Author’s response to reviews

Title: Childhood MMR Vaccination and the Incidence Rate of Measles Infection: A Ten Year Longitudinal Cohort Study of American Children born in the 1990s

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Version: 1 Date: 13 Jan 2019

Author’s response to reviews:

Thank you for the opportunity to revise our manuscript. We have addressed the Reviewers’ comments and have made changes to the manuscript accordingly. We include a point-by-point response to the comments. All changes to the manuscript are indicated in the text by highlighting.

Response to Reviewers’ Comments

Abram Luther Wagner, PhD, MPH (Reviewer 1):

Comment 1: In the Abstract first sentence, you mention "exposed" individuals - I think "vaccinated" would be a better term throughout paper.

Response to Comment: The manuscript was revised to remove exposed/unexposed persons, and, instead, refer to them as vaccinated or unvaccinated.

Comment 2: The methods sentences "on a 64-bit based PC with dual core Intel® (Santa Clara, CA, USA) Xeon® CPU x5680 at 3.33 GHz, 6 cores, and 12 logical processors, with 44.0 GB of RAM, and utilizing Microsoft (Redmond, WA, USA) Windows 7 Ultimate operating system was used to examine the IHRD." seem unnecessary to me.

Response to Comment: This information was kept in the manuscript to provide readers with important information regarding the computer hardware and software utilized to analyze the database.
Comment 3: Some material from methods could be moved to results, for instance "Overall, it was observed that 76 persons were diagnosed with measles in the unexposed cohort. In the MMR vaccine exposed cohort, a total of 55 persons were diagnosed with measles, but only 12 were diagnosed with measles post-MMR vaccine administration"

Response to Comment: This language was included in the methods section to explain how the MMR vaccinated cohort was slightly reduced in size by eliminating those MMR vaccinated persons that were diagnosed prior to vaccine administration.

Comment 4: In the methods - how did you control for the variable "date of birth"? Was it entered as a continuous variable or did you categorize it?

Response to Comment: The manuscript was revised to reflect that it was a continuous variable as follows, “All models were constructed without adjustment for covariates (Model I) and with adjustment for the covariates of gender (categorical variable), date of birth (continuous variable), and county of residence (as a continuous variable) (Model II).”

Comment 5: Do you know how many cases were reported to the national notifiable disease system from Florida in this time period (compared to what you found in the Medicaid system)? It seems there might be some sort of selection bias -although I don't think it would have a huge impact on your estimates.

Response to Comment: Unfortunately, the information requested is not publically available, so it was not possible to undertake this comparison.

Walter Orenstein (Reviewer 2):

Comment 1: There are a number of clarifications needed to improve the quality of the analysis and overall manuscript.

Comment 2. Were the measles cases laboratory confirmed or the data were not available? This should be clarified. In other words, the authors should make clear that the diagnoses were based on clinical judgment and not on specific clinical or laboratory-based criteria.
Response to Comment: The manuscript was revised to address the comment by inserting the following sentence to the Methods Section, “No information was available regarding whether measles cases were laboratory confirmed or not.”

Comment 3. In the analysis, are the authors making the assumption that both the 'exposed' group and 'unexposed' group had the same chance of exposure to wild type measles virus? If so, that needs to be made explicit.

Response to Comment: Yes, and the text was revised accordingly in the Methods Section as follows, “It was also assumed in this study that chances of exposure to wild type measles virus were equal in the vaccinated and unvaccinated cohorts.”

Comment 4. In the description of the study population, there needs to be some description of the geographical area of residence of those included in the analysis. This is important to better understand the chances of exposure to wild type measles virus during the long study period (1990-2009). In addition, there should be some description of the overall number of measles cases detected by year in the area of residence of the study population. If these data are not available to the authors, then this needs to be clearly stated as a limitation.

Response to Comment: As requested, the manuscript was revised to reflect this potential limitation of our study as follows, “Another potential limitation of this study was that limited information was available regarding the area of residence of persons over the multiple years of this study. It was assumed that chances of exposure to wild type measles virus were equal in the vaccinated and unvaccinated cohorts examined. It is possible that there may be differences in the chances of wild type measles virus exposure in different geographical areas over different years. This potential phenomenon should be further examined in future studies.”

