Author’s response to reviews

Title: The impact of repeated vaccination on influenza vaccine effectiveness: a systematic review and meta-analysis

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Version: 1 Date: 02 Nov 2018

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BMED-D-18-01247

Alessandro Recchioni
Associate Editor
BMC Medicine

Dear Mr. Recchioni,

Thank you for the opportunity to revise our manuscript submission to BMC Medicine. We have addressed the reviewer comments in the responses provided below and in the manuscript where possible.

Below please find our responses to the reviewer comments. Please let us know if you require any additional information.

Thank you again for all your help and support during this process.

Sincerely,
Reviewer reports:

Reviewer #1:
Reviewer Comment: This is an update to a previous paper, which was retracted due to erroneous inclusion of invalid data. The revised version retains the strengths of the original paper. In particular, the paper addresses three separate questions of interest. Two of these questions focus on repeated vaccination from the patient perspective (conditional on receipt or non-receipt of last year's influenza vaccine, should a patient receive the current year's vaccine?). The third focuses from the policy perspective - is there the possibility of sub-optimal vaccine protection in the long term due to repeated annual vaccination? The analyses are appropriate to the questions of interest, and the conclusions justified by the results.

Author response: Thank you for your careful review of our submission and for your comments.

Reviewer #2:
Reviewer Comment: I commend the authors on re-submitting the article. A mention about the previous retraction, and a note of how this review differs from the retracted article is warranted.

Author Response: We have included a description of this at the start of the Results section on page 8 lines 153 to 156. We welcome any suggestions the editorial team may have as to how best to word this description.

Currently, the added text in the manuscript is as follows:

“The results presented below have been corrected from our previously published review on this topic. The previous article included one study that did not meet the inclusion criteria, omitted one estimate from an included study and included two estimates from populations that were also completely included in other estimates.”

Reviewer Comment: I note the search only was performed to 2016 - could the search be repeated to include studies between 2016 and 2018?

Author Response: At this time, we have not updated the literature search to include studies published between 2016 and 2018. As this is a corrected version of a prior manuscript we feel that updating the search could significantly change the article rather than be a correction of the prior analyses, which was the intention when the journal invited us to resubmit our manuscript.
Reviewer Comment: It isn't completely true to say that the results are only relevant for policy makers rather than individuals. For example, individuals could choose to get vaccinated only every second year, or (perhaps less likely) skip vaccination if early season surveillance shows H3N2.

Author Response: We have attempted to address this comment on page 12 lines 249-252 by changing the sentence in question to read, “Of relevance to the policy-maker (but not of pragmatic relevance to the patient, who cannot alter his/her vaccination history or predict future influenza strain circulation),…”.

We feel that while the H3N2 data may lead to a consideration of skipping vaccination based on early season surveillance of H3N2, there are a number of reasons why this would not be recommended. Skipping vaccination would mean relying on prior season immunization for protection against H1N1 and B and we know that vaccination in both seasons is better than relying on prior season vaccination for H1N1 and B. In addition, early indications of H3N2 may not predict what will circulate in the upcoming season, and it would be difficult to determine the extent of influenza B circulation which typically emerges later in the season. Finally, VE results for H3N2 varied from year to year, and our results were particularly influenced by the findings from 2014-15. Skipping a vaccination in an H3N2 year may in fact result in poorer protection in that year, although on average our study found that vaccination in the prior and both seasons had similar VE.

Reviewer Comment: Were there any indications that the effect of repeated vaccination may be influenced by vaccine coverage? One potential confounder is natural infections (those not vaccinated in the previous year may have had influenza infection, whether symptomatic or asymptomatic, and may be better protected than if they had had vaccine). Indirect evidence of this might be found in the elderly who generally have a higher vaccine coverage than younger age groups.

Author Response: We were not able to assess the effects of past influenza infection based on the included studies. We noted that as a limitation of our study in the Discussion section: “Second, our study did not account for past influenza infection, which may have provided some protective effect against laboratory-confirmed influenza in subsequent seasons. A patient’s first exposure to influenza vaccination or infection can impact subsequent responses to vaccination or infection (referred to as original antigenic sin or back-boosting), which was not accounted for in this study,” (page 14 lines 303-307. We do not believe that the effects of vaccine coverage will have influenced our results because an indirect effect of high coverage (in the case that this occurs) would impact all groups similarly and has been accounted for in our study design that compares estimates from the same study rather than across studies.
Reviewer Comment: VE, and delta VE have an awkward statistical distribution. Wouldn't it be simpler to use a model that pooled estimates of the OR of vaccination (or differences in OR) to infer VE and delta VE, rather than trying to pool VE and delta VE directly?

