Evidence Report/Technology Assessment Disposition of Comments Report

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

Draft review available for public comment from June 24, 2013 to July 24, 2013.

Research Review Citation: Maglione MA, Gidengil C, Das L, Raaen L, Smith A, Chari R, Newberry S, Hempel S, Shanman R, Perry T, Goetz MB. Safety of Vaccines Used for Routine Immunization in the United States. Evidence Report/Technology Assessment No. 215. (Prepared by the Southern California Evidence-based Practice Center under Contract No. 290-2007-10062-I.) AHRQ Publication No. 14-E002-EF. Rockville, MD: Agency for Healthcare Research and Quality; July 2014. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. 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.

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Peer Reviewer Comments

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 1	Executive Summary—Page ES-7 lines 45-48	Not clear if 3,034 selected should be the sum of 383 potential references plus 2,506 excluded references.	3.034 was the total of 383 background articles, 2,506 articles rejected at full text review, and 145 accepted for abstraction. We conducted an update search while the report was under review; the numbers have been updated.
Peer Reviewer # 1	Executive Summary—Page ES-10 line 13	Identified only 1 study of the safety of the immunization schedule (DeStefano 2013). Smith and Woods (Pediatrics 2010;125:1134-41) {#8283} also looked at aspects of the immunization schedule and neurodevelopment outcomes.	The safety of the vaccine schedule was studied in a 2012 IOM report; we summarize their findings and only mention individual studies published after that report.
Peer Reviewer # 1	Executive Summary—Page ES-14 Table	Rotarix requires only 2 doses, not 3.	Typo, we have corrected.
Peer Reviewer # 1	Executive Summary—Page ES-15 Table	Provide reference for hep B vaccine and increased IgE	The reference is Gruber, 2008. We have removed the reference numbers from the table; articles are cited in the text and the tables in the results section of the report. Full citation is listed in the reference list at the end of the report.
Peer Reviewer # 1	Executive Summary—Page ES-17 Table	Provide reference for IPV and food allergy	This also comes from Gruber, 2008.
Peer Reviewer # 1	Executive Summary—Page ES-17 Table last row	Only DTaP-IPV-Hib is a combination or multiple vaccines, all the others seem to be evaluations of individual vaccines	We have changed the name of this section to “Miscellaneous and combination vaccines”
Peer Reviewer # 1	Executive Summary—Page ES-18 Table last row	No references provided (and generally the entire Table is inconsistent in listing references)	Because it makes the Executive Summary unwieldy, we have removed references from the table. References are present in the text, as well as in the results tables for each vaccine in the main report.
Peer Reviewer # 1	Executive Summary—Page ES-19 line 3	Not clear what is meant by “3.7 additional cases per person-year	Our apologies for the typo. We have changed to “3.7 additional cases per 100,000 person-years.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 1	Executive Summary—Page ES-19 line 33	Should acknowledge that an IOM (2002) review specifically of Hep B vaccine and demyelinating neurological disorders concluded that the evidence favors rejection of a causal relationship with incident MS or MS relapse. This inclusion would be consistent with the inclusion previously (p. 28 line 18) of additional evidence (outside the current review) regarding MMR and autism.	We now cite the 2002 IOM report in the section on Hep B vaccine.
Peer Reviewer # 1	Introduction	Introduction is clear.	Thank you. No response needed.
Peer Reviewer # 2	Introduction	The introduction focuses on vaccines in the adult and pediatric schedules which is quite clearly stated. It then becomes curious why the results of the new metaanalysis on H1N1 (monovalent) vaccine has such weight. It is hard to know what to do with that information as the monovalent vaccine is no longer an option. A consumer may ponder the safety of any H1N1 containing vaccine based on this seemingly important finding?	We were asked by our expert panel to include studies of 2009 monovalent H1N1 vaccine. An association with GBS was found; although the strength of evidence is high, the risk is extremely low. We emphasize that no association has been found with seasonal vaccines that include an H1N1 strain.
Peer Reviewer #3	Introduction	This (*the introduction*) was very clear and helpful.	Thank you. No response needed.
Peer Reviewer # 4	Introduction	The authors should specifically state the time period (i.e. years) that the review was conducted for articles added to the IOM report. The end date is identified but the actual time period should be listed.	We searched from a year before publication of the IOM report. For vaccines not included in that report, we searched from the inception of each electronic database. We have clarified in the text.
Peer Reviewer # 1	Methods	Methods are generally well-described and appropriate.	Thank you. No response needed.
Peer Reviewer # 2	Methods	Inclusion and exclusion criteria seem logical. Outcome measures are defined by what researchers have chosen to focus on.	Thank you. No response needed.
Peer Reviewer #3	Methods	The inclusion and exclusion criteria, search strategies, and outcome measures were explicitly stated, justifiable, logical, and appropriate.	Thank you. No response needed.

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Peer Reviewer # 4	Methods	The introduction to the review was excellent. The request for the review was explicitly described as was the strength of the existing data/documents that exist on this topic. A summary of the types of vaccine safety studies that have been conducted was well described.	Thank you. No response needed.
Peer Reviewer # 4	Methods—Page 40, line 38	Page 7, Line 38. The authors should specifically state the time period that the review was conducted for articles added to the IOM vaccine document. The end date is identified but the actual time period should be listed. Consider adding... "Additional studies from xxxx through Oct. 2012 were reviewed".	We searched from a year before the IOM search date. For vaccines not included in that report, we searched from the inception of each electronic database. We have clarified in the text.
Peer Reviewer # 4	Methods—Page 8	Also in ES) T(he authors should add references for the 4 study designs.	We have added reference to the Cochrane Handbook.
Peer Reviewer # 4	Methods—Page 8	(Also in ES) The authors should add the word "study" after Cohort and move "comparing two or more groups" to after "Follows". The line should read: Cohort Study—Follows two or more groups....	We corrected during internal review. This person was given an unapproved draft.
Peer Reviewer # 4	Methods, Page 41, line 41	Page 8, Line 41. The authors should further separate out or use a subheading. It is an analytic method not an actual study design. Those readers not familiar with the science may misconstrue the intent/description as an actual study design. This is even more of a reason for the authors to reference the study designs described previously as well as this analytic method.	We fixed during internal review. This person was given an unapproved draft. We have added references for each study design described.
Peer Reviewer # 1	Results—Page 49 line 22	Would be helpful to include the proportion of women with Grade 3 pain	In Bhatla, 2010, 20.5% of the HPV group and 4.0% of the placebo group reported Grade 3 pain. We have added this to the text.
Peer Reviewer # 1	Results—Page 53 line 23	See previous comment re hep B vaccine and MS: Should acknowledge that an IOM (2002) review specifically of Hep B vaccine and demyelinating neurological disorders concluded that the evidence favors rejection of a causal relationship with incident MS or MS relapse. This inclusion would be consistent with the inclusion previously (p. 28 line 18) of additional evidence (outside the current review) regarding MMR and autism.	Thank you. We now cite the 2002 IOM report in the section on Hep B vaccine.

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Peer Reviewer # 1	Results—Page 60 lines 25-31	Not clear why Hib vaccine is included in a section on influenza vaccines	Your point is well taken. We have created a separate section on Hib.
Peer Reviewer # 1	Results—Page 64	Missing references on influenza vaccine safety and febrile seizures, including: Lee 2011, Am J Prev Med 41:121-8; and Tse 2012, Vaccine 30:2024-31.	We have added both Lee, 2011 and Tse, 2012 to the results section.
Peer Reviewer 1	Results—Page 66 Table 20	AE not indicated for some of the studies, the cells for "Results re vaccine" and "Results re risk factors" not clear or possibly reversed in some instances (this comment probably applies to other tables as well).	We have checked all tables for accuracy and revised accordingly.
Peer Reviewer # 1	Results—Page 81 line 28	Missing sample size (this one caught my eye, but all tables should be reviewed for completeness).	Thank you for noting. Sample size is 250; we have inserted.
Peer Reviewer # 1	Results—Page 83	Should include more recent results from Australia and from the FDA PRISM study (I do not currently have the references)	These studies were published after our initial literature search. We have added them to the final report.
Peer Reviewer # 1	Results—Page 84	Paragraph has several typographical errors; lines 25-27 should be Rotarix and quality of studies should be "high", whereas Australian study (lines 21-23) quality is more on the "low" side.	We have corrected typos. However, the Australian study quality is moderate, as discussed in the text.
Peer Reviewer # 1	Results—Page 86	Results not presented for the Shui study.	Our apologies; the data has been added.
Peer Reviewer # 1	Results—Page 87 lines 4-6	No results presented in Table or text on Haber 2013 study (Self-control risk interval design using VAERS data).	We apologize; this was a word processing error. VAERS uses passive surveillance, thus this study did not meet our inclusion criteria. Please see methods.
Peer Reviewer # 1	Results—Page 94 line 21	"**" after mediastinal disorder is missing footnote.	In the "vaccinated vs unvaccinated" tables, ** indicates statistical significance. We have added to table legends.
Peer Reviewer # 1	Results—Page 95 lines 4-8	Chao et al 2012 was not a VSD study.	Thank you; correction made.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 1	Results—Page 97	"Studies of combination vaccines or multiple vaccines"—This section should be relabeled "Miscellaneous". Several of the studies are of single pathogen vaccines (e.g., polio, hep B, varicella). Actually, consideration should be given to deleting this entire section. It has the feel of something that was thrown together at the last minute, it is somewhat incoherent, and inadequately attempts to cover a fairly large and complex topic that is probably beyond the scope of the review.	We believe this was an issue of semantics. We did not study adverse events related to the administration of multiple vaccinations simultaneously. We have retitled "Miscellaneous and combination vaccines."
Peer Reviewer # 1	Results—Page 97 lines 50-57	Should include Maher 2004 (Pharmacoepidemiol Drug Saf 131:1-9) since this is one of the few or only studies that evaluated number of vaccines received in infancy and risk of asthma.	This study found no association between number of vaccines and risk of asthma. Regarding *vaccination schedule*, we summarize the findings from the 2012 IOM report dedicated to this topic rather than summarize individual studies such as Maher, 2004
Peer Reviewer # 1	Results—Page 98 line 9	Add Mullolly 2011, Vaccine 29:7611-7	As this study was already included in our draft report, the comment is unclear.
Peer Reviewer # 1	Results—Page 98 line 25	A more appropriate reference (rather than Chen 1997) would be Barlow 2001, NEJM 345:656-61	Studies already included in the 2011 IOM report, such as Barlow, 2001, were not described individually. Chen,1997 was described because it was not covered by the IOM report.
Peer Reviewer # 1	Results—Page 99 line 39	Strength of evidence that MMR vaccine causes febrile seizure is strong and is a conclusion of the 2011 IOM review.	We agree. This is discussed in the section on MMR vaccine.
Peer Reviewer # 1	Results—Page 99 line 31-48	Should mention 2002 IOM review "Multiple Immunizations and Immune Dysfunction" {#21239}	We now cite the 2002 IOM report in the section on Hep B vaccine. Regarding multiple immunizations, we also mention the more recent 2012 IOM report on immunization schedule.
Peer Reviewer # 1	Results—Page 110 line 25-36	Besides Hummel 2000, several other studies have been published on vaccines and type 1 diabetes (see the 2002 IOM review noted above)	We have included all studies in type 1 diabetes that meet our criteria. Please see the appendix for reasons for exclusion of specific studies.
Peer Reviewer # 2	Results	Based on the inclusion criteria I am not aware of other studies which could have been included.	Thank you. No response needed.
Peer Reviewer # 3	Results	The amount of detail in the results is appropriate for this type of publication and was clear and understandable.	Thank you. No response needed

