simply NOT getting through to a large segment of the general public. About 25% of my patients' families (children with chronic illness) in the past month refused influenza vaccine because they think that the risk/benefit ratio is not worthwhile. They cite the opinions of neighbors, relatives, TV talk shows, social media, etc. about the horrible side effects and lack of efficacy of influenza vaccines and only get the ones that we say are required for school or required for their chronic disease. Please invest in packaging this scientific paper for a publicity campaign of dissemination in lay language and infographics and memorable stories, to use social media, popular media like talk shows, prime-time commercials, and trusted community leaders in minority groups. One interesting approach by a group	Thank you. We agree that this review addresses only one aspect of information needed to inform strategies to increase immunization rates.

Commentator & Affiliation	Section	Comment	Response
		at CDC or HRSA addressed faith-based groups by drawing a parallel between divine provision of an ark to save Noah and his family and God providing scientists and doctors with skills to develop vaccines to save people. Without changing the general public perception of routine immunizations, the public health potential of vaccines is hobbled. - Lewis Hsu, MD, PhD, Pediatric Hematology-Oncology, Chicago.	

Public Reviewer #4, Phyllis Arthur, Biotechnology Innovation Organization (BIO)	General	BIO supports the examination of vaccine safety data by the Department of Health and Human Services (HHS) Agency for Health Research and Quality (AHRQ) and Office of Infectious Disease and HIV/AIDS Policy (OIDP). BIO is the worlds largest trade association representing the biotechnology industry across human health, food and agriculture, and industrial and environmental applications. BIOs members include vaccine developers and manufacturers who work closely with myriad stakeholders, including the public health and advocacy communities, to support policies that help ensure access to innovative and life-saving medicines and vaccines for all individuals. No medical intervention is without risk. While the vast benefits of vaccines greatly outweigh the risks, it is important to study potential adverse events. BIO appreciates the evidence-based and transparent process which AHRQ has undertaken in preparing the report, Safety of Vaccines Used for Routine Immunization in the United States: An Update. The fact that no new safety concerns were identified through the literature review is a testament to the high standards by which vaccines are evaluated and the effectiveness of	Thank you

Commentator & Affiliation	Section	Comment	Response
		systems for continuous safety monitoring for vaccines used across the lifespan.BIO and our members thank AHRQ and OIDP for the time and resources dedicated to reviewing vaccine safety. We hope that transparent evaluations such as this report will bolster confidence in the safety of vaccines used in the United States.	

Public Reviewer #5, Patricia D'Antonio, The Gerontological Society of America	General	On behalf of The Gerontological Society of America (GSA), thank you for the AHRQ Evidence-based Practice Centers (EPC) work to help healthcare decision makers patients and clinicians, health system leaders, and policy makers, among others make well-informed decisions and thereby improve the quality of healthcare services. GSA honors aging across the lifespan and is the nation [and] #039;s oldest and largest interdisciplinary organization devoted to research, education, and practice in the field of aging. The principal mission of the Society and its 5,400+ members is to advance the study of aging and disseminate information among scientists, decision makers, and the public. GSA has a long-standing commitment to improving adult immunization rates and expanding the number of professionals around older adults who support vaccination. GSA hosts the National Adult Vaccination Program (NAVP), started in 2011 with the purpose of affecting policy and improving adult immunization rates. To help achieve its goals, the NAVP convened a workgroup of vaccine and policy experts to provide strategic recommendations and direction that focus on improving adult immunization	Thank you

Commentator & Affiliation	Section	Comment	Response
		rates and creating sustainable change. We routinely bring together stakeholders to discuss issues of importance and make recommendations to address the specific needs of older adults. We have done this with influenza vaccination, raising vaccination rates in long-term care facilities, creating the Immunization Champions, Advocates, and Mentors Program, and we are currently working on understanding shared clinical decision-making best practices. Our workgroup focused on the safety of vaccines in adults (KQ1). We agree with the conclusions of the reviewers that there is no new evidence of increased risk with varied strength of evidence or insufficient evidence for key adverse events, including for newer vaccines such as recombinant influenza vaccine, adjuvanted inactivated influenza vaccine, recombinant adjuvanted zoster vaccine, and hepatitis B vaccine with novel immunostimulatory adjuvant. We thank them for their comprehensive effort to review the evidence to ensure continued safety of vaccines.	