Author Response:

We chose to express our findings in terms of vaccine effectiveness (VE) instead of odds ratios (OR) as estimates each year of how well the vaccine works are generally represented as VE. Therefore VE is the term most familiar and intuitive to the reader (and is on the same scale as the OR). We had explored the use of ratios instead of absolute differences, but this has less interpretability for public health given that a ratio of 2, for example, could indicate either very large or very small differences in VE on the absolute scale. We believe that absolute differences in VE are more relevant given the annual fluctuation in absolute VE due to changes in circulating strains and how well the vaccine strain is matched, as well as being more applicable for public health messaging.

Reviewer #3:

Thanks to the authors for reviewing the paper and submit a new version. This is an important paper contributing to the current discussion of the role of previous influenza vaccination.

Reviewer Comment: Abstract: From the figures presented in the Results section, it is not obvious that the conclusion is "our results support current season vaccination. But the results as such, do not support current vaccination for all types/subtypes.

Author Response: We have addressed this comment by adding the following clarification to the first sentence in the conclusion of the Abstract, “because VE for vaccination in the current season only is higher compared to no vaccination in either season for all types/subtypes, and for H1N1 and influenza B, vaccination in both seasons provides better VE than vaccination in the prior season only,” (page 3 lines 49-51). In our analyses we did find some circumstances where repeated vaccination resulted in lower VE for those vaccinated in both seasons compared to the current season only. However, for H1N1 and influenza B vaccination in both seasons is better than vaccination in the prior season only. For H3N2, vaccine effectiveness was similar for vaccination in both seasons or prior season only and lower for both seasons than current season only. It is also important to note that results for H3N2 were particularly influenced by the 2014-15 season and the impact of repeated vaccination on VE for all types/subtypes can vary from year to year (amendment to manuscript made on page 3 lines 55-57).

Reviewer Comment: Methods: Age group, sub-population selection: In the discussion section, authors say: "Finally, because VE can vary by age group and influenza type/subtype, this study was strengthened by the detailed stratification of results by type/subtype, as well as by using VE estimates for the most specific patient groups (e.g., age-stratified groups rather than 'all ages')". Age group selection is not explained in the methods. In table 1, we can see the age groups included. Refer to it in the methods?
Author Response: In the Methods on page 6 lines 123 to 124 we clarified our description that where possible we extract data by age group and report the most specific results reported in the original studies: “Whenever possible, we extracted VE reports by influenza type/subtype and age group provided in the articles and only included the most specific results reported (e.g., by age group or influenza type/subtype) in the meta-analysis”.

Reviewer Comment: Also it would be good in table 1, to explain for countries in which there is no universal vaccination programme, whether the estimates included in the meta-analysis were for the overall population or for the vaccine target population.

Author Response: There were no studies that represented only regions with universal vaccination programs. For example, while Ontario, a province within Canada, has a universal program, other provinces included in the Canadian VE estimates do not and it was not possible to separate out Ontario-specific estimates by vaccination history from the national estimates overall. Many studies included participants who would be eligible for vaccination under a targeted program, but again the results were not presented in the original studies in a way that would allow differentiation of these groups. As such, we are unable to update the table as suggested by the reviewer.

Reviewer Comment: Results: Page 10, first paragraph: "The results for individual seasons were inconsistent with the overall result except for the 2014-2015 season (Supplementary Table 2)". This sentence is not clear. When looking at the supplementary table 2 comparing vaccinated in both seasons compared to current season, results are quite consistent.

Author Response: In order to make this sentence more clear we have added to this sentence on page 10 lines 208-211 to read, “For the H3N2 comparison, the results for individual seasons were inconsistent with the overall result except for the 2014-2015 season (i.e., ΔVEs were not statistically significant in the comparison of both seasons versus current season for any season except for 2014-15)”. For the H3N2 analysis comparing both seasons to current season vaccination only, the overall result (for which ΔVE is −20%; 95% CI:−36%, −4% and statistically significant) is consistent only with the 2014-15 season (for which ΔVE is −54%; 95% CI:−88%, −20%) and the other seasons analyzed did not have significant results.