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 3	Results, Page 93, line 25	Under children and adolescents, hemophilus influenza type b (Hib) vaccine is included under the section on Influenza Vaccines. However, Hib is not an influenza virus but a bacterium, despite the fact that the word influenza appears in its name. These should be separated and Hib should have its own section, as they are unrelated.	Your point is well taken. We now have a separate section on Hib.
Peer Reviewer # 3	Results	I suggest that the labels for each of the tables should reflect the fact that the information is an update to the IOM report and not a comprehensive list of studies. This is stated clearly in the text but not in all of the tables.	As you note, we have emphasized this throughout the text. Due to space limitations, we have not repeated this in the tables.
Peer Reviewer #3	Results, Page 117, line 26	Next to last paragraph that begins with "Two case-control studies conducted in Latin America…"—the sentence mentions both RotaTeq and Rotarix vaccines, but clearly is only referring to one. Similarly, the word RotaTeq occurs twice in sequence in the preceding paragraph.	Corrections have been made. The Latin American studies used Rotarix.
Peer Reviewer #3	Results, Page 148, line 8	Pregnant Women, Influenza Vaccines—I think the first paragraph refers to Table 30, not Table 29.	Typo corrected.
Peer Reviewer # 4	Results	The authors had a monumental task in evaluating the number of studies identified for review. In general the characteristics are clearly described. The Evidence Tables accurately and concisely reflect the studies and allow the reader to better assess the study methods, results and quality. Consider putting a direct reference to the Evidence Tables contained in the Appendix at the bottom of Summary Tables in the body of the document.	Thank you. We now refer to the Evidence Tables Appendix in a note below each summary table.
Peer Reviewer # 4	Results	The authors should consider limiting the use of the term "protective effect" regardless of the statistical significance, unless they can state with certainty that the vaccine alone truly protects the patient from the identified outcome. This is especially important for the audience that this document is geared to inform.	We have removed the term "protective effect" throughout the report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 4	Results	Some of the results and key messages can be better assessed and presented in the Adult Vaccine Section. The authors should succinctly describe those studies that had no AEs confirmed and make sure that key methods and outcomes where AEs were confirmed are more explicitly defined. Moreover, a description of the EPC ranking and assessment should be more prominent in this summary section. The authors should perhaps lead with the strength of the evidence similar to how the information is presented in the Adolescent and Pregnant Women summary sections.	We described the methods of each included study as succinctly as possible given the length limitations of the report. We also describe the AEs as best as possible. On many occasions, the AEs were not well described, and severity was impossible to determine. Often the only description of an AE was its inclusion in a list of AEs reported. We have made this clear throughout.
Peer Reviewer # 4	Results—Page 52, line 49	Page 19, Line 49. Can a "protective effect" be stated with confidence? Lack of association with the given AE or AEs of interest should be stated not "protective effect"	We used the term "protective effect" not to indicate a lack of association, but to indicate a negative association between vaccination and that AE. Still, we have revised to remove the term "protective effect."
Peer Reviewer # 4	Results—Page 57, line 3	Page 24, Line 3. Suggest replacing "protective effect" with decreased or lack of association of the vaccine with the AE of interest.	We have removed the term "protective effect" throughout the report.
Peer Reviewer # 4	Results—Page 57, line 10	Page 24, Line 10. Insert authors name so that it's easier to correlate with the detailed table which describes each study	Due to word count limitations, we do not always state the author's name in the text. However, each study has the same reference number in both the text and the tables, so readers can match up.
Peer Reviewer # 4	Results—Page 57, line 10	Assuming this refers to the Johnston study; however, results listed in the table don't reflect a "composite death" as described in the narrative. The table results reflect death categorized as noncardiovasuclar, cancer and other. If the major cardiac events identified resulted in a "composite death" it should be listed in the table- study results/title. If not, the authors should change the narrative so that the actual outcomes measured are reflected/summarized and match those in the table.	The text refers to Johnstone, 2012. We have revised to state that the outcomes include composites such as "death from cardiac causes" and "death from other outcomes" so that the text and table match.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 4	Results,—Page 58, line 36	Page 25, Line 36. The studies reporting a "protective effect" leave the reviewer with questions about their actual strength. The authors should qualify this statement so as not to give the impression that the studies discussed confirm that "influenza vaccines' are "protective" against cardiovascular and cerebrovascular events and that no other variables could have contributed to this "protective effect". The reviewer prefers the term "lack of association".	We have removed the term "protective effect" throughout the report.
Peer Reviewer # 4	Results—Page 66, line 36	Page 33, Line 36. Same as above the authors should consider replacing "protective effect' with "lack of association".	We have removed the term "protective effect" throughout the report.
Peer Reviewer # 4	Results—Page 66, line 46	Page 33, Line 46. This summary of the Johnston study and the potential association or lack of association of the pneumococcal vaccine and outcomes presented are somewhat ambiguous. The study summary and presentation for influenza had flaws and left several questions as discussed earlier.	We have revised to include the Johnstone study in both the influenza and the pneumococcal vaccine sections, and have clarified the results.
Peer Reviewer # 4	Results—Page 72, line 4	Page 39, Line 4. Recommendation for entire Zoster section. The authors should assure that control groups where identified are defined. A brief description of the actual AEs assessed with the reported ORs should be included. If the general category is all that was listed in the studies this should be listed as a weakness in the summary.	We clearly state that the specific AEs assessed and associated ORs were not reported in several of the Zoster studies. Instead, only general categories were reported. We note this as a major weakness in the Results, Discussion, and Executive Summary. Regarding the control groups, the RCTs identified found no significant baseline difference between the control and vaccine groups. The column "population" describes the study participants.
Peer Reviewer # 4	Results—Page 80, line 6	Page 47, Line 6. The author should list the type of study conducted (i.e. controlled trial, cohort etc).	Weinberg, 2010, is a randomized controlled trial of Varivax vs placebo in HIV positive subjects. We state this in the text and corresponding table.
Peer Reviewer # 4	Results—Page 82, line 6	Page 49, Line 6. Isn't anaphylaxis considered an AE? The authors should state "other AEs".	Thank you, we have corrected this typo.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer # 4	Results—Page 49, line 17	Page 49, Line 17. The authors should define how the control group was identified.	Ngan, 2010, is a double blind randomized controlled trial of healthy Chinese women conducted in a single Hong Kong clinic. Bhatla, 2010, is a double blind randomized controlled trial of healthy Indian women conducted in 4 hospitals. (Both studies were mentioned on page 49, line 17.) This information appears in the text and the corresponding table.
Peer Reviewer # 4	Results—Page 97, line 30	Page 64, Line 30. List author in study description	The citation lists authors as the Italian Multi-center Study Group for Drug & Vaccine Safety in Children. Due to word count limitations, we do not always state the author's name in the text. However, each study has the same reference number in both the text and the corresponding tables, so readers can match up.
Peer Reviewer # 1	Summary/ Discussion	The authors have made a reasonable stab at identifying some areas of possible needed research. Translation into research would require considerations of priority and feasibility, including possible costs.	The scope of this report was specifically limited to identifying research gaps. The sponsor has indicated that considerations of priority, cost, and feasibility of future research were outside the scope.
Peer Reviewer # 2	Summary/ Discussion	The research needs in pregnancy section is quite abbreviated. There are more unknowns in pregnancy than lack of data on Tdap. A reliable system of determining when in pregnancy (large populations of pregnant women) the vaccine was given will be hugely important as one determines the vaccine AEs. The need for large numbers of pregnant exposures is particularly important given the relative low frequency of some birth defects and defining which are random versus causal to vaccine or even high frequency events like miscarriage. In addition, nothing is known about the patient factors which may influence the effect of the vaccine. Another unknown and potential AE in pregnancy is the effect on the newborn's immune system/reaction to newborn vaccinations.	Your points are well taken; we have added to the Research Gaps section.
Peer Reviewer #3	Summary/ Discussion	The implications of the major findings are clearly stated.	Thank you. No response needed

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	Summary/ Discussion	The use of electronic health records from large databases is stressed as an approach to studying adverse events in pregnant women, but an inherent difficulty in this is that not all data bases are able to directly link maternal and infant records or can do so only with some difficulty. And vaccines, most notably influenza vaccine, can be obtained outside of the health care system (a problem not unique to pregnancy) through pharmacies, the work place, etc., which could lead to misclassification of exposures.	Your point is well taken; we have added to the Research Gaps section.
Peer Reviewer # 4	Summary/ Discussion	The implications of the major findings are clearly stated. To my knowledge no relevant and important studies were omitted. A general description of the limitations of the studies are explicitly stated. The research section is clear, however more specific examples of studies needed to fill the gap in research could be added.	Thank you. The sponsor agency indicated that prioritization of gaps or research recommendations are out of scope
Peer Reviewer #3	Research Gaps, Page 163	The last paragraph probably needs its own title to distinguish it from the section on pregnant women above.	We have separated the last two paragraphs from the research gaps regarding pregnant women. We added a header “general.”
Peer Reviewer # 1	Clarity and Usability	The report is adequately structured. It seems to be still in an early draft phase requiring careful copy editing for typographical errors and consistency of format and content, particularly of the tables.	The report you received was a draft for peer review. The final version has been copy edited.
Peer Reviewer # 2	Clarity and Usability	Yes it is organized. Not sure what to do with the H1N1 information on GBS. Yes, will inform policy and should stimulate research in areas devoid of information such as pregnancy.	No response needed.
Peer Reviewer #3	Clarity and Usability	The report is well structured and organized, the main points are clearly presented, and it should easily be used to inform policy and practice.	Thank you. No response needed.
Peer Reviewer # 4	Clarity and Usability	The Report is well structured and organized. Perhaps a direct reference to the Evidence Tables can be placed under the Summary Tables in the body of the document. This will allow the audience to go directly to the Appendix as needed if/when they have further questions about a study.	Thank you. We now refer to the Evidence Tables Appendix in a note below each summary table.

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Peer Reviewer # 4	Clarity and Usability	The conclusions can be used to inform practice decisions. They can also be used to inform policy decisions where the strength of the evidence is high.	Thank you. No response needed
Peer Reviewer # 1	General	This report provides some useful compilations of studies on the safety of specific vaccines that were not included in the 2011 IOM review or have been published subsequent to that review.	Thank you. No response needed
Peer Reviewer # 2	General	Yes, the report is useful. Target populations and audience are clear.	Thank you. No response needed
Peer Reviewer #3	General	This is a very nice and thorough update to the 2011 IOM report and should serve as a valuable reference for its intended audience.	Thank you. No response needed
Peer Reviewer # 4	General	The report was well written and clinically relevant. The request from the OASH to conduct the review was explicitly stated. The authors did a very good job of identifying the vaccines reviewed and how and why additional ones not included in the IOM report were added. The authors description on the search process, databases accessed, review processes for including specific studies and the grading of quality and scoring of the studies was excellently described.	Thank you. No response needed
Peer Reviewer # 4	General	The key questions are explicitly stated. However, the key question regarding degree of severity of the adverse events, though relevant to the actual review of the study is not reflected consistently in the study summary, results, summary tables or evidence tables. This is a key question in the review but perhaps a statement reflecting that the information will be reported only as identified in certain studies can be added.	We have stated throughout the report that the degree of severity of AEs was often unreported in the studies, as was information that might allow our team to make a judgment about severity. If information was reported in a study, it is described in our report. We have revised the methods section to state “If a study reported severity, or if adequate information was provide for our investigators to categorize severity, we used CTCAE classifications.
Peer Reviewer # 4	General	The overall review was very good. It initially appeared that certain information included was a bit redundant; however, the need for a brief summary followed by further explanation and the subsequent information added a great deal to the report and should be maintained.	Thank you. No response needed

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General	Because of my area of expertise, my comments are largely confined to the study of pregnancy exposures. I think the document might more fully outline the issues involved in studying adverse events related to pregnancy exposures, especially under research gaps. While the key questions review separate the concept of adverse events in the pregnant woman from those in the fetus, these are not well delineated in the discussion and are not mentioned at all in the executive summary. Some of the factors that make this area difficult to study are that the pregnancy outcome typically occurs weeks to months after vaccination, which requires longer follow-up in prospective studies to ascertain, and that not all effects may be immediately apparent after birth. A critical requirement in studying the effects of pregnancy exposures is the gestational timing of the exposure (vaccination), particularly for gestational age-dependent outcomes such as spontaneous abortion and fetal death. Other than the study by Xu, 2012, this concept is not mentioned. I think the document could be a stronger voice for the need to address these factors further.	We have revised to include these points in the discussion section.

TEP Comments

Commentator & Affiliation	Section	Comment	Response
TEP # 4	Abstract	The abstract provides an adequate summary of objectives and methods. It may be helpful to include a statement indicating that this review specifically excludes data reviewed for the IOM report—it is not initially clear how the review relates to the IOM report.	We have clarified in the abstract.
TEP #1	Executive Summary	Table D--please write out "EPC" in the footnotes	We have spelled out the "EPC—Evidenced-based Practice Center" in the footnotes for Table D.
TEP #1	Executive Summary – Page 21	Delete lines 3-4	We have revised the future research section to be less prescriptive.
TEP #1	Executive Summary – Page 21	Delete lines 16-19: "The risk with Rotarix could be investigated further in US populations, unless there are known underlying factors that would make children in Latin American more vulnerable to this medical condition or the dosage/formulation differs from that used in the US"	We have revised the future research section to be less prescriptive.
TEP #1	Executive Summary – Page 21	Delete lines31-32 "Large scale epidemiological studies are needed to investigate further."	We have revised the future research section to be less prescriptive.
TEP #1	Executive Summary – Page 21	Delete line 27 "These issues warrant further study."	We have revised the future research section to be less prescriptive.
TEP #1	Executive Summary – Page 21	Delete lines 34-39 "Given the relatively recent introduction of the recommendation to administer the Tdap vaccine during pregnancy, passive surveillance systems might be regularly monitored for AEs in this population. This is a particular concern for women with multiple pregnancies over a period of a few years. Preliminary analyses of VSD could also identify adverse events associated with the vaccine and possible related risk factors." I would just state the finding regarding influenza vaccine and pregnancy. The rest of this is speculation and recommendations that are not part of this report	TEP members recommended that we include these points regarding Tdap.

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TEP # 1	Executive Summary – Page 21	Line 44 delete “even larger”; Many populations in entire countries are not much bigger than the VSD population	We have deleted “even larger.”
TEP # 2	Executive Summary— Page 12, line 52	Under objectives, is there any reason that short term was not defined as either 30 days or 42 days? If the reason is that different studies define it as 30 and 42 days, would explain.	The wording of the key questions was developed by the review sponsor before our involvement. We assume that the short term was defined as “within 30-42 days” because some studies used 30 days, while others used 42 days.
TEP # 3	Executive Summary— Discussion Page 29, line 6	In the ES Discussion, (second to last paragraph) “Persons who avoid vaccinations (whether purposely or not) may differ from those who receive vaccinations in terms of race, gender, age, SES, and pre-existing medical conditions..”, you note that observational studies should control for potential confounders. Would consider adding that some of these factors may be unmeasured and challenging to adequately control for.	We have added “environmental exposures” as a confounder that is difficult to control for. The results section includes tables that list all variables that were controlled for in each post-licensure study.
TEP # 3	Executive Summary— Discussion, Page 29, line 12	In the SCCS description, would consider stating that SCCS does not implicitly control for time varying confounding such as age or seasonality. This is implied, but readers may be less familiar with the SCCS design.	We have tried to make this clear in our revised description of Self-Controlled Case Series (SCCS).
TEP # 4	Executive Summary— Background, Page 11, Table A	Table A: MCV4 is recommended for infants as young as 9 months in specific circumstances and can be given as young as 2 months- please update the table or clearly indicate in the title that these are recommendations up to date as of October 2011.	Table A lists the 2011 ACIP recommendations, as the table’s title now clearly indicates. (Although the age recommendations have changed, no additional vaccines have been recommended for children.)
TEP # 4	Executive Summary— Background, Page 11, Table B	Line 4- please change MPSS to MPSV	We have made the changes to Table B and Table 2.
TEP # 4	Executive Summary— Objectives, Page 12	The authors indicate that the review is based upon the 2011 schedule, yet the schedule for pregnant women includes the 2013 recommendation for Tdap vaccination during every pregnancy please resolve this discrepancy.	The table displays the schedule as of 2011. (See title of table.) As requested by a panel member, we include a footnote indicating the 2013 change in the Tdap recommendation for pregnant women,

Commentator & Affiliation	Section	Comment	Response
TEP # 4	Executive Summary—Objectives KQ1, Page 12	Please explain distinction between collected and reported. In the results section, each table of adverse events is labeled 'reported adverse events.' How does this differ from 'collected' adverse events? Does this imply AE's that are actively elicited vs those that are passively reported?	The key questions contain separate sub-questions regarding "what adverse events are collected" and "what adverse events are reported" for each vaccine. This language was provided by the sponsor of this systematic review. We interpreted "collected" as meaning pre-defined and actively elicited by the study investigators. We interpreted "reported" as any adverse events that actually took place and appear in the published studies, whether in the control group or the vaccine group. We combined these questions together. In the results section, we present one table of all AEs reported in studies on clinical trials, and a second table presenting AEs assessed in post-licensure studies.
TEP # 4	Executive Summary—Methods, Page 14, line 51	Methods: what is meant by 'used the IOM reports as a springboard?' does this mean that their methodology and results were reviewed and considered to be appropriate conclusions? This review used a different system to assess quality of evidence- does this impact interpretation of data reviewed in the IOM report? For example, an IOM conclusion of 'convincingly supports' is considered high strength of evidence and while 'favors acceptance' is considered moderate support? It may be helpful to indicate how the authors' approach for this report differs from or is similar to the approach used by the IOM.	We reviewed the IOM methodology and accepted it's conclusions as appropriate. The IOM report included mechanistic studies as well as individual case reports. We have added language to clarify how their approach differs from ours.