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #1, Anonymous	Does this report describe both the problem and the evidence in a way that you could understand?	Yes, well-written.	Thank you
Public Reviewer #5, Patricia D'Antonio, The Gerontological Society of America	Does this report describe both the problem and the evidence in a way that you could understand?	Yes. We find the report to be comprehensive and written in a way that is understandable.	Thank you
Public Reviewer #6, John Kennedy, AMGA	Does this report describe both the problem and the evidence in a way that you could understand?	This report will prove to be a useful resource for AMGA [and] #039;s high performing medical groups and health systems seeking education on vaccine safety and for those whose patients are demonstrating vaccine hesitancy.	Thank you
Public Reviewer #1, Anonymous	Does this report describe both the problem and the evidence in a way that you could understand	Yes	Thank you

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #5, Patricia D'Antonio, The Gerontological Society of America	Does this report describe both the problem and the evidence in a way that you could understand?	Yes. We find the report to be comprehensive and written in a way that is understandable.	Thank you
Public Reviewer #2, Jean Salera-Vieira, Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN)	Could you find and understand the results and conclusions?	Yes. Please note: This is an organizational response from AWHONN. For any questions, please contact Jean Salera-Vieira, Director of Clinical Program Development, at jsaleravieira@awhonn.org	Thank you
Public Reviewer #5, Patricia D'Antonio, The Gerontological Society of America	Could you find and understand the results and conclusions?	Yes. We find the report to be comprehensive and written in a way that is understandable.	Thank you

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #7, Maryalice Jordan-Marsh, University of Southern California (USC)	General	Thank you for this opportunity to comment. Overall, I found the review very reassuring. I strongly recommend that you add a handout for practicing clinicians that hits the high points to share with patients. In this era of anti-vaxers, it is critical that we provide support for those at the point of care. The handout should have sections specific to pregnancy, to low weight infants and highlight any warnings and advisements. For example, for low weight babies, although there are some risks to the rotatvirus vaccination, these are babies most at risk from failure to be immunized. The handout should provide relevant links for clinician use and for patient use—maybe two handouts. Thank you.	Thank you

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #8, Anonymous	General	Do not mandate vaccines! Parents have the right to informed consent! Government should not be involved in the medical decisions of our children. Also, we need safety and efficacy studies – for short and long term risk. More than ever every child should be allergy tested and have a thorough wellness check prior to giving same treatment to all patients. Every persons genetics are different therefore every person deserves healthcare that is right for them. It is the most inhumane act to vaccinate a newborn baby. Parents will no longer stand for this. Please consider this groups plea to save our children.	This report reviews the safety of vaccines only, and does not comment on mandating vaccines.
Public Reviewer #9, Sanofi Pasteur	Evidence Summary	1. Evidence Summary: KQ1 – Safety of vaccines in adults, spontaneous abortion is listed for Hepatitis B and Influenza in Table ES1. Strength of Evidence (SoE) for safety of vaccines in adults. However, it is not listed in Table ES3. SoE for safety of vaccines in pregnant women. It seems strange and better justify why report this way.	Thank you for noting this. As these studies were not of pregnant women per se (and did not separate out this sub-group), they are included under studies of adults. We have now revised the text to note the rationale for reporting in this way.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #9, Sanofi Pasteur	Methods	2. KQ2 – Safety of vaccines in children and adolescents: “children” and “children and adolescents” seem exchangeable as both terms are widely used throughout this review. I would suggest using one term consistently, for example, “children (including adolescents)”.	We have reviewed the report and modified the wording to ensure that we are consistent throughout (using the term “children” throughout, and noting up front in the report that this term includes adolescents).
Public Reviewer #9, Sanofi Pasteur	Methods	3. My impression is that studies worldwide, not only the studies conducted in the US, are included in this review, if the studies were conducted in human participants for whom the vaccines are recommended in the US. If so, better clarify in Methods – Review Approach.	This assumption is correct, and we have clarified this in the Methods – Study Selection to indicate that non-U.S. English language studies were included if the vaccines studied were included in the CDC immunization schedules and the formulations were approved for use in the U.S.
Public Reviewer #9, Sanofi Pasteur	Methods	4. In the footnote of Figure 1. Analytic framework for safety of vaccines used for routine immunization in the United States (page 9), it states that “This report is focused on reported adverse events associated with vaccines”. Better clarify this report’s focus “adverse events associated with vaccines” in Methods section, not just put it the footnote of Figure 1.	We have clarified this by moving the text from the footnote to the first sentence of the section entitled “Analytic Framework” in the Methods section.
Public Reviewer #9, Sanofi Pasteur	Results	5. Figure 6. Critical appraisal of included studies (page 15): The font of labels for each bar is too small to read, please consider modifying this figure for better reading.	We have fixed the font of each bar so to make it easier to read.