Reviewer Comment: Authors may want to discuss heterogeneity between estimates (some I2 are around 30%) and sample size issues for some estimates.

Author Response: Heterogeneity due to differences in geography and patient populations is somewhat expected in studies estimating influenza vaccine effectiveness, though it was relatively low across our nine overall meta-analyses (one estimate had an I2 of 35%, two estimates had an I2 of 26%, and all other estimates had an I2 of <5%). According to the Cochrane guidelines, pooled estimates with an I2 statistics of <40% may indicate that heterogeneity is not important, and strengthens the rationale for pooling the results (1).
While there were some studies with smaller sample sizes, the methods used to conduct the meta-analyses were appropriate to weight estimates based on sample size.

Reviewer Comment: Please, review the paragraph on age groups. "Finally, because VE can vary by age group and influenza type/subtype, this study was strengthened by the detailed stratification of results by type/subtype, as well as by using VE estimates for the most specific patient groups (e.g., age-stratified groups rather than 'all ages')). It seems to me, that the estimates selected are overall and not by age group. This would be rather a limitation as ideally, we would like to see results stratified by age group or presence of chronic conditions.

Author Response: VE estimates for age groups were added separately to each meta-analysis where possible, however, we did not conduct subgroup analyses by age group or presence of chronic conditions. In Table 1, the age groups that are included in the analyses are indicated when it was possible to extract for multiple age groups. Further, as described in a prior response, we clarified the wording in the Methods section (page 6 lines 123 to 124) to explain that we extracted data where possible by age group and included those data in the meta-analyses.

Reviewer Comment: Was there any difference in observations between primary care studies and hospital studies? Any difference between study designs (TND, cohort, case-control)

Author Response: We did not assess the differences in observations between primary care studies and hospital studies, or between study designs. Our study design considered differences in VE within individual studies rather than comparing VE estimates across studies. On page 13 lines 283-286 we discuss the strengths of this approach and on line 284-285 have added “such as study design or study settings (e.g., outpatient vs. hospital-based studies)” as examples of study differences that were controlled for by our comparison being done within studies. In addition, we did not assess differences by study setting because the majority of our studies were located in an outpatient setting. Only two studies were from inpatients only, as noted in the Results section (page 8, line 174), making stratified comparisons challenging due to the lack of estimates specific to this setting.

Reviewer Comment: Conclusions: The authors conclude from the patient’s perspective. One of the objectives was to also assess the policy perspective. The reader is expecting also a conclusion from the policy perspective.

Author Response: We have added to the following sentence in the conclusions about the policy perspective: “From a policy perspective, although VE was lower against H3N2 and B for individuals vaccinated in both seasons compared to those vaccinated in the current season only, this result may vary from season to season” (page 16 lines 338-340).

Reviewer Comment: References: when referring to the study 16 (Castilla et al.), it would be more correct to say "in Navarra region (Spain)." The TND in Navarra includes only patients
from this region (Hospital and Primary care level). Then, in the Spanish TND, patients from Navarra are also included. It is therefore better to specify "Navarra region" to make it clearer to which study you are referring to.

Author response: Thank you for the important clarification. When referring to study 16 we have called it the Navarra region (page 11 line 224). We also added a sensitivity analysis to the Results section as follows: “To address overlapping patients in the 2010-11 season analyses in Spain (one conducted in the Navarra region [20] and one that included eight regions in Spain [19]), we performed a sensitivity analysis removing the Navarra region study [20] from the H1N1 meta-analyses and found that it had no effect on the results for any of the three comparisons. When we removed the Navarra region study we found that for H1N1 VEboth – VEprior only was 25% (14%, 35%); VEcurrent only was 62% (51%, 71%); and VEboth – VEcurrent only was 2% (–9%, 13%). The original estimates for H1N1 were 25% (14%, 35%), 62% (51%, 70%), and 3% (–8%, 13%), respectively,” (pg. 10 lines 212-218).

References