Commentator & Affiliation	Section	Comment	Response
TEP # 4	Executive Summary—Results	**Results: comments also apply to full report** In general, it would be helpful to include specific criteria applied by the authors to grade evidence (i.e. study design, study population size, etc.). Some of this information is summarized in the appendices but for the reader, it would be helpful to include a column in the study descriptions that points out specific weaknesses described in the methods like bias, precision, etc. Then the reader can refer to the appendix if they would like to review more specific information about these issues. It is otherwise difficult to understand why a particular study provided stronger or weaker evidence.	We have added quite a bit of text to describe methodological issues with specific studies. Rather than add a column to the results tables, we have added a note "ADDITONAL STUDY DETAILS PRESENTED IN APPENDIX C. EVIDENCE TABLES" under each results table.
TEP # 4	Executive Summary—Results	It would also be helpful to indicate why there is insufficient data- this is sometimes included but not consistently- is it because there are no studies or the existing studies are weak or contradictory? This is a big difference and has some implications for research gaps.	We have added further information regarding why evidence is considered "insufficient" where applicable. On most occasions, this was the IOM conclusion and we found no additional studies. An IOM conclusion of "insufficient" usually meant that they identified case reports but no epidemiological studies using active surveillance with adequate controls.
TEP # 4	Executive Summary—Results	Please explicitly indicate that some of the EPC conclusions are based entirely upon the IOM report results while others are based upon the IOM report plus new EPC data or EPC data alone. There appears to be some inconsistency in the conclusions drawn from the evidence summarized in Table D (see below).	We have clarified in the text right before Table D in the Executive Summary.
TEP # 4	Executive Summary—Results, Table D (and Table 32), Page 21, line 22	Table D (and Table 32): Diptheria, Tetanus, Acellular Pertussis (pg E-12, lines 22 ff)- the authors list one trial that does not show an association between these vaccines and adverse events- this information is not captured in the conclusion. As mentioned above, this is not consistent with the synthesis of the evidence presented for Hepatitis A where there was also one study identified showing no association with serious adverse events.	The only IOM conclusion listed for Diptheria Toxoid, Tetanus Toxoid, and Acellular Pertussis vaccine in adults is that evidence "convincingly supports" a casual relationship between tetanus vaccine and anaphylaxis. Our identification of one new trial of SK Td vaccine in 20 young males in Korea where anaphylaxis was not reported is insufficient to change that conclusion.

Commentator & Affiliation	Section	Comment	Response
TEP # 4	Executive Summary—Results, Table D (and Table 32), Page 21, lines 34	Hepatitis A (pg ES-12, lines 34 ff)- the authors indicate that there is no evidence that the vaccine is associated with any adverse events based upon one post-licensure study and the IOM report indicates that the evidence does not convincingly support or favor an association with a series of specific outcomes- the conclusion is that there is insufficient evidence that there is an association with any adverse events. This does not seem to match the information presented- the IOM findings do not indicate inadequate data- their finding suggests that existing evidence is sufficient enough to allow for their conclusion that available information does not convincingly support an association with the listed outcomes.	We apologize for a word processing error. We have removed "the IOM report indicates that the evidence does not convincingly support or favor an association." The IOM actually concluded that evidence is "**inadequate to accept or reject"** a relationship between Hep A vaccine and MS, GBS, Bell's Palsy, transverse myelitis, and chronic inflammatory disseminated polyneuropathy. Our conclusion is based on their findings plus one additional post-licensure study.
TEP #4	Executive Summary—Results, Table D (and Table 32), Page 21, lines 34	Also for Hepatitis A, 'convincingly supports' and 'favors acceptance' are repeated	We have corrected this error. The IOM actually concluded that evidence is "**inadequate to accept or reject"** a relationship between Hep A vaccine and the listed AEs.
TEP # 4	Executive Summary—Results, Table D (and Table 32), Page 23, lines 10	MMR in children (pg ES-14)- increased ED visits interpreted as association with febrile seizures-would this be considered indirect evidence?	Yes, we consider this indirect evidence.
TEP # 4	Executive Summary—Discussion, Page 28, line 5	ES 19, line 5- add 'additional' in front of 'evidence'. This report does not really review all of the evidence regarding safety- it specifically focuses upon evidence not reviewed for the IOM report.	We have made the change to the ES and to the report.
TEP # 1	Introduction - Page 1 line 25	Change to "two strains included in the HPV vaccine"	We have made this change.
TEP # 1	Introduction—Page 3 lines 11-13	Change to "..the Vaccine Adverse Event Reporting System (VAERS), co-administered by the FDA and the Centers for Disease Control and Prevention (CDC), CDC's Vaccine Safety Datalink, and CDC's Clinical Immunization Safety Assessment project"	Thank you, we have made this change.
TEP # 2	Introduction	Looks good	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
TEP # 3	Introduction	The Background/Introduction is well organized and gives a clear description of a clinical evaluation of a vaccine. In the ES background, could consider pointing out that vaccine safety is of particular importance because vaccines are given to healthy individuals. This is mentioned in the Introduction, but you could consider briefly expanding on this point.	The second page of the introduction states that vaccines are unique when compared with many other medications because they are administered to a large population of mostly young health people to prevent rather than treat disease. We feel this is sufficient, given the length of the report.
TEP # 4	Introduction	Introduction- Effectively highlights key issues- despite public health impact, gaps in vaccine uptake exist, especially in face of expanding recommendations and increasing concerns regarding vaccine safety. The authors include a description of the clinical trial/approval process to illustrate the rigor applied to licensure- this is helpful.	Thank you. No response necessary.
TEP # 4	Introduction—Tables 1 and 2, Page 34 and 35	Tables 1-2: As above, please include a statement indicating that these are recommendations as of 2011. The authors indicate that the report covers vaccines recommended as of 2011- do the authors mean vaccines included in the schedule as of 2011 or published recommendations as of October 2011? Table 3 includes the recommendation to administer Tdap to pregnant women during each pregnancy—this recommendation was published in March 2013. For Table 1, MCV is recommended to infants as young as 9 months in specific circumstances. The adult table does not include PCV13 which is now recommended for adults in specific circumstances.	The goal of this project was to address the safety of all vaccines recommended as of October, 2011. The text and table headings have been revised to make this clear. The project was close to completion when the recommendations were updated in March, 2013; our experts asked us to add a footnote regarding the new recommendation that Tdap be administered during every pregnancy.
TEP # 4	Introduction—Page 36, lines 45-51	Page 3, Lines 45-51. The authors indicate that this work builds upon the IOM report- as described above, it would be helpful to be more specific regarding the use and interpretation of the IOM results. It would also be helpful to explicitly indicate that the authors are not reviewing papers used in the IOM report but are accepting conclusions from the IOM report.	Thank you. We have clarified throughout the text.
TEP # 1	Methods	Overall the methods are clearly stated and logical	Thank you; no response necessary.

Commentator & Affiliation	Section	Comment	Response
TEP # 1	Methods—Page 6 line 18	I think you include Pandemrix in the influenza section which has ASO3 so need to clarify here or take out of results section later	Vaccines using ASO3 were excluded from this report, as this adjuvant is not used in the US. We included no controlled trials of vaccines with AS03. In an earlier version of the report, we included a post-marketing study (Dieleman, 2011) conducted in four European countries. Pandemrix was one of several vaccines used; results were not stratified by vaccine, so we have removed this study. We had also included a study of pregnant women conducted in Scotland (Mackenzie, 2012) that included Pandemrix and Celvapan; this study has also been removed. We also removed Aljadhey, 2012, which studied Saudi Arabian children vaccinated with Pandemrix.
TEP # 2	Methods	I would recommend you add additional explanation and emphasize what the null finding here means. This relates also to information below on tables.	We have removed the term “null” from the conclusions table and throughout the report. We now state as “no association” between a vaccine and particular AE.
TEP # 3	Methods	The authors included appropriate study designs and the exclusions were justifiable. Search strategies were logical and explicitly described in the text and in the appendix.	Thank you. No response necessary.
TEP # 3	Methods/Article Review—Page 41, line 4	Under article review, could you please clarify whether the two researchers reviewed all titles and abstracts identified or if one of the two researchers reviewed each title and abstract.	Two researchers reviewed every title and abstract identified. In other words, all abstracts were reviewed by at least two researchers. We have clarified.

Commentator & Affiliation	Section	Comment	Response
TEP # 3	Methods/Study Inclusion—Page 41, line 35	Could you please clarify the sentence: "The analysis controls for time and other covariates that don't vary within person during the study period."	Each subject serves as his or her own control, and the rate of AEs (within a specified time range) before and after the vaccination are compared. For example, one could compare the onset of a particular medical condition in the month before vs the month after vaccination. Characteristics such as the child's race and gender do not change during those two months. Factors like the child's age and the weather do change, so those factors are not controlled for. We have revised our description of self-controlled case series methodology to clarify.
TEP # 3	Methods/Study Inclusion—Page 42, line 17	Could consider expanding upon why non-English-language studies were excluded.	Prior research on vaccinations suggested that the risk of language bias was low. We state this in the text.
TEP # 4	Methods	The methods are comprehensive with appropriate inclusion/exclusion criteria and analytic approach for the trial data. Some suggestions are made to improve clarity.	Thank you. No response necessary.
TEP # 4	Methods	As above in the executive summary section, please indicate the distinction between collected and reported adverse events.	The key questions contain separate sub-questions regarding "what adverse events are collected" and "what adverse events are reported" for each vaccine. This language was provided by the sponsor of this systematic review. We interpreted "collected" as meaning pre-defined and actively elicited by the study investigators. We interpreted "reported" as any adverse events that actually took place and appear in the published studies, whether in the control group or the vaccine group. We combined these questions together. In the results section, we present one table of all AEs reported in studies on clinical trials, and a second table presenting AEs assessed in post-licensure studies.

Commentator & Affiliation	Section	Comment	Response
TEP # 4	Methods, Inclusion/ Exclusion Criteria	Inclusion/Exclusion criteria clearly described. Analytic approach used to calculate odds ratios using data from clinical trials and cohort studies seems appropriate given the rarity of some of the reported adverse events.	Thank you. No response necessary.
TEP # 4	Methods—Page 40, lines 52-54	Page 7, lines 52-54. The authors indicate that they developed a list of AE's based upon reports to VAERS, VICP and the FDA Mini-Sentinel program. Before including reported events on their final AE list, did the authors consider biologic plausibility or potential mechanism? Mechanism is included in the conceptual framework but it is not clear how this may have played a role in the search strategy or assessment of adverse events.	When developing the list of AEs for our search terms, biological plausibility was considered. We distributed a draft list to our Technical Expert Panel (TEP) and they suggested additional AEs based on biological mechanism. In the results tables, we include data for all AEs reported in each study, regardless of biological plausibility.
TEP # 4	Methods—Page 42, line 32	is there a reference for CTCAE? Line 33- How are serious adverse events defined?	Each category of AE (i.e. fever, headache) is rated on a scale of 1 to 5, with 1 being very mild and 5 being death due to the event. The definition of "serious" differs by AE type; we could not list the definition for each type due to space limitations. The CTCAE is referenced; their code guide is quite lengthy but available on line for public use.
TEP # 4	Methods—Page 43, lines 16-29	Page 10, lines 16-29: The authors present the McHarm criteria for the assessment of methodological quality. It appears that this tool applies a point based upon specific criteria. Please provide a reference to the appendix that more clearly describes the criteria and please provide a score range. The subsequent summary tables in the results section include a McHarm score but without knowing the expected range, it is difficult to interpret these scores. The reviewer guessed that one point was given for each specific question in the tool but this was not until seeing the tool in the appendix.	We now note that the McHarm instrument is presented in Appendix B. We have added a description of the scoring. One point is given for each of 15 items, so the score can range from 0 to 15.