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Public Reviewer #9, Sanofi Pasteur	Results	**Influenza** Pharmacovigilance review: Sanofi Pasteur agrees with the key findings on safety of Influenza vaccines in adults: high SoE for trivalent influenza vaccines on most frequently reported adverse events such as injection site reaction and systemic reaction (fever, myalgia, malaise). Similar observation for Quadrivalent Influenza vaccine in the most current studies, however, these studies are not published yet, thus not included in this assessment. Low SoE on cardiovascular events, asthma, seizure, strokes and deaths.	Thank you

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Public Reviewer #9, Sanofi Pasteur	Results	**Influenza** [continued] Medical Review: Reviewed AHRQ assessment report for influenza vaccines, specifically Recombinant RIV4-Flublok- Reviewed all sections following Key question 1 for adults – RIV3 was not in last report of 2014- At that time, RIV3 was lumped with all other SD egg-based vaccines. In this report, there is low strength of evidence given the small number of studies used in the review. References included Dunkle articles PSC 12 (ages >50), Dunkle PSC 16 (ages 18-49), Cowling - immunogenicity and safety only for those 65-82 yrs and the PI. Some data was categorized as insufficient evidence as no reporting on the outcomes (primarily neuro endpoints such as acute disseminated encephalomyelitis; GBS, seizures, transverse myelitis) was done. We have no concerns regarding content around Flublok (RIV4).	Thank you.

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Public Reviewer #9, Sanofi Pasteur	Results	**Meningitis** Pharmacovigilance review: The age groups are not clearly defined. It would have been adequate to further differentiate infants (e.g. from birth through 15 or 18 months as in the recommended immunization schedule from CDC) within the [children]/[adolescent] category and older adults/elderly within the [Adult] category. For example, the clinical trial they are referring to for MenQuadFi in adults was actually a study conducted in older adults and elderly.	Thank you. In order to better inform the reader, we now clearly describe the age groups in which the studies were conducted for the meningitis vaccines.
Public Reviewer #9, Sanofi Pasteur	Results	Table 1 – "Adolescent" population is not mentioned for some of the vaccines while they represent primary population recommended for routine use (HPV, MCV4…)	We have clarified that children includes adolescents up front in the report (i.e., when we use the term "children", it encompasses both children and adolescents as applicable).
Public Reviewer #9, Sanofi Pasteur	Results	AHRQ found no new evidence of increased risk for the "key" adverse events they have considered. However: It is not very clear with the criteria/factors used to support the associated strength of evidence (low, moderate…).	We have added text to the Executive Summary and the Methods of the report to make clear the different levels of strength of evidence.