Comment 5. For each of the comparison groups, there should be a description that gives a better understanding if they are evenly clustered or distributed over the long study period. Presumably, measles cases decreased over time during 1990-2009, and likely were virtually nil after measles was eliminated in the U.S. with the last case in 2000. Therefore, the likely chance of exposure would have been quite different in 1990 versus 2009.

Response to Comment: The manuscript has been revised to address this point. Table 5 was created to track the yearly number of measles cases in the vaccinated and unvaccinated groups. Further, a limitation was added to discuss this issue and its potential impact on vaccine effectiveness, as follows, “An additional potential limitation of this study was that measles cases were not uniformly diagnosed during the study period from 1990-2009. As revealed in Table 5, it
was observed that most cases of measles were diagnosed in the early 1990s period, and by the 2000s virtually no cases of measles were diagnosed, regardless of vaccination status. This phenomena most probably reflects increasing “herd immunity” from increasing MMR vaccine coverage in the overall population. As described previously about “herd immunity” [22], the consequence is that the chance of exposure to measles throughout the study period examined significantly decreased regardless of vaccination status, and as a result, this may have reduced the vaccine effectiveness observed in the present study in comparison with previous studies examining measles vaccine effectiveness. Namely, unvaccinated persons were deriving a benefit of protection against measles infection from vaccinated persons. It would be interesting in future studies to evaluate the impact of increasing “herd immunity” on population measles disease patterns.

Comment 6. In Table 2, the demographic summary of the persons diagnosed with measles examined in this study, it would be helpful to provide a description of the cases separately for each of the two comparison groups. Also, it would be helpful to include a variable for the 'age of onset' of measles.

Response to Comment: Table 2 has been revised to provide all of the information requested.

Comment 7. The authors only discuss the effectiveness of a single dose of measles vaccine. However, based on Figure 1, follow-up went through 120 months (10 years of age), which suggests ample time for delivery of 2nd doses of vaccine. Can the authors calculate the effectiveness of 2 doses of measles containing vaccine (MCV) compared with one dose and 0 doses? If not, the authors should explain in the discussion and/or limitations.

Response to Comment: The present study examined only persons not receiving any doses of measles containing vaccine or a single dose of MMR vaccine. As described below persons receiving other doses of measles-containing vaccine were excluded.

Comment 8. The authors should mention in the methods how two dose recipients were handled. Were they excluded after receiving the 2nd dose?

Response to Comment: The Methods Section was revised to state that persons receiving anything other than a single dose of MMR vaccine were excluded as follows, “All persons receiving more than 1 dose of MMR vaccination or other measles-containing vaccines were excluded from the present study.”
Comment 9. In the Discussion, the authors should offer some potential reasons that they found lower VE than was found in previous studies. In the Discussion, the authors mention three "measles cases" that had been vaccinated with MMR within 30 days prior to the onset of measles. These were likely vaccine reactions, and therefore not cases. Were they excluded from the analysis? That is not clear in the text of the Figure of the study flowchart.

Response to Comment: This Discussion section was revised to include further limitations about observing reduced vaccine effectiveness as a potential consequence of "herd immunity" as mentioned above. In addition, the Figure of the study flowchart was revised to include a footnote clearly identifying that those persons were included in the study.

Comment 10. In the Discussion, lines 48-52, the authors refer to measles vaccine reactions as 'measles cases'. These should not be referred to as measles cases. And based on limitations of these date, there is a lack of evidence from this study that supports the authors calculation of a statistic and conclusion that: "The results of the present study suggest that MMR vaccine-associated measles cases are rare with a rate of 0.91 per 10,000 MMR recipients (95% confidence interval = 0.19 to 2.67) being diagnosed with a measles infection within 30 days of MMR vaccine administration."

Response to Comment: The text was revised accordingly to reflect that they are measles vaccine reactions and not measles infections.

Comment 11. Further, to remove the potential confusion of MMR reactions with measles cases, the authors should consider removing all cases of measles within 30 days of vaccination and focus the analysis only on cases occurring in unvaccinated or in vaccinated persons more than 30 days post vaccination date.

Response to Comment: This comment may have merit, but we believe it is crucial to present the data as it was collected, so that the reader has a full view of the data.