Commentator & Affiliation	Section	Comment	Response
TEP # 4	Methods, Page 43-44, lines 32ff	Pages 10-11, lines 32 ff- The authors thoroughly describe the grading system used in their interpretation of results. Table 4 clearly presents each element with examples and indicates how each element is to be applied. Since the authors appear to utilize the results of the IOM report in their conclusions, it may be helpful to indicate how the IOM results are interpreted and how their approach is similar to or different than the IOM classification system. This is important because the results present both IOM results and the authors review results-conclusions appear to reflect both the IOM and this review's results.	Thank you, we have added to the methods section. In sum, the IOM report included mechanistic studies and individual case reports to weigh the biological plausibility of AEs. Our study included only trials and epidemiological studies of humans.
TEP # 1	Results	I think there is too much detail in both the tables and text and some studies that I am familiar with are not properly characterized--particularly no mention of limitations in any of the studies.	We have tried to mention the strengths and weakness of specific studies.
TEP # 1	Results—Page 18	Influenza vaccines: please use the same language throughout when referring to the 2009 H1N1 monovalent influenza/A vaccine--I would use 2009 pH1N1 which is frequently used in the literature. Also in this section please clearly state when both live and inactivated are included in the studies and specifically note the seasons included for the "seasonal influenza vaccines" for example on page 23 line 14 state that it is 2009-10 TIV	We now consistently refer to as 2009 H1N1 monovalent influenza vaccine. This usage is consistent in the literature we reviewed. (pH1N1 was not used often in the studies we identified.) Each table in the report now lists the specific vaccine assessed and season, where available. Please note that some epi studies assessed AEs associated with "any influenza vaccine:" in those cases we list as "influenza, unspecified."
TEP # 1	Results—Page 25 line 23	Not clear if this is specifically meant to be the 2009 H1N1 strain line 25-after surveillance systems please add: established or enhanced during the 2009 H1N1 pandemic	We have made this revision.
TEP # 1	Results—Page 25 line 26	After "per million vaccines" add: "administered"	We have made this revision.

Commentator & Affiliation	Section	Comment	Response
TEP # 1	Results—Table 8	Dieleman study clarify that most of these vaccines were adjuvanted with either ASO3 or MF59; this may be the case for the Grimaldi-Bensouda et al as well; please check and clarify this in the table since the US did not use adjuvanted vaccines during H1N1 Farez et al--please include country for source of data	Studies of vaccines adjuvanted with ASO3 or MF59 were excluded from this report, as these adjuvants are not currently used in the US. Our draft report included no controlled trials of these vaccines Our draft did include several post-marketing studies (Dieleman, 2011; Mackenzie, 2012; Aljadhey, 2012) that included some patients who received vaccines containing ASO3 adjuvant. These studies were removed from the final version of the report. Grimaldi-Bensouda did not identify whether the vaccines studied included an adjuvant; we have made that clear in the table and text. Regarding Farez et al, the study was conducted in Argentina. The table now lists the country where data was collected.
TEP # 1	Results—Page 33 line 41	Replace “versions” with “formulations”	We have made this revision.
TEP # 1	Results—Page 49 line 16	Not sure what this means, isn’t there only one formulation of Cervarix (by definition)?	Clinical trials of a vaccine sometimes test different formulations. Once the specific vaccine is approved, there is only one formulation available. The two trials of Cervarix you refer to used the same formulation, so we have revised the text.
TEP # 1	Results—Page 49 line 18-19	Regarding OR for fatigue (OR 1.69, 95% CI 0.56-3.34): Not sure this should be stated as “more likely to experience the non-serious AEs, fatigue” since it is not significant (statistically) and also does not agree with data in the table for HPV	We have corrected this typo. OR for fatigue is significant:1.69 (95% CI 1.05–2.72).
TEP # 1	Results—Table 13	Ngan study—need to clarify fatigue data	We have corrected this typo. OR for fatigue is significant:1.69 (95% CI 1.05–2.72).

Commentator & Affiliation	Section	Comment	Response
TEP # 1	Results—Page 53, lines 40-48	None of this is really relevant to this report (this is VE data); also this was published in 2003 and could have been included in the recent IOM report so it was not included for some other reason (i.e. it couldn't have been published after the IOM search)	Refers to Hedland, 2003. We are unfamiliar with term "VE" data. We have deleted "published after the IOM search dates" as this was incorrect.
TEP # 1	Results—Page 53, lines 49-51	Is this part of the same study since tetanus was not noted above?	Yes, this is part of the same study, Hedlund, 2003.
TEP # 1	Results—Page 60 line 21	Should include year of season and add 2009 to monovalent H1N1	We have added throughout the report.
TEP # 1	Results—Page 64 line 20	(Pandemrix)-Should specifically state this is an adjuvanted (ASO3) influenza vaccine which is not used in the US	Vaccines using ASO3 were excluded from this report, as this adjuvant is not used in the US. In an earlier version of the report, we included a post-marketing study (Dieleman, 2011) conducted in four European countries. Pandemrix was one of several vaccines used; results were not stratified by vaccine, so we have removed this study. We also included a study of pregnant women conducted in Scotland (Mackenzie, 2012) that included Pandemrix and Celvapan; this study has also been removed. We also removed Aljadhey, 2012, which studied Saudi Arabian children vaccinated with Pandemrix.
TEP # 1	Results—Page 64 line 34-35	Not sure what the difference between "any influenza vaccine" and "seasonal vaccine" is	Several post-licensure studies assessed the relationship between receipt of "any influenza vaccine" and AEs. These studies did not differentiate between live and attenuated vaccine, nor did they stratify results by whether the vaccine include H1N1 strain. The table now refers to "influenza vaccine, unspecified" for these studies.

Commentator & Affiliation	Section	Comment	Response
TEP # 1	Results—Page 65 line 13-14	says: “Results indicate that the influenza vaccination was not associated with urea cycle disorders at any post vaccination risk period.” This must be wrong—all the children enrolled had urea cycle disorders so the study was not assessing an association of vaccination with urea cycle disorder but if vaccination was associated with some other AEs among children with urea cycle disorders (or possibly signs of regression, so worsening urea cycle disorder symptoms)	Our apologies. Morgan, 2011 is a self-controlled case series (SCCS) assessing whether hyperammonemic episodes (HAE) are more likely to arise within 21 days of influenza vaccination than at other times in children with urea cycle disorders. We have revised the text accordingly.
TEP # 1	Results—Page 65 SUMMARY	Clarify in the summary whether the seasonal and 2009 H1N1 vaccines are both live and inactivated for all these findings	We have clarified to the best of our ability, according to information provided in the studies.
TEP # 2	Results (Comment is under Results, but pertains to Table D in Executive Summary)	Have some comments about Table D in the Exec Summary: The IOM column is great. However, the column of EPC conclusions as is may lead to misunderstandings. This is likely the part of the report that will receive most attention, so clarity here is paramount. This column may be a little confusing as is to the reader, because it appears to oscillate between quality of evidence and conclusions re; associations of outcomes. It is likely that readers will confuse the terms “high”, “moderate”, etc. as association conclusions, instead of the intended quality of evidence. Consider adding a separate column to address quality of evidence, and keep a new conclusions column.	We have revised the table to make clear that the terms high, moderate, etc refer to the strength of evidence (SOE), rather than the level of risk. It is possible to have a high strength of evidence that there is no risk; for example, with MMR and autism. It is also possible to have high or moderate strength of evidence for an extremely rare adverse event. This is the case with the association between 2009 H1N1 vaccine and GBS, where rate is estimated as 1.6 cases per million vaccines administered.
TEP # 2	Results	Also, this reader was struck by the finding that only flu vaccine in pregnancy data could be found, and only a few studies. There are many studies re: flu vaccine in pregnancy, and some have addressed safety. It is realized that the studies that are out there may not fit the inclusion criteria. In addition, there are investigations re: Td in pregnancy in the developing world that may be relevant.	Our search efforts were extensive and thorough. We believe all studies of pregnant women that met our inclusion criteria appear in the report. Reasons for exclusion of specific studies are listed in the appendices.
TEP # 2	Results	If this paucity of studies is indeed validated, then a strong statement of need (perhaps in the abstract) should be made, as this may help move this research and policy agenda forward.	Your point is well taken. However, per the sponsor agency, the Research Gaps section identifies gaps but does not prioritize research needs or make research recommendations.

Commentator & Affiliation	Section	Comment	Response
TEP # 3	Results	The amount of detail presented in the results section is appropriate. The tables greatly help to present the data. Could consider commenting on the severity in more slightly more detail in the ES.	Thank you. We tried to make clear that the severity of AEs was inconsistently reported, as was information that would allow our investigators to make their own determination.
TEP # 3	Results/Table 32 (also Table D in ES)—Page 154	Could consider adding a footnote next to "IOM" to let reader know that this information has been previously presented.	We considered this, but we think the text makes this clear throughout the report.
TEP # 3	Results/Figure 2 and Figure A in ES (Article Flow)—Page 47	Figure 2 and p 13 and under Study Inclusion Were self controlled risk interval studies included in the total articles accepted for abstraction?	Yes
TEP # 3	Results—Page 106	Under Rotavirus P 106 Please note that a new report is available (http://www.mini-sentine.org/work_products/PRISM/Mini-Sentinel_PRISM_Rotavirus-and-intussusception-Report.pdf)	Thank you, we have added this study.
TEP # 4	Results	While the authors present detailed information regarding the criteria used to grade the quality of evidence, the results do not consistently include information about which criteria were or were not fulfilled. This information is included in the appendix, but it would be helpful to provide a summary in the tables included in the results section.	In the results section tables, we use the McHarm score to summarize how the each study met the criteria regarding ability to assess AEs properly. In the text, we try to note strengths and weaknesses of the studies. We now have a bold notation under each table indicated that the entirety of data is available in Appendix C for those who are interested.
TEP # 4	Results—Page 49, Table 5	Similar to comments above, the first part of the key question for each population requests both collected and reported adverse events yet Table 5 includes only reported adverse events- is there a specific distinction that needs to be emphasized here? Should the title of the table be "Adverse events collected and reported in trials of adults?" Do the authors mean to indicate that they were not able to answer the first question about collected adverse events?	We interpreted "collected" as meaning pre-defined and actively elicited by the study investigators. We interpreted "reported" as any adverse events that actually took place and appear in the published studies, whether actively elicited or reported spontaneously. We explain this distinction in the text. We report all in one table. We have changed the title of Tables 5, 16, and 30 to "Adverse events collected or reported."

Commentator & Affiliation	Section	Comment	Response
TEP # 4	Results	Did the authors consider biological plausibility before calculating odds ratios for any of the adverse events or were OR's calculated for all events for which there were enough observations?	ORs were calculated for **all** reported events.
TEP # 4	Results—Study Summary Tables	In general, it would be helpful to summarize the strengths/weaknesses of each study so that the reader can more easily understand how these studies contribute to the strength of the evidence. As discussed above, it is difficult to know how to interpret the McHarm score or to fully understand the authors conclusions. While this information is available in the appendix for readers, a summary within the context of the paper would be helpful.	We have revised to summarize in the text in each section.
TEP # 4	Results—Page 87, line 33	Page 54, line 33- please change 'years' to 'yeast'	Typo has been corrected.
TEP # 4	Results—Page 93, lines 25-31	Page 60, lines 25-31: would present data regarding Hib vaccine separately from influenza virus vaccines	Your point is well taken. We have created a separate section for Hib.
TEP # 4	Results—Page 98, lines 33-37	Page 65, lines 33-37: the authors indicate that seasonal influenza vaccines are not associated with any serious adverse events in the short term, but there is inadequate evidence to accept or reject association with a series of specific outcomes- this initially seems contradictory. Does this mean that for the SAE's specified in the trials, there was no association but these SAE's may or may not have included the specific outcomes included in the IOM report?	Clinical trials have reported no SAEs in the short term. The series of outcomes listed as having inadequate evidence to accept or reject an association are long term outcomes such as chronic diseases that may not be apparent in the 42 days post-vaccination (short term).
TEP # 4	Results—Page 103, lines 13-15	Page 70, lines 13-15: Please see comment from executive summary- the authors cite evidence that MMR vaccination is associated with increased emergency room visits and that this supports an association with febrile seizures- this seems consistent with the authors' definition of indirect evidence.	Yes, we consider the ER visits indirect evidence of AEs.
TEP # 4	Results—Page 121, lines 5-9	Page 88, lines 5-9: Hepatitis B- the authors present mechanistic data from the IOM report that favors acceptance of an association between the vaccine and anaphylaxis among those who are sensitive to yeast. However, the authors also explicitly indicate in their methods that mechanistic studies are not included in the review. This is a summary of results from the IOM report but this seems inconsistent to accept mechanistic data.	As stated in the Executive Summary and Methods section, we accepted the IOM's conclusions as valid. We did not include additional mechanistic studies published after the IOM report, but we only revisited conclusions if additional studies were found that met our criteria.

Commentator & Affiliation	Section	Comment	Response
TEP # 4	Results—Page 128, line 40	Page 95, line 40: please remove strength after 'insufficient'.	Revision made.
TEP # 4	Results—Page 148, line 14	Page 115, line 14- please add 'compared to unvaccinated' in front of 'women'.	Revision made.
TEP # 4	Results—Page 150, line 12	Page 117, line 12- please add 'influenza' in front of 'vaccine season…'	Revision made.
TEP # 1	Summary/ Discussion—Page 119	please delete :"We also discuss the implications of our findings for future research" on lines 14 and 15	We have reworded to indicate that we discuss "research gaps" rather than implications for future research.
TEP # 1	Summary/ Discussion	third paragraph under limitations should take into account study designs and which may carry more weight--ie SCCS control for non-time varying covariant but not seasonality, while cohort studies (back vs non back) cannot capture potential differences between those who get vaccinated and those who do not.	Thank you. We describe the strengths and weakness of the study designs in this section.
TEP # 1	Summary/ Discussion	VAERS data not only does not consider the rate of events in non-vaccinated populations but cannot calculate rates or risk since there is no denominator data	We agree, thus our exclusion of studies which used VAERS data. We have made this statement stronger.
TEP # 1	Summary/ Discussion—Page 120 beginning on line 6	I believe most studies minimally define clearly if the study is for live, attenuated or inactivated flu vaccines and if both they usually stratify the results. I agree many studies lump several seasons together but usually they define which seasons are included and finally it is still not clear if you are speaking specifically about the 2009 H1N1 strain	We have specified wherever possible. Some epi studies assessed AEs for "any influenza vaccine" and did not stratify by type or season.
TEP # 1	Summary/ Discussion—Page 120 lines26-30	please add "In the US the CDC's Vaccine Safety Datalink (VSD) uses data obtained through such systems at nine large health care organizations, enabling high quality studies." Also delete "even larger" from line 28 since many countries have populations no larger than the VSD of over 9 million persons	We replaced the existing sentence with the one suggested at lines 26-27 and removed "even larger" from line 28
TEP # 1	Summary/ Discussion—Table 32	Is very helpful.	Thank you. No response necessary.
TEP # 3	Summary/ Discussion	Limitations were clearly described. The discussion section was well structured.	Thank you. No response necessary.