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Public Reviewer #9, Sanofi Pasteur	Results	Also; for MenQuadFi in particular, and I assume for the other vaccines in general, they calculated Relative Risks for the “key AEs” using numbers (#cases, rates,…) from clinical trials that were not designed/powered to assess/characterize the “key” AEs. Is this really appropriate?	Clinical trials are typically powered to assess effectiveness rather than safety or a specific adverse event, with rare exceptions. We recognize that the rarity of key adverse events means that many, if not most, trials are underpowered to detect their presence, which makes combining data across trials all the more important.
Public Reviewer #9, Sanofi Pasteur	Results	MenQuadfi References 70 and 71 appear to be duplicates	We used two different comparisons from the same study, and thus included the reference twice (one labeled as "a" and the other as "b"
Public Reviewer #9, Sanofi Pasteur	General	Also noted AHRQ is not using “TM” or “®” for any of the registered vaccines; not sure if this is appropriate.	We have revised the report to be consistent with AHRQ's EPC report guidelines (which require use of a trademark symbol after a trade name at the first mention in a chapter and in major headings; after first mention, the symbol may be dropped.).
Public Reviewer #10, Anonymous	General	Data Source indicate the search date; does the search date and the end of search period of the web are the same? To me it is not clear.	We have revised the text to ensure the search dates are clear.
Public Reviewer #10, Anonymous	General	Only published ADR data literature are included in the study; in my opinion this has introduced a bias in the data collection.	We include data published in papers, but we also searched for and used any data present in clinical trials entries (e.g., in clinicaltrials.gov).

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Public Reviewer #10, Anonymous	General	In real world, not all data get published. Especially for vaccines, the report of ADR may occur at the drug dispensing site or call centers or vaccine administration site without getting documented. How do you account for these missed reporting or documentation?	We agree that not all data may be collected or published, although the United States has a robust system for monitoring vaccine safety after licensure. We pursued all available data to the extent possible through extensive searches.
Public Reviewer #10, Anonymous	General	The causative factors considered in assessing the relative risk to the vaccine exposure is not presented in the abstract or how the relative risk was determined.	Given the space constraints in the abstract, we have not included the methodology in great detail; however, the basis of the relative risk (including individual study contributions) is fully discussed in the main report as well as in Appendix A (Methods).
Public Reviewer #10, Anonymous	General	Finally, the strength of evidence (SoE) will be naturally high for the old vaccines when old data is integrated with the new one. Rather providing the individual data along with the combined data will help the reviewer/reader to visualize the real picture.	We agree that the longer a vaccine has been in use, the more evidence there may be to serve as the basis for the strength of evidence statements. All study-level results data are provided by vaccine in the Evidence Tables which can be found in Appendix D.
Public Reviewer #10, Anonymous	General	Further, providing current ADR risk for old and new vaccine for the current study period will help the readers to visualize the real difference and do further data mining, on subjects of their interest, without going through a literature search to identify the difference and then work through the data.	For those readers who are interested in more detailed information for each vaccine and each study reviewed, please see Appendix D.

Public Reviewer #11, Rebecca Coyle, American Immunization Registry Association (AIRA)	General	On behalf of the American Immunization Registry Association (AIRA), we thank you for the opportunity to submit comments on the Draft Comparative Effectiveness Review: Safety of Vaccines Used for Routine Immunization in the United States prepared by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center. AIRA is a national membership organization that promotes the development and implementation of immunization information systems (IIS) as an important tool in preventing and controlling vaccine-preventable diseases. IIS, also known as immunization registries, are confidential, population-based, computerized databases that record all immunization doses administered by participating providers to persons residing within a given geopolitical area. At the point of clinical care, an IIS can provide consolidated immunization records and a forecast for immunizations due for use by a vaccination provider in determining appropriate client vaccinations. At the population level, an IIS provides aggregate data on vaccinations for use in surveillance, quality improvement, and program	Thank you