Comment 12. Could the better effectiveness associated with older age at 1st vaccination be associated with missing data on 1st vaccination (i.e., perhaps the 1st documented vaccination was really a 2nd vaccination because the 1st one was not documented). While this appears unlikely, the authors should at least mention the possibility and why they think it is or is not unlikely.

Response to Comment: The limitations was revised to include a discussion of this point as follows, “Another potential limitation of the present study was that the better vaccine
effectiveness associated with older age of receiving MMR vaccination might be associated with missing data on the first vaccination (i.e., perhaps the first documented MMR vaccination was really a second MMR vaccination, because the first was not documented). This would appear to be unlikely, since the ages examined for receipt of MMR vaccination were all before the second birthday, and the ACIP does not recommend administration of a second dose of MMR vaccine at such a young age [1].”

Comment 13. It would be useful to include 95% CI around VE estimates in the text and the tables.
Response to Comment: The text was revised accordingly.

Comment 1. Abstract: In the results, two age groups are overlapping: "12-15 months" and "15-20 months".
Response to Comment: The text was revised to state 12-15 months and 16-20 months.

Comment 2. Table 4 - can the authors add a footnote to the table describing the differences between Model I and Model II?
Response to Comment: A footnote was added explaining the different models.

Comment 3. For Tables 3 and 4, it would be helpful to add a column for VE and also include the 95% CI's.
Response to Comment: The tables were revised to include this information.

Samuel Ghebrehewet, M.D. (Reviewer 3):
Comment 1: Terminologies (need to be reviewed throughout the document):Abstract - line 19, "de-identified" would it be better to use the term - "anonymous" or "anonymised" or "non-identifiable"; line 34, "Incident diagnosed cases of measles...", this is not clear, what does this mean? also ".incident cases of measles..." is used throughout the document and needs to be clear, e.g., is it referring to "sporadic" cases; line 39, "MMR vaccine exposure..." I think it is better to reword this e.g., "MMR vaccine recipient(s)"
Response to Comment: The text was revised to address these concerns.

Comment 2: Methods - the sub-title "Exposures" again, "Recipients" may be a better word.
Response to Comment: The text was revised to address this concern.

Comment 3: Under outcomes - line 56, "...only 12 were diagnosed with measles post-MMR vaccine administration." Post-MMR vaccination is not defined, i.e., is it 2 weeks, 3 weeks, 4 weeks or longer after vaccination? Later on the authors the authors seem to suggest 30 days as a cut-off point.
Response to Comment: The Methods Section was revised to state as follows, “In the MMR vaccinated cohort, a total of 55 persons were diagnosed with measles, but only 12 were diagnosed with measles post-MMR vaccine administration (at least one day after MMR vaccination)”

Comment 4: Under discussion - line 19-24 "It would seem, at least in the US, in more recent years with the end of endemic measles transmission that for most children administration of MMR vaccine > 15 months would be more appropriate than < 15 months.” This statement does not take into account the administration of the 2nd dose. This study did not look at those who received 2 doses, therefore, in a country such as the US and most developed countries, where the general risk of exposure to measles is low, low levels of measles antibodies after the first in those individual who will go on to receive 2nd dose will have little impact. The statement / recommendation would be more appropriate for countries where the risk of measles infection is high, i.e., there is low MMR uptake, especially for the 2nd dose. lines 36 - 46, it would be useful to comment or expand the discussion on differentiating "vaccine induced vs wild infection" through further microbiological tests in genomics.
Response to Comment: The text was revised include comments raised by the reviewer as follows, “It would seem, at least in the US, in more recent years with the end of endemic measles transmission that for most children administration of MMR vaccine at ≥ 15 months would be more appropriate than < 15 months, although the impact maybe more limited because most children will subsequently receive a second childhood dose of MMR vaccine. It is also worth considering in countries where the risk of measles infection is high and there is low MMR vaccine uptake, especially for the 2nd dose of MMR vaccine, that administration of MMR vaccine at ≥ 15 months maybe a means to improve long-term protection against measles infection.” In addition, the Discussion section was revised to comment on vaccine induced vs wild infection as follows, “It would be interesting in future studies to use microbiological tests to
determine whether such measles reactions are truly vaccine-associated or the result of wild-type measles infections.”