Commentator & Affiliation	Section	Comment	Response
TEP # 3	Summary/ Discussion	Might expand the discussion about power to detect rare events beyond controlled trials.	We emphasize throughout the report that RCTs often the lack of power to detect very rare adverse events.
TEP # 3	Summary/ Discussion	Could also consider the difficulty in determining one unified finding from multiple studies with different designs and potentially in different populations.	Thank you, we mention this in the limitations section.
TEP # 4	Summary/ Discussion	In general, the discussion synthesizes the information summarized in the results tables and provides justification for the authors' conclusions. Insufficient data is listed for many outcomes. The authors do indicate why there is insufficient data (lack of available studies versus quality of studies) for some but not all outcomes- it would be helpful to consistently provide this information. The overall conclusion seems to be that more large-scale epidemiologic studies are needed to assess highlighted outcomes for which there is insufficient data. This section could benefit from some additional information to indicate why these specific outcomes are highlighted and what specific weaknesses exist for outcomes with insufficient data -this would better inform next steps. This could also help readers prioritize next steps.	Thank you, we have tried to clarify. In most cases, a conclusion of insufficient data means that no epi studies were identified. Often, the IOM reached that conclusion (they included mechanistic studies and case reports) and we found no epi studies published after their search dates.
TEP # 4	Summary/ Discussion—Limitations	Limitations: This section adequately summarizes the key limitations for this review	Thank you. No response necessary.
TEP # 4	Summary/ Discussion—Table 32, Page 154	Table 32- please see comments for Table D Many of the EPC conclusions are based upon the IOM findings, however, there is some inconsistency. For example, IOM findings that evidence is 'inadequate to accept or reject' a relationship with specific outcomes is presented as 'insufficient' evidence for those same outcomes (when no additional evidence is identified) for some but not all vaccines included in the review.	We have revised for consistency. Where the IOM found that evidence is 'inadequate to accept or reject' a relationship with specific outcomes; we rated as 'insufficient' evidence for those same outcomes when no additional evidence was identified.
TEP # 1	Research Gaps—Page 129 line 14-15	Please delete "There is particular concern regarding monovalent H1N1 vaccine and trivalent influenza vaccines that include H1N1 strains."	We have deleted this sentence.

Commentator & Affiliation	Section	Comment	Response
TEP # 1	Research Gaps—Page 129 line 16	Please clarify this is 2009 pH1N1 vaccine	We now refer to as "2009 monovalent H1N1 vaccine" throughout, as the literature used this term consistently. (The term pH1N1 was not often used in the studies we identified.)
TEP # 1	Research Gaps—Page 129 lines 36-37	Please delete "Both MS and GBS are concerns regarding vaccines for MMR and hepatitis A and B. Further post-licensure studies are suggested."	Making specific research recommendations was outside of the scope, so this was deleted.
TEP # 1	Research Gaps—Page 129 line 43	Please change to: "Large scale studies may help to determine patient risk factors"	Change made.
TEP # 1	Research Gaps—Page 129 line 49-52	Please delete: "The risk with Rotarix could be investigated further in US populations, unless there are known underlying factors that would make children in Latin American more vulnerable to this medical condition or the dosage/formulation differs from that used in the US." You may add that studies are underway at the FDA and CDC to assess if there is an increased risk of intussusception following both rotavirus vaccines currently used in the US. Data was shown at the ACIP meeting in June 2013	This draft was submitted before the June 2013 ACIP meeting. We have included the new study in the final version of the report and deleted the sentence you refer to.
TEP # 1	Research Gaps—Page 130 line 5	Delete: "These issues warrant further study"	Deleted.
TEP # 1	Research Gaps—Page 130 line 8-9	Delete: "Large scale epidemiological studies are needed to investigate further."	Deleted.
TEP # 1	Research Gaps—Page 130 line 12-16	Delete lines 12-16--this language is out of scope for this report again line 21 delete "even larger"	We removed "even larger"

Commentator & Affiliation	Section	Comment	Response
TEP # 4	Research Gaps	The authors frequently indicate that there are insufficient data to draw conclusions about an association between many of the reviewed vaccines and specific outcomes- it may be helpful to indicate here whether this means that there are no studies, poorly designed studies or both. This will provide the reader with a better understanding of why these specific outcomes were identified as research gaps. In some ways, the report may leave more questions- insufficient data can be interpreted as a possibility that there is a relationship between an outcome and a vaccine- this could undermine confidence in vaccine safety. In describing the need for future study, it would therefore be helpful to provide some context i.e., more data is needed but these outcomes are rare in general. This is very different than there being insufficient data to draw a conclusion because there are studies with conflicting results. For events that are extremely rare, it may be difficult to obtain sufficient data to reliably answer the question. To guide decision-making, a discussion of potential risk needs context. Otherwise, a reader may be left with the impression that vaccination carries significant potential risk for which there are no clear answers without considering the risks associated with forgoing vaccination or the risk of some of these outcomes without vaccination. The authors include a description of mechanisms for ongoing surveillance and the implementation of large epidemiologic studies to meet the research gaps listed in this section. Agree that it may be useful to combine the findings from this report with a systematic reassessment of studies from the IOM report.	Thank you, we have revised to address these issues.
TEP # 4	Appendix—Search Methodologies	Search strategy appears to be appropriate and includes a comprehensive list of terms for each vaccine	Thank you. No response needed.

Commentator & Affiliation	Section	Comment	Response
TEP # 4	Appendix—Evidence Tables	Comprehensive- includes specific criteria used to assess the strength of the evidence provided by the studies. As discussed above, it would be helpful to indicate which of these criteria (i.e. selection bias, ascertainment of exposure/outcome) were not fulfilled in the results tables presented in the full report. There could be a reference to this appendix if the reader is interested in looking up specific details.	We have added a reference to the Evidence Tables (Appendix C) below the in text tables.
TEP # 4	Appendix—Evidence Tables	What is the difference between grade and severity used in the summary of adverse events? Does grade refer to the severity rating system described in the methods?	In the evidence tables," grade" refers to the CTCAE level of severity, as described in the methods section. Some studies reported severity, and a few others contained information that allowed our investigators to rate. Many studies did not address severity.
TEP # 1	Clarity and Usability	This report is well structured and easy to follow. It is very thorough and extremely helpful to have all this information in one place. It is clear but could use some editing in general. The conclusions cannot really inform policy but can help providers know what to expect when vaccinating and help with practice decisions. The report can and does point out gaps in vaccine safety knowledge which will help investigators direct some of their efforts.	No response necessary.
TEP # 2	Clarity and Usability	Please see comments re: research on vaccines in pregnancy, strong policy/research agenda statement justified.	The sponsor agency indicated that prioritization of gaps or research recommendations are out of scope.
TEP # 3	Clarity and Usability	The report is well structured and well organized. Conclusions can be used to inform policy and/or practice decisions. Could consider summarizing research gaps into bullets or a table to help simplify the recommendations for the reader.	Thank you for your suggestion. The sponsor agency indicated that prioritization of gaps or research recommendations are out of scope The Research Gaps section follows AHRQ format.
TEP # 4	Clarity and Usability	This report is comprehensive but there are some suggestions to improve clarity;	We revised the draft report for clarity after addressing reviewer comments and adding new studies identified during the review period.

Commentator & Affiliation	Section	Comment	Response
TEP # 1	General	The report is meaningful to not only clearly state known adverse events associated with vaccines but also to identify gaps where further research may be considered. the target audience is explicitly stated on page 3 and the key questions are clearly stated and are appropriate beginning on page 13 under objectives in the ES.	Thank you. No reply needed.
TEP # 2	General/ Abstract	YES to all above ?s. I think the conclusion in the abstract is not explicit enough. Would recommend getting rid of or changing the sentence: "the findings of this review support those of earlier reviews". This assumes all readers know what those findings are. It is understood that this is in addition to the IOM report, however, it should still work as a standalone paper.	Thank you, we have removed the line "the findings of this review support those of earlier reviews".
TEP # 3	General	The report is well written and clearly defines the objectives and key questions. The results are meaningful, and the tables help to summarize the large amount of data. The report targets the appropriate audience, healthcare decision-makers, and will be useful in developing clinical practice guidelines. Under the last section of the main report, Research Gaps, could consider making bullets of the specific points (or a table). Could also consider moving the last few sentences of the limitations where you describe VSD to the end of Research Gaps- this is a system that could be used to help answer some of the questions. Could also consider adding a sentence about Mini-Sentinel's Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program (http://www.mini-sentinel.org/).	We have added mention of the PRISM program.