		operations, and in guiding public health action with the goals of improving vaccination rates and reducing vaccine-preventable disease. In addition to serving as a reliable source for timely, accurate, and complete data for assessing vaccination coverage, IIS are an important data source for studies evaluating vaccine safety. Multiple evaluations of adverse events have relied on IIS vaccine administration data to assess the potential association of vaccine exposure with various outcomes of interest for safety investigations. For example, the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program and Vaccine Safety Datalink (VSD) have both linked to IIS for more complete immunization data as part of studies assessing the safety of H1N1 vaccine.1 IIS also house important details on the vaccine products administered, such as manufacturer and lot number facilitating timely response in the case of safety scares related to the vaccine product that need to be acted on. AIRA commends this effort to carry out such an extensive review of the safety of vaccines across the lifespan. As the US prepares to introduce numerous novel vaccines utilizing new	

		vaccine technologies to respond to the COVID-19 pandemic, proving these vaccines are safe is imperative to the success of the mass vaccination campaign and maintaining confidence in all vaccines. Given the variability in strategies used to assess safety as demonstrated in your review, we would like to take this opportunity to call attention to a potential need to evaluate the methods in which vaccine safety is being monitored across the US and to consider opportunities to standardize and modernize these efforts. It may be possible that IIS data can be leveraged on a larger scale to support rapid, population-level studies. For example, IIS could be used to verify what type of COVID vaccine a person received should there be an adverse event. It can also be used to review a person's comprehensive vaccination record. There might be a need to evaluate safety and/or efficacy with co-administered vaccines (COVID + flu) or vaccines administered within a certain timeframe of a COVID vaccine. IIS enhancements and development of standards to support linking data across systems should be prioritized to ensure readiness of our systems to track safety. We offer AIRA as a resource and welcome any	

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		opportunity to support future vaccine safety efforts. AIRA greatly appreciates your efforts to continue to evaluate the evidence of safe vaccines including identification of gaps for future exploration. Thank you again for this opportunity to comment.	

Public Reviewer #12, James C. Appleby, Chief Executive Officer, The Gerontological Society of America	General	On behalf of The Gerontological Society of America (GSA), thank you for the AHRQ Evidence-based Practice Center's (EPC) work to help healthcare decision makers – patients and clinicians, health system leaders, and policy makers, among others – make well-informed decisions and thereby improve the quality of healthcare services. GSA honors aging across the lifespan and is the nation's oldest and largest interdisciplinary organization devoted to research, education, and practice in the field of aging. The principal mission of the Society — and its 5,400+ members — is to advance the study of aging and disseminate information among scientists, decision makers, and the public. GSA has a long-standing commitment to improving adult immunization rates and expanding the number of professionals around older adults who support vaccination. GSA hosts the National Adult Vaccination Program (NAVP), started in 2011 with the purpose of affecting policy and improving adult immunization rates. To help achieve its goals, the NAVP convened a workgroup of vaccine and policy experts to provide strategic recommendations and direction that focus on improving adult immunization	Thank you

		rates and creating sustainable change. We routinely bring together stakeholders to discuss issues of importance and make recommendations to address the specific needs of older adults. We have done this with influenza vaccination, raising vaccination rates in long-term care facilities, creating the Immunization Champions, Advocates, and Mentors Program, and we are currently working on understanding shared clinical decision-making best practices. Our workgroup focused on the safety of vaccines in adults (KQ1). We agree with the conclusions of the reviewers that there is no new evidence of increased risk with varied strength of evidence or insufficient evidence for key adverse events, including for newer vaccines such as recombinant influenza vaccine, adjuvanted inactivated influenza vaccine, recombinant adjuvanted zoster vaccine, and hepatitis B vaccine with novel immunostimulatory adjuvant. We thank them for their comprehensive effort to review the evidence to ensure continued safety of vaccines. We find the report to be comprehensive and written in a way that is understandable. We thank AHRQ for its continued	

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		efforts to protect the public and promote public health.	