Public Comments

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Structured Abstract, Page 7, line 8	"Papilloma virus" should be one word.	We have changed it throughout the report
Merck & Co., Inc.	Executive Summary, Page 11, line 15	ES-2: Reference 4 is not the most recent publication describing vaccination rates. Please see Noninfluenza Vaccination Coverage Among Adults-United States, 2011. MMWR 2013;62:1-7 and update if necessary.	MMWR 2013:62 was published after we submitted the draft report for peer review. Our report does not refer to specific vaccination rates; we simply state that rates in US adults are below Healthy People 2020 targets. The statement remains true given the new data, so no revision is necessary.
Merck & Co., Inc.	Executive Summary, Page 11	ES-2: Tables A and B appear to be referencing the 2011 recommended vaccines (Reference 10) Please be advised that the recommendations were updated in 2013: http://www.cdc.gov/vaccines/schedules/. We request that the tables, and therefore possibly the literature searches, be updated where necessary.	The goal of this project was to address the safety of all vaccines recommended as of October, 2011. The project was close to completion when the recommendations were updated in 2013.
Merck & Co., Inc.	Executive Summary, Page 11, line 24	"Papilloma virus" should be one word.	We have changed it throughout the report
Merck & Co., Inc.	Executive Summary, Page 11, Table A	ES-2 & Page 2: The HPV vaccine recommendation for males is for ages 9-21. This should be stated separately from the female recommendation of 9-26.	We have made that distinction in Tables A and 2.
Merck & Co., Inc.	Executive Summary, Page 11	ES-2: Afluria®, an inactivated influenza vaccine, is approved in patients >=5 years of age. Please consider including Afluria.	We included studies of all approved formulations available in the US. No studies that met our inclusion criteria referred to Afluria. We abstracted the brand name from the studies whenever it was reported; many studies, especially those reporting on early phases of development, did not report a brand name.
Merck & Co., Inc.	Executive Summary, Page 11, Table B	ES-2: "increased risk of hepatitis A" should be "increased risk for hepatitis A". Please revise.	We have made the changes to Table B and Table 2.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Executive Summary	ES-3: Because of the stated concerns, vaccines tend to be held to a higher safety standard than other medical interventions (Chapter 76 by Offit and DeStefano in *Vaccines* by Plotkin and Orenstein 6th ed.). We recommend that this fact be noted in the introductory material and the conclusion.	As vaccines are given to healthy, younger people, we agree that considerations are "unique." We have noted this in the introduction.
Merck & Co., Inc.	Executive Summary, Page 12	ES-3: Regarding MMR vaccine, adults are not routinely given this vaccine, although all are recommended to be immune from them, either by means of vaccination or prior infection. Please qualify the statement.	We have revised to state that MMR is recommended only for adults who have not been previously vaccinated or have not become immune due to prior infection.
Merck & Co., Inc.	Executive Summary, Page 14	ES-5: "Haemophilus influenzae" should be italicized.	We have made this change throughout the report.
Merck & Co., Inc.	Executive Summary, Page 15	ES-6: There is no mention of CDC's Vaccine Safety Datalink project. Was it used? If so, please include it.	We mention VSD throughout the report; we included many studies which used VSD.
Merck & Co., Inc.	Executive Summary, Page 16, line 44	ES-7: Five articles could not be obtained. As far as we can determine, these five articles are not listed anywhere in the report. Had they been listed, we or others might have been able to aid the EPC in obtaining them. Please list them in the final report so that readers may judge the potential impact of their omission.	We have added a list in the appendix. Of the five, three are unpublished studies requested from pharmaceutical companies. One is a news report about the early rotavirus vaccine that was taken off the market and thus excluded from this project. The fifth is an erratum to a 1991 study of Hib in Native Americans. We feel the impact of their omission is minimal.
Merck & Co., Inc.	Executive Summary, Page 18 Figure A	ES-9: Typo: "excludes" should be "excluded."	"Excludes" is correct usage here. We use as a noun: excludes are the studies we excluded, while includes are the studies we included.
Merck & Co., Inc.	Executive Summary, Page 20, Table D	ES-11: Please state whether anaphylaxis was associated with egg allergy or if it is observed in nonallergic patients as well.	We have revised to state that anaphylaxis was associated with allergy to gelatin and/or egg.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Executive Summary, Page 20, Table D	Page ES-11, Pneumococcal polysaccharide vaccine in adults. Table D states that the authors found no placebo-controlled trials of the current US version. Based on information in the second paragraph of page 33 of the document, it appears that this statement is related to the comparison of PCV13 to PCV7. PCV13 and PCV7 are pneumococcal conjugate vaccines, not polysaccharide vaccines. A 14-valent pneumococcal polysaccharide vaccine (PPSV14) as licensed in the United States from 1977 to 1983. It was succeeded by the 23-valent form (PPSV23) in 1983. There are published controlled trials assessing the safety of 23-valent pneumococcal polysaccharide vaccine in adults. A recent example is Musher et al, Safety and antibody response, including antibody persistence for 5 years, after primary vaccination or revaccination with pneumococcal polysaccharide vaccine in middle-aged or older adults, J Infect Dis 2010:516-524. In this study, participants received either PPV23 or a saline placebo, followed by the alternative treatment 30 days later. The data through day 30 is relevant to your assessment. While this study is listed in the Appendices as rejected because of design, we urge you to reassess whether it should be included. Other studies with a variety of aims have also been published, which are described further below.	We found no placebo-controlled trials assessing the **safety** of 23-valent pneumococcal polysaccharide vaccine (PPSV23) in adults. As you note, PPSV23 is the only version currently available in the US. We found many efficacy studies that did not report adverse events. The outcomes reported were Community Acquired Pneumonia (CAP) and mortality, which are efficacy outcomes. Per the methods section of our report "Studies were included for analysis if the total number of people in each group and the number of people with events in each group were reported." We also collected data on whether adverse events (AEs) were predefined, whether the mode of collection was active or passive, whether the study specified who collected the harms data, etc. **If a study did not explicitly state that no adverse events took place, it was excluded.** As you point out, Musher, 2010, was excluded due to cross-over design.
Merck & Co., Inc.	Executive Summary, Page 21, Table D	ES-12, MMR in adults. The EPC conclusion stated in the 2nd column of low strength of evidence for transient arthralgia in women is different from the IOM findings that the "evidence favors acceptance of a causal relationship" documented in the middle column. This suggests that there were some additional findings from the EPC, but these were not specified in the right-hand column. Did the EPC independently evaluate the strength of evidence previously evaluated by IOM? If not, a statement describing the strength of evidence is unwarranted here. Please revise accordingly. Also, unlike the other rows on this page, this row does not mention if additional trials were found. Can this information be clarified?	Our apologies. No new studies of transient arthralgia were identified. We have revised strength of evidence to moderate.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Executive Summary, Page 21, Table D, line 9	ES-12, -20: The conclusion "In clinical trials, adverse events were often reported only in broad categories…" may not be accurate after the EPC takes into account the fact (discussed in detail under Results, below) that the publication by Simberkoff et al., is a supplemental analysis of the publication by Oxman et al. which goes into considerably greater detail, including an appendix. Moreover, abstracted data appears to have overlooked additional data presented in the text of the publications. Please consider revising this conclusion.	Our report includes the Simberkoff data. Also, we have removed two publications on zoster vaccine trials from our draft report, as you pointed out they are duplicates. We have revised to say there were **some** studies where AEs were reported in broad categories.
Merck & Co., Inc.	Executive Summary, Page 21	ES-12: "We found only two post-licensure studies; the only adverse events associated with Zoster vaccine were cellulitis and allergic reactions. (No cases of anaphylaxis were reported.)" It is not clear why reference 74 is not considered when composing this statement. Please reconsider. In addition, the Baxter study (Vaccine 2012;30:6636-41), which probably postdates the current searches, is another post-licensure study. Vaccine-related anaphylaxis is reported in the literature in reference 70. Hypersensitivity reactions are labeled events. Please consider whether the product label constitutes evidence.	We have added Baxter, 2012 which post-dated our original search. The statement in quotes refers to adverse events in post-licensure studies. Reference 74, Murray, 2011 is a clinical trial, as is reference 70, Schmader, 2012 Regarding hypersensitivity, product labels were used to identify AEs/search terms for the electronic searches for evidence. If labels referred to research studies, those studies were retrieved and screened for inclusion. Only research studies that met our inclusion criteria were considered evidence.
Merck & Co., Inc.	Executive Summary, Page 21	The statement on cellulitis is not consistent with the statements in the referenced article. From the article: "A small increased risk of cellulitis, 1-7 days following vaccination found by case-centered method may well represent inflammatory or allergic reactions rather than true infectious cellulitis. This finding is consistent with the SPS safety study…	We have revised to note the authors' conclusions regarding inflammatory or allergic reactions.
Merck & Co., Inc.	Executive Summary, Page 23, Table D	ES-14: The EPC conclusions refer to measles inclusion-body encephalitis. The M-M-R II product label specifies that this has been observed in immunocompromised individuals (in whom the vaccine is contraindicated) who were inadvertently vaccinated with measles containing vaccine. Please specify this specific population here, and specify other populations elsewhere, were appropriate. Unless the EPC has evidence of this event occurring outside of this population, the statement is misleading.	We have revised to specify immunocompromised patients in regard to measles inclusion-body encephalitis. We have also specified populations throughout the report where appropriate.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Executive Summary, Page 23, Table D, line 14	ES-14: The statement "…this is consistent with the IOM's findings that the MMR vaccine is associated with febrile seizures" is speculative. Unless the EPC has evidence supporting an association between these events, the statement should be removed.	We report evidence that both febrile seizures and ER visits are associated with MMR vaccines. ER visits provide indirect evidence of AEs.
Merck & Co., Inc.	Executive Summary, Page 23, Table D, line 26	ES 14: For rotavirus, the table only lists one US safety study. There are at least two others. See Below.	We have added the new US safety studies published after we conducted our initial electronic searches.
Merck & Co., Inc.	Executive Summary, Page 24, Table D, line 13	ES15: AHRQ does not normally consider mechanistic evidence. Please reevaluate whether to include IOM's consideration of mechanistic evidence. Despite the IOM's favorable mechanistic association between HPV vaccination and anaphylaxis, other studies have found no such association. Please see Klein NP et al, Arch Pediatr Adolesc Med. 2012;166(12):1140-1148. Moreover, true yeast sensitivity is extremely rare. If the statement on anaphylaxis is to be included, please include some statement as to the frequency of yeast sensitivity.	Methods were determined a priori in conjunction with the sponsor and a Technical Expert Panel (TEP). The protocol was posted online in 2012. We have added Klein, 2012 which was published after our original electronic search.
Merck & Co., Inc.	Executive Summary, Page 24, Table D	ES-15: While it is true that Chao et al. did not find a significant association between Gardasil® and syncope, the event is frequently reported and appears on the product label. Please consider whether the product label is considered evidence for the purposes of this report. See also CDC MMWR (2008) 57(17);457-460	Product labels were used to **identify** AEs/search terms for the electronic searches for evidence. If labels referred to research studies, those studies were retrieved and screened for inclusion. Only research studies that met our stated inclusion criteria were considered evidence.
Merck & Co., Inc.	Executive Summary, Page 25, Table D, line 7	ES-16: There should be a comma after "anaphylaxis" in the first line.	We have made that change to Tables D and 31.
Merck & Co., Inc.	Executive Summary, Page 25, Table D	Regarding the text "disseminated Oka VZV without other organ involvement, disseminated Oka VZV with subsequent infection resulting in pneumonia, meningitis, or hepatitis in individuals with demonstrated immunodeficiencies", please clarify if the "with demonstrated immunodeficiencies" refers to all of the prior diagnoses or just hepatitis.	"with demonstrated immunodeficiencies" refers to all of the listed diagnoses.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Executive Summary, Page 25, Table D, line 38	ES-17 and ES-18, combination vaccines or multiple vaccines In the right column, the second line of the third paragraph should state “purpura was,” rather than “purpura were.”	We have made that change throughout the report
Merck & Co., Inc.	Executive Summary, Page 25, Table D	The text at the end of the third paragraph regarding the incidence and reported severity of these AEs was very helpful, and provides important context in assessing vaccine safety. Is it possible to provide this type of information for the other vaccines discussed?	Yes, we supply this data wherever available.
Merck & Co., Inc.	Executive Summary, Page 28, line 27	ES-19: Typo: “Barre” should be “Barré.” The EPC may wish to run a find/replace for this word combination throughout the document and Tables.	We have replaced “Barre” with “Barré” throughout the report.
Merck & Co., Inc.	Executive Summary, Page 28	ES-19: “results translate to about 1.6 additional cases per million persons vaccinated.” This is a great way to put the frequency of adverse events in perspective. More statements of this nature would help the reader understand how to place the statistics reported in this review into real-world terms, which in turn would aid in realistic decision-making. Please consider reporting more calculations like this.	Thank you, we supply these statistics wherever they were provided in the studies or calculable by our team.
Merck & Co., Inc.	Executive Summary, Page 29, line 43	ES-20: “They often reported only broad categories such as “injection–related adverse events,” “systemic adverse events,” “one or more adverse events” or “serious adverse events,” rather than specifying type or severity. Vaccinated groups often had significantly higher risk of these “categorical” events.” This last sentence implies statistical significance which is not true. Consistently across clinical studies, we have seen statistically significantly higher number of overall adverse events, which is due for the most part to the statistically significantly higher number of injection-site reactions. It is not accurate to say that the clinical studies have often reported significantly higher risk of systemic adverse events or serious advents as a category. Please modify this language accordingly.	We have deleted implication of association with SAEs. However, in two of the six trials (Schmader, 2012; Vermeulen, 2012) vaccination was associated with systemic AEs. Please see Table 10 for data.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Executive Summary, Page 29, line 53	ES-20: "One investigated post-vaccination herpes zoster incidence in patients with preexisting conditions; another investigated serious adverse events (such as acute myocardial infarction, stroke, and Bell's palsy) in the weeks following vaccination in healthy patients." This sentence is unclear and potentially misleading with regard to the post-licensure studies. Given the indicated age of Zostavax® is the majority of subjects enrolled as healthy volunteers would be expected to have some pre-existing conditions. With regard to the second half of the sentence, it appears to reference the Tseng study, which was not specific to serious adverse events. Thus it did not "investigate" serious adverse events. Rather, serious adverse events were among the outcomes reported. Please revise this language.	Tseng, 2010 investigated pre-specified adverse events within pre-defined risk windows. From Tseng, 2010 "Five major groups of events of interest included Group 1: Stroke and Cerebrovascular diseases, Group 2: Cardiovascular diseases, Group 3: Meningitis, encephalitis and encephalopathy, Group 4: Ramsay-Hunt Syndrome and Bell's palsy, and Group 5: Medically attended reactions (reactions leading to a medical visit)." Thus we stand by our language regarding assessment of serious adverse events. Regarding the population, we have changed "healthy" to "MCO enrollees." Minimum age studied was 50. Whether these subjects had any pre-existing conditions is a matter of speculation, as the study did not discuss.
Merck & Co., Inc.	Executive Summary, Page 30,	ES-21: Inclusion-body encephalitis is rare, and is much more common in wild-type infection. Please include a measure of the rate of occurrence of this AE.	The rate was neither reported nor calculable from the evidence identified.
Merck & Co., Inc.	Executive Summary, Page 30	ES-25: "We concur with the IOM's conclusion of a causal relationship between influenza vaccines and anaphylaxis in persons who may be allergic to ingredients." Please specify the ingredients considered by the IOM to be potentially associated with anaphylaxis.	The ingredients associated with allergic reaction are gelatin and egg. We have stated this in the results section and in the table.
Merck & Co., Inc.	Executive Summary, Page 29, line 36	Page ES-21, Research gaps The first paragraph on this page states that MS is a concern for MMR. Please clarify why this is the case.	We have removed the word "concern." This paragraph states that the IOM found evidence "inadequate to accept or reject" a causal relationship; this is an area for future research.
Merck & Co., Inc.	Executive Summary, Page 30	The second paragraph under "children": as noted earlier in the comment for page ES-14, it is important to specify that MIBE following measles vaccine has been observed in immunocompromised individuals (in whom the vaccine is contraindicated) who were inadvertently vaccinated with measles-containing vaccine.	We have specified that MIBE occurred in immunocompromised patients; we have removed this issue from the research gaps section of the report.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Introduction, Page 34, Table 1	PG 1: The authors indicate that 27% of women aged 14-59 are affected by HPV infection. This data is taken from a paper looking at point prevalence of HPV infection in women aged 14-59 but does not sufficiently address the lifetime prevalence of HPV infection in the population. Approximately 80% of people will be infected with HPV during their lifetimes. Please see Weaver BA. *J Am Osteopath Assoc.* 2006;106(3 suppl 1):S2–S8	The lifetime prevalence of HPV and the other diseases prevented through vaccination is beyond the scope of this report. We have removed the reference regarding the point prevalence of HPV infection
Merck & Co., Inc.	Methods, General Comment	A large number of important references do not appear in the report (See comments under References, below). Some are recent, and probably post-date the original searches run for the review. These were presumably identified in the updated searches. Others should have been identified, but do not appear in the review. While it is possible we are misinterpreting the study inclusion criteria, it is also possible that the search strategies are somehow flawed. If the EPC finds that they have missed a sizeable number of relevant studies, please consider revising the searches for all vaccines.	Thank you for suggesting additional studies. Most were identified by our searches and excluded for various reasons. Others were published after our initial searches; we screened these studies and included several. Each study suggested is addressed in the corresponding row below.
Merck & Co., Inc.	Results, General Comment	Please note that comments on Results may apply to the Executive Summary and Conclusions sections as well.	Thank you, we have made sure the report is consistent throughout.
Merck & Co., Inc.	Results, Page 34, Tables 1-3	As was noted for the executive summary tables, vaccination scheduling recommendations have been revised. Please revise accordingly.	The goal of this project was to address the safety of vaccines recommended as of October, 2011. We have clarified throughout the report and in the tables. The project was close to completion when the recommendations were updated in 2013.
Merck & Co., Inc.	Results, Page 49, Table 5	Page 16, table 5, Pneumococcal polysaccharide vaccine. Please consider adding information from the placebo-controlled trial by Manoff of 23-valent pneumococcal polysaccharide vaccine in adults: Manoff SB, Liss C, Caulfield MJ, Marchese RD, Silber J, Boslego J, Romero-Steiner S, Rajam G, Glass NE, Whitney CG, Carlone GM. Revaccination with a 23-valent pneumococcal polysaccharide vaccine induces elevated and persistent functional antibody responses in adults aged >=65 years. J Infect Dis 2010;201(Feb 15):525-33.	Manoff, 2010 is an efficacy study that does not report adverse events. Per the methods section of our report “Studies were included for analysis if the total number of people in each group and the number of people with events in each group were reported**.” If a study did not explicitly state that no adverse events took place, it was excluded.**

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Results, Page 50, Table 6	Page 17, table 6, Pneumococcal polysaccharide vaccine. There are a number of case control studies and other observational studies of pneumococcal polysaccharide vaccine in adults. It's not clear how the studies that were reviewed in this report were selected for inclusion. For instance, the text on page 33 suggests that one selection criterion may have been study only of pneumococcal polysaccharide vaccine; however, the table includes studies in which subjects received influenza vaccine as well. There are other studies in which both vaccines were used. Please clarify what is being investigated for each analysis. See below for suggestions of other combination vaccine studies that bear on the subject.	This table lists the reason for exclusion of each specific study suggested by Merck. Appendix D lists reasons for all excluded studies. The methods section of the report describes the inclusion criteria for the project.
Merck & Co., Inc.	Results, Page 49, Table5	Page 16: Table 5. Varicella and Zoster are combined and the terms that fall under these vaccines are a combination of general terms, system organ class, and specific AE terms. The differences between these types of terms should be more clearly explained. It's not clear which specific studies (varicella or zoster vaccine studies) support which terms. There is more information about injection site reactions, including specific AE terms, in the product circular which are not noted here. Again, please consider whether the FDA mandated labeling is considered to be evidence.	Product labels were used to identify AEs/search terms for the electronic searches for evidence. If labels referred to research studies, those studies were retrieved and screened for inclusion. Only research studies that met our stated inclusion criteria were considered evidence.
Merck & Co., Inc.	Results, Page 48	In addition, the text supporting the table makes it clear that AE terms reported in the placebo group are included, but the table title should specifically state "In unvaccinated and vaccinated patients," otherwise it could easily be misinterpreted that these were only reported in the vaccine group. The supportive text indicates that the table does not imply association with the vaccine but they list as one of their categories discontinuations for vaccine-related AEs without acknowledging discontinuations for AEs in general. Please be clear in the descriptions of AEs. If the publication was ambiguous, please state this, but further ambiguity should not be added.	The AE terms in the table come directly from the studies. We make this clear in many places in the report. As you acknowledge, the supportive text indicates that the table does not imply association with vaccination.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Results	Page 17: "Table 6 lists all AEs and medical conditions investigated…" It is not clear what is meant by "investigated." Does this mean that these were pre-specified AE terms evaluated by the investigators or does this mean these are reported terms? Please clarify.	The term "investigated" encompasses both the AEs pre-specified by the researchers,(regardless of whether such AEs occurred) and all other AEs reported (regardless of whether they were pre-specified or mentioned spontaneously by the patient).
Merck & Co., Inc.	Results	Page 33: As noted above, several placebo-controlled trials of currently available pneumococcal polysaccharide vaccines are available. The EPC may wish to consider revising their searches in this area.	We have responded regarding each specific study you suggested for inclusion.
Merck & Co., Inc.	Results	Page 39: "We identified eight trials of Zoster vaccine; results are summarized in Table 11." Does the quoted sentence refer to Table 10? If so, please revise.	In the draft version of the report, trials of zoster vaccine were presented in Table 10. The tables were renumbered in the final version.
Merck & Co., Inc.	Results	Page 39: In relationship to reference 70—"How AEs were determined to be related to vaccination was not described". The publication authors note that causality assessments were made by study investigators. They specifically note this for SAEs and deaths, but the same practice was followed for all AEs.	You are correct; the study authors note that causality assessments were made by study investigators. However, the criteria for **how** adverse events were determined to be related to vaccination by investigators is not reported.
Merck & Co., Inc.	Results, Page 72, line 28	Page 39: The study design for reference 72 is inaccurately described. "…who received Zostavax at study start and 28 days later." This was a cross-over study design. Patients received either a single dose of Zostavax or placebo. Subjects who received Zostavax first received placebo as a second vaccination and subjects who received placebo first received Zostavax as a second vaccination. Two doses of Zostavax were not administered. Please revise the description and consider whether any odds ratio calculations need to be revised based on this change.	We have revised the text to clarify that this was a crossover study. We report AEs from the pre-crossover period of the trial.
Merck & Co., Inc.	Results, Page 72, line 30	Page 39: "The only AE associated with vaccination in the overall study population was injection-site AE." Please clarify whether the term "associated" refers to reported causality or statistical association.	This statement refers to statistical association (OR 19.84, 95% CI 6.77—58.12).
Merck & Co., Inc.	Results, Page 72, line 30	Page 39: Please note also that the patients in this study constitute a Special Population: Participants had a prior history of herpes zoster.	We have removed any reference to "special populations."

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Results, Page 72, line 47	Page 39: In the paragraph beginning "Regarding special populations…" It is questionable whether these patients constitute a special population. Because the targeted population tends to be older, it is to be expected that the majority suffer from one or more of the listed conditions. Patients in other studies report a similar array of comorbidities. Please reconsider whether these patients constitute a special population.	We have removed any reference to "special populations."
Merck & Co., Inc.	Results, Page 72, line 43	Page 39: With regard to reference 75—"No statistically significant differences in adverse events between vaccinated and unvaccinated groups were reported." The study collected only serious adverse events. Please insert the word "serious" before "adverse events" wherever necessary and define what the study meant by "serious."	Thank you. We have inserted the word "serious" and added more detail on AEs collected in the sub-study.
Merck & Co., Inc.	Results, Page 72 and Page 73,74	Page 39 and Table 10: References 71 and 76 both describe the same publication. The number of patients abstracted is slightly different between them. Please eliminate one of the references, re-assess how the number of patients was determined, and revise any calculations to reflect both the reduced number of studies and the corrected number of patients. The number of studies will also need to be reduced by one in sections where this information is provided. Further, this study did not enroll special populations. The text reads as if the listed medical conditions were requirements for entry into the study, which is not correct. The study enrolled the same population as other studies—immunocompetent adults. These are the typical medical history conditions you find in adults of this age. Please ensure that this is clear.	Thank you for the clarification. We have removed the duplicate listing and have revised the tables and text accordingly. We have also removed the term "special population."
Merck & Co., Inc.	Results, Page 72 and Page 74	Page 39: Similarly, references 73 and 75 describe different analyses of the same study. In addition, the 38,000+ sample size reported is correct in terms of overall study participants, but some of the analyses are based only on the individuals in the Adverse Event Monitoring Substudy which comprised a subset of 6600+ subjects. Please revise the text, tables and calculations accordingly. The McHarm scores for the study will also require revision.	Thank you for the clarification. We have revised the tables and text accordingly.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Results, Page 86	Page 53, multiple vaccines/other vaccines in adults. The Hedlund et al study of influenza and pneumococcal vaccines is described here. This study might be better placed in the pneumococcal polysaccharide vaccine section above, because other similar studies are described there. In addition, these vaccines are not listed in the combination vaccine section of the executive summary. Please consider revising. Several studies somewhat similar to the Hedlund study were not captured by the study's search methods. These include the following: Alfageme I, Vazquez R, Reyes N, Muñoz J, Fernández A, Hernandez M, Merino M, Perez J, Lima J. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax 2006;61:189–95. {#21244} Furumoto A, Ohkusa Y, Chen M, Kawakami K, Masaki H, Sueyasu Y, Iwanaga T, Aizawa H, Nagatake T, Oishi K. Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease. Vaccine. 2008;26(Aug 5):4284-9. {#21245} Kawakami K, Ohkusa Y, Kuroki R, Tanaka T, Koyama K, Harada Y, Iwanaga K, Yamaryo T, Oishi K. Effectiveness of pneumococcal polysaccharide vaccine against pneumonia and cost analysis for the elderly who receive seasonal influenza vaccine in Japan. Vaccine. 2010;28(Oct 8):7063-9. {#21246} Jackson L, Neuzil K, Yu O, Benson P, Barlow W, Adams AL, Hanson CA, Mahoney LD, Shay DK, Thompson WW; Vaccine Safety Datalink. Effectiveness of pneumococcal polysaccharide vaccine in older adults. New England Journal of Medicine 2003;348(18):1747–55. {#21247} Vila-Corcoles A, Ochoa-Gondar O, Hospital I, Vilanova A, Rodriguez T, Llor C, EVAN Study Group. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the {#12899}elderly population: The EVAN-65 study. Clinical Infectious Disease	The suggested studies were identified by our searches. All were excluded as efficacy studies which do not report adverse events. Per the methods section of our report "Studies were included for analysis if the total number of people in each group and the number of people with events in each group were reported." **If study did not explicitly state that no adverse events took place, it was excluded.** For example, Alfageme, 2006 was an efficacy study which reported % with Community Acquired Pneumonia—this is an efficacy outcome. Study also reported a mortality rate "around 19%" in both groups. No other AEs were mentioned

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc. (continued)	Results, Page 86 (continued)	Vila-Corcoles A, Ochoa-Gondar O, Hospital I, Vilanova A, Rodriguez T, Llor C, EVAN Study Group. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the {#12899} elderly population: The EVAN-65 study. Clinical Infectious Diseases 2006;43:860–8.	The suggested studies were identified by our searches. All were excluded as efficacy studies which do not report adverse events. Per the methods section of our report "Studies were included for analysis if the total number of people in each group and the number of people with events in each group were reported." **If study did not explicitly state that no adverse events took place, it was excluded.** For example, Alfageme, 2006 was an efficacy study which reported % with Community Acquired Pneumonia—this is an efficacy outcome. Study also reported a mortality rate "around 19%" in both groups. No other AEs were mentioned.
Merck & Co., Inc.	Results, Page 76, line 35	Page 43: "In the eight clinical trials we identified, dosage varied from 18,700 to 89,000 PFU (plaque-forming units) per 0.5 ml." Not all of the studies identified administered a 0.5 mL dose. In addition, PFU is a measure of potency. It would be more accurate to state that the potency varied, rather than the dose.	We have replaced "per 0.5 ml" with "per dose." We have replaced the word "dose" with "potency" where appropriate.
Merck & Co., Inc.	Results, Page 76, line 38	Page 43: "Although not always noted in the publications, studies using doses in the high end of the range are likely Phase II trials." This statement is speculative. Please consider removing or revising.	We contacted FDA and attempted to verify this information; however, we were advised it was confidential and could not be shared with our team. Thus, we have removed the language regarding Phase 2 trials.
Merck & Co., Inc.	Results, Page 76, line 39	Page 43: "The dosage currently licensed in the US is 19,400 PFU per 0.65 ml." This implies that every dose contains exactly 19,400 PFU/0.65 mL which is not correct. Per the product label: A single 0.65 mL dose will not contain less than 19,400 PFUs when reconstituted. Please revise accordingly.	We have revised to state that a 0.65 mL dose will not contain less than 19,400 PFUs when reconstituted.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Results, Page 76, line 48	Page 43, ES-12, 122: "We found only two post-licensure studies; the only adverse events associated with Zoster vaccine were cellulitis and allergic reactions. (No cases of anaphylaxis were reported.)" It is not clear why reference 74 is not considered when composing this statement. Please reconsider. In addition, the Baxter study (Vaccine 2012;30:6636-41), which probably postdates the current searches, is another post-licensure study.	We have added Baxter, 2012 which post-dated our original search. The statement in quotes refers to adverse events in post-licensure studies only. Reference 74, Murray, 2011 is a clinical trial, as is reference 70, Schmader,2012 .
Merck & Co., Inc.	Results, Page 76	Vaccine-related anaphylaxis is reported in the literature in reference 70.	The statement in quotes refers to adverse events in post-licensure studies only. Reference 74, Murray, 2011 is a clinical trial, as is reference 70, Schmader, 2012.
Merck & Co., Inc.	Results, Page 76	Hypersensitivity reactions are labeled events. Please consider whether the product label constitutes evidence.	Product labels were used to identify AEs/search terms for the electronic searches for evidence. If labels referred to research studies, those studies were retrieved and screened for inclusion. Only research studies were considered evidence.
Merck & Co., Inc.	Results, Page 76	The statement on cellulitis is not consistent with the statements in the referenced article. From the article: "A small increased risk of cellulitis, 1-7 days following vaccination found by case-centered method may well represent inflammatory or allergic reactions rather than true infectious cellulitis. This finding is consistent with the SPS safety study…"	We have added the language regarding inflammatory or allergic reactions.
Merck & Co., Inc.	Results, Page 76, line 42	Page 43: "Only one trial reported more specific events; this trial used broad categories…" This statement is inaccurate. For example, references 72 and 73 note specific injection site AEs. Reference 70 notes headache and VZV-like rashes. Reference 74 notes the most common SAEs by System Organ Class (SOC). Please reexamine the references and revise the statement.	We have revised the language on the categorical reporting of AEs.
Merck & Co., Inc.	Results, Page 86, line 8	Page 53: Typo: "arthlagia"	We have corrected the typo.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Results, Page 91, Table 16	Page 58, table 16.It's not clear why AEs from MMR and varicella vaccines are not included here. If it is because there are no new trials since the IOM report, please state this. The table extends over 2 pages. On the 2nd page (page 59), are the AEs in the left column related to Rotavirus or to combination vaccines? Please clarify this.	MMR and varicella vaccines are now included, as studies were published while the report was under review. We have fixed the page break issues.
Merck & Co., Inc.	Results, Page 92, Table 17	Page 59, table 17, AEs in postmarketing studies. As with table 16, it's not clear why only some of the vaccines considered in this report are included here	All vaccines are not included in the table.
Merck & Co., Inc.	Results, Page 102	Pages 69-72, MMR in children. Meningitis is mentioned on page 70. The risk may vary by virus strain. The U.S. prescribing information for M-M-R® II states, "Cases of aseptic meningitis have been reported to VAERS following measles, mumps, and rubella vaccination. Although a causal relationship between the Urabe strain of mumps and aseptic meningitis have been shown, there is no evidence to link Jeryl Lynn™ strain mumps vaccine to aseptic meningitis." Please consider the role of viral strain in the assessment.	We have added a sentence "although a causal relationship between the Urabe strain of mumps and aseptic meningitis have been shown, there is no evidence to link Jeryl Lynn™ strain mumps vaccine to aseptic meningitis."
Merck & Co., Inc.	Results, Page 117, lines 21 and 25	Page 84: Typos: "RotaTeqRotateq" "RotaTeqwith"	We have removed the duplicate word and put a space between RotaTeq and with.
Merck & Co., Inc.	Results, Page 117	P. 84: "The only post-licensure study conducted in the U.S. (Shui, 2012) found no association between RotaTeq and intussusception at any time after vaccination." Please add the study by Loughlin et al. (Pediatr Infect Dis J 2012;31:292–296) and the study by Belongia et al (Pediatr Infect Dis J. 2010 Jan;29(1):1-5)—both studies did not find an association RotaTeq and intussusception.	Loughlin, 2012 and Belongia, 2010 did not meet our inclusion criteria.
Merck & Co., Inc.	Results, Page 117, line 15	P. 84 "Both RotaTeq and Rotarix were associated with cough, runny nose and irritability in children. There is moderate strength evidence from several RCTs for these mild, short-term adverse events." Please reassess the data to determine whether these conclusions are warranted. Our examination of the tables finds only limited data on these AEs.	Thank you. We have reassessed and removed this conclusion.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Results, Page 117, line 21	PG84: "However, a high quality epidemiological study (N = 296,023) found RotaTeqRotaTeq associated with intussusception in children 1 to 21 days following the first of three required doses. Strength of evidence is moderate given size and quality of that study, conducted in Australia." The fragment "of three required doses" is inaccurate, as Rotarix requires two doses. Please truncate the sentence to read" …first dose." Please double-check which drug is utilized in the above study and name it accurately.	This study included analyses on both Rotateq and Rotarix. RotaTeq was associated with intussusception in children 1 to 21 days following the first of three required doses. We have corrected the typo "RotaTeqRotaTeq."
Merck & Co., Inc.	Results, Page 119	PG86: There are no results reported. The column labeled "results for risk factors" for this study contains the values "Dose1: 0 Days, Dose2: 2 Month, Dose3: 2 Month—this does not correlate with any known data for this paper. Also, in the column "vaccines", this study has a "1" in the cell—it should say "RotaTeq".	Thank you. We have replaced with correct data from Shui, 2012.
Merck & Co., Inc.	Results, Page 120, line 5	PG87: The row describing Haber et al. contains no data.	Haber, 2013, uses VAERS data from passive surveillance. Thus, this study did not meet our inclusion criteria. We apologize for the earlier mistake of listing the author name in this table.
Merck & Co., Inc.	Results, Tables 22 and 23	Tables 22 23. "Post-marketing studies of rotavirus vaccines in children and adolescents" Please remove "and adolescents".	We have removed the word "adolescents" from both tables 22 and 23
Merck & Co., Inc.	Results, Page 119, line 37	PG86: "Children receiving RotaTeq in US (N=117,575)" This study (Shui I. M. et al., 2012) does not state number of subjects, only number of doses administered. Please remove the current N and instead insert: 786,725 total RV5 doses, which included 309,844 first doses and revise any calculations accordingly.	We confirmed that the analysis was based on 786,725 total doses and revised the text to reflect this.
Merck & Co., Inc.	Results, Page 123	Page 90: Studies published since the IOM report show no association between anaphylaxis and HPV vaccination Klein NP et al, Arch Pediatr Adolesc Med. 012;166(12):1140-1148 Yih et al. PEDIATRICS Vol. 127 No. Supplement 1 May 1, 2011 pp. S54 -S64	Klein, 2012, {was published after our initial electronic search; we have added this study. Yih, 2011 reports on assessment of the potential associations between five vaccines and 5 to 7 pre-specificied adverse outcomes. This is a review of studies published elsewhere.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Results, Page 132	Page 99, combination/multiple vaccines in children. In the purpura section on the top of the page and in the last paragraph on the page, we suggest specifying whether the finding for varicella vaccine was in children 11 to 17 months or years of age. From the table, it appears that this is years of age.	The table is correct; the finding for varicella vaccine was for children 11 to 17 years of age (Leary, 2012). We have added "years" after "children aged 11 to 17" in the text.
Merck & Co., Inc.	Research Gaps, Page 162—163	Pages 129-130, Research gaps. Same comments as above for MMR, including Please clarify why MS is a concern regarding MMR vaccines. Measles inclusion body encephalitis has been observed in immunocompromised persons. This is a risk factor that could be stated here.	We have revised to state that vaccination is associated with measles inclusion body encephalitis "in immunocompromised persons"
Merck & Co., Inc.	Research Gaps, Page 162, line 44	P. 129: "Purpura were also associated with MMR as well as with vaccination against varicella and hepatitis A; however, most cases were considered mild and acute." This is a statement of a conclusion rather than a description of a research gap. Please remove it from this section.	We have deleted this statement from the research gaps section.
Merck & Co., Inc.	Research Gaps, Page 162, line 47	P. 129 "Post-licensure studies in foreign countries have associated both Rotarix and RotaTeq with intussusception 21 days following vaccination. However, a large U.S. study found no association. The risk with Rotarix could be investigated further in US populations" Note that intussusception is only noted after the first dose. Note also that there are now at least three US studies (add Loughlin et al. Pediatr Infect Dis J 2012;31: 292–296 and Belongia et al Pediatr Infect Dis J. 2010 Jan;29(1) 1-5).	Loughlin, 2012 and Belongia, 2010 were identified in our initial searches and did not meet our inclusion criteria.
Merck & Co., Inc.	Research Gaps, Page 162 -163	Pages 129-130, Research gaps. General comment: as noted above, it would be helpful to add information on incidence of specific events and intensity, where these data are available.	We supply this data in the results and conclusions sections whenever it is available.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Research Gaps, Page 162, line 21	PG 129: “They often reported only broad categories such as “injection–related adverse events,” “systemic adverse events,” “one or more adverse events” or “serious adverse events” rather than specifying type or severity. Vaccinated groups often had significantly higher risk of these “categorical” events.” This last sentence implies statistical significance which is not accurate. Consistently across clinical studies, we have seen statistically significantly higher number of overall adverse events which is due for the most part to the statistically significantly higher number of injection site reactions. It is not accurate to say that the clinical studies have often reported significantly higher risk of systemic adverse events or serious advents as a category. Please modify this language accordingly.	We have deleted implication of association with SAEs. However, in two of the six trials (Schmader, 2012; Vermeulen, 2012) vaccination was statistically associated with systemic AEs. Please see our table in the Zoster section of Results for data.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Research Gaps, Page 162, line 30	PG 129: "One investigated post-vaccination herpes zoster incidence in patients with preexisting conditions; another investigated serious adverse events (such as acute myocardial infarction, stroke, and Bell's palsy) in the weeks following vaccination in healthy patients." This sentence is unclear and potentially misleading with regard to the post-licensure studies. Given the indicated age of ZOSTAVAX almost everyone who is enrolled as a healthy volunteer would be expected to have some pre-existing conditions. With regard to the second half of the sentence, it appears to reference the Tseng study, which was not specific to serious adverse events. Thus it did not "investigate" serious adverse events. Rather, serious adverse events were among the outcomes reported. Please revise this language.	Tseng, 2010 investigated pre-specified adverse events within pre-defined risk windows. From Tseng, 2010 "Five major groups of events of interest included Group 1: Stroke and Cerebrovascular diseases, Group 2: Cardiovascular diseases, Group 3: Meningitis, encephalitis and encephalopathy, Group 4: Ramsay-Hunt Syndrome and Bell's palsy, and Group 5: Medically attended reactions (reactions leading to a medical visit)." Thus we stand by our language regarding investigation of serious adverse events. Regarding the description of the population, we have changed "healthy" to "MCO enrollees." Minimum age studied was 50 years. Whether these subjects had any pre-existing conditions is a matter of speculation, as the study did not discuss. Your statement "almost everyone enrolled as a healthy volunteer" would "be expected to have some pre-existing condition" because they are 50 years of age or older" is not supported by evidence.
Merck & Co., Inc.	Table 10, Page 73	Table 10: (1) In the vaccine column Zostavax is described with different names. This may be a reflection of some manuscripts stating zoster vaccine and some stating Zostavax, but it is the same vaccine. Please consider whether for clarity if the description should be consistent throughout the tables.	We used "Zostavax" when we were sure the formulation was the same as the product currently on the market. Some early trials used formulations with strengths different from the current Zostavax product; for clarity, we list the vaccine exactly as identified in those studies.
Merck & Co., Inc.	Table 10, Page 73	(2) There is a comment that adjuvants (live vaccine, no adjuvant) and preservatives are not reported in the literature, but this information is available in the product circular. Please consider whether the product circular should be referenced.	As formulations used in clinical trials (especially Phase II trials) sometimes differ from the final product on the market, we decided against this. We abstracted the formulations verbatim from the studies.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	Table 10, Page 73	(3) Zostavax Dose 1 is indicated as being administered at 0 Days. Some of the studies considered day of vaccination to be Day 1 not Day 0. This is outlined in the manuscripts. Please consider whether this column should be revised to match the manuscripts.	For consistency, we always used Day 0 for first dose. That way comparison can be made across vaccine formulations/brands displayed in the tables.
Merck & Co., Inc.	Table 32, Page 155	Table 32, Page 122: Typo: “arthragia”	We have corrected to “arthralgia.”
Merck & Co., Inc.	Figures A and 2, Literature Flow	Figures A and 2: As stated previously (ES-7) five articles could not be obtained. As far as we can determine, these five articles are not listed anywhere in the report. Had they been listed, we or others might have been able to aid the EPC in obtaining them. Please list them in the final report so that readers may judge the potential impact of their omission.	We have added a list in the appendix. Of the five, three are unpublished studies from pharmaceutical companies who did not respond to our requests. One is a news report about the early rotavirus vaccine that was taken off the market and thus excluded from this project. The fifth is an erratum to a 1991 study of Hib in Native Americans. We feel the impact of their omission is minimal.

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	References, Page 164	Several important studies appear to have been omitted: Neuzil KM, et al. JAMA. 2011;305:1424-31 Kang S, et al. In J Gyn Cancer. 2008;18:1013-9 Slade BA, Leidel L, Vellozzi C, Woo EJ, Hua W, Sutherland A, Izurieta HS, Ball R, Miller N, Braun MM, Markowitz LE, Iskander J. Postlicensure safety surveillance for quadrivalent human papillomavirus recombinant vaccine. JAMA. 2009 Aug 19;302(7):750-7. doi: 10.1001/jama.2009.1201. NP, Hansen J, Chao C, Velicer C, Emery M, Slezak J, Lewis N, Deosaransingh K, Sy L, Ackerson B, Cheetham TC, Liaw KL, Takhar H, Jacobsen SJ. Safety of quadrivalent human papillomavirus vaccine administered routinely to females. Arch Pediatr Adolesc Med. 2012 Dec;166(12):1140-8. doi: 10.1001/archpediatrics.2012.1451. Macartney KK, Chiu C, Georgousakis M, Brotherton JM. Safety of human papillomavirus vaccines: a review. Drug Saf. 2013 Jun;36(6):393-412. doi: 10.1007/s40264-013-0039-5. Baxter R, Bakshi N, Fireman B, Lewis E, Ray P, Vellozzi C, Klein NP. Lack of association of Guillain-Barre syndrome with vaccinations. Clin Infect Dis. 2013 Jul;57(2):197-204. Baxter R, Tran TN, Hansen J, Emery M, Fireman B, Bartlett J, Lewis N, Saddier P. Safety of ZostavaxTM—A cohort study in a managed care organization Vaccine 30 (2012) 6636–6641. Vila-Córcoles A, Ochoa-Gondar O, Rodriguez-Blanco T, de Diego C, Satue E; for the EPIVAC Group. Ineffectiveness of pneumococcal vaccination in cardiovascular prevention: The CAPAMIS Study. JAMA Intern Med 2013 May 27:1-3. (Note that this is an update of Vila-Corcoles et al 2012) (Reference 68)	Neuzil, 2011 is dosing trial conducted in Vietnam. Excluded due to no placebo group. Kang, 2008 is an RCT which we have added to our report. Slade, 2009 is a study using data from VAERS, a passive surveillance system, and thus was excluded. Hansen, 2012 was published after our initial electronic searches. We have now included. Macartney, 2013 is a non-systematic review and thus excluded. Baxter, 2013 was published after our initial electronic searches. We have now included. Baxter, 2012 was published after our initial electronic searches. We have now included. Vila-Corcoles, 2012 is a clinical trial which presents no safety data.
Merck & Co., Inc.	Appendix, Page 212,	Page B-12, change acronym from PSV23 to PPSV23 (CDC's preference)	We have changed it throughout the Appendix
Merck & Co., Inc.	Appendix, Page 217	Page B-17, change acronym from PSV23 to PPSV23 (CDC's preference)	We have changed it throughout the Appendix
Merck & Co., Inc.	Appendix, Page 221	Page B-21, change acronym from PSV23 to PPSV23 (CDC's preference)	We have changed it throughout the Appendix

Commentator & Affiliation	Section	Comment	Response
Merck & Co., Inc.	General Comments	General Comment: We did not find any definitions of the common adverse events (which probably varied to unspecified degrees among studies). Similarly, event severity was poorly described. In many cases, the objective frequency of an event is described poorly, or not at all. An understanding of the severity of an adverse event is necessary for decision-makers to determine whether a given change in its rate of incidence is considered acceptable. Not all decision-makers are equally versed in applicable areas of epidemiology and clinical medicine. Please include a glossary of adverse events, defining intussusception, oculorespiratory syndrome, pyrexia, Guillian-Barre Syndrome, etc, or concise versions of the Brighton definitions of these conditions. Also please define what is meant by the word "severe." If different researchers define it differently, provide definitions.	The report emphasizes throughout that the definitions varied from study to study, We have also stated throughout the report that the degree of severity of AEs was often unreported in the studies, as was information that might allow our team to make a judgment about severity. If information was reported in a study, it is described in our report. We revised our discussion section to further emphasize these issues.