Reviewer’s report

Title: Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control

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Title: Elucidating the impact of the pneumococcal conjugate vaccine programme on pneumonia, sepsis and otitis media hospital admissions in England using a composite control

This valuable manuscript has improved a lot, and I am happy with most of the answers by the authors. However, there are still some comments I would like to highlight.

MAJOR COMMENTS

1) There are still a number of discrepancies in the text that need to be sorted out.

   o in the beginning of the methods, the number of ICD-10 diagnosis fields is mentioned 3 times (20 fields, first diagnosis field, any of the individual's diagnoses). This is confusing and repeating the same information many times. The text should be logical what was collected, and what was analysed (as the main outcome and in sensitivity analyses)

   o row 115: "Respiratory 115 infections mentioning influenza were excluded (J101, J102, J108, J111, J112, J118). "However, some of the diagnoses are listed in the supplement.

   o row 215: "Disease trends for pneumococcal pneumonia were broadly similar to those reported for IPD for individuals up to 45 - 64 years of age," I would not agree. They seem similar until 15 to 24 years of age.

   o row 270: "Significant reductions in the incidence of otitis media with tympanostomy were seen in all age groups"

   ♦ Not in 65+
The adjusted case ratios in younger age groups were broadly similar between risk and non-risk groups (except 2-4 year olds), where among older individuals the impact among risk groups is lower, or even less clear.

- they seem to be similar until 5-14 years of age.

- the end of the sentence is not understandable.

“may have otherwise occurred in the 65+ years age group” this is not understandable.

- the addition is not clear "though the reduction in inpatient pneumonia activity is likely to be less than this as the reported reductions included outpatient appointments which we did not include in our analysis

- reduction compared to the 4% or 20% estimate?

- Usually the relative reduction for outpatient cases has been LOWER compared to inpatient cases.

- "We were unable to detect a large reduction in admissions for all otitis media diagnoses," Not true with the updated analyses.

2) The identification of the control condition "urinary tract infections" seems odd, as only one ICD10 code (N390) is included, but the potentially more common diagnoses N10 and N30 are missing. I think this is a serious omission and makes the interpretation of this control condition difficult. Furthermore, it is highlighted in the discussion as being the best proxy for pneumonia.

MINOR COMMENTS

The population estimate methods should be described earlier in the methods and not within "Identification of risk groups", especially when population data are not available for the risk groups.

In the Finnish studies, the culture-confirmed IPD cases were EXCLUDED from the case definitions to describe the additional disease burden of IPD. Would this be possible for the current study data also? If not, this difference should be mentioned somewhere in the text.
The chapter "Sensitivity analysis" is repetitive and in wrong order. The added text should be written first, after which the changes in the elderly can be highlighted if necessary. I guess the intention of the "less specific" identification of cases is rather to be more sensitive, i.e. including more true cases, rather than including false positives.

Row 407: "It is also unclear what the contribution of the pneumococcus is to non-specific sepsis" The phrase " in the current data" should be included in this sentence.

In the discussion, the benefits of the current methodology to time-series analysis should be discussed.

The figure legend for the differently colored lines is missing in most supplement figures.

BASED ON THE EARLIER REVIEW, I AM NOT SATISFIED WITH THE ANSWERS RELATED TO THE FOLLOWING COMMENTS.

1) Pneumonia outcome. The outcome of "pneumonia of unspecified causative organism" remains somewhat unclear. Mostly it seems to refer to J18 only. However, the appendix lists all pneumonia diagnoses. It remains unclear whether these are used at all in any analyses. The selection of one dg only (J18), although the most prevalent one, may result in bias due to secular trends in case there are changes within pneumonia in the uses of the different codes. Defining "any pneumonia" using all pneumonia-related codes would potentially result in a more robust definition. After all, the aim of a non-specific (but sensitive) outcome should be to show the reduction in overall disease, which is important for the public health viewpoint.

   a. Also other than J18 have unknown etiology in most cases (like J15)

   b. Although 95% of diagnoses are J18, it is lower in younger age groups and the proportion is calculated for all the data between 2004 and 2015. Thus, there may be secular changes in these proportions which now remain obscure for a critical reader. The best way to answer to these critics would be to include all diagnoses in a sensitivity analysis.

2) The figures 1 and 2 seem important and excellent, but the scales were not legible. Thus, the message of these could not be fully reviewed, especially the incidences of each of the outcome, highly relevant for overall disease burden.

   a. the incidence of pneumococcal sepsis is low compared to IPD. This should be mentioned in the results explicitly. Also in the discussion, the fact this syndromic detection based on
ICD10 codes was not able to detect any additional disease burden compared to the lab-confirmed IPD which is presumed to be of high specificity but low sensitivity. This is also in contrast to the Finnish results.

b. the incidence of pneumococcal pneumonia is low. It was roughly 20% of the IPD incidence in the various age groups. This suggests that the "pneumococcal pneumonia" most probably refers to bacteremic pneumonia.

3) Table 2: Ratio IRR disease endpoint not given for IPD?

a. Most of the lab-confirmed IPD is likely hospitalized, so the comparison would be valid for the most part. Another way would be to exclude the non-hospitalized?

b. the reporting of mean ratio IRR for IPD would be interesting for the methodological nature of this article. Furthermore, it would be extra interesting the present the results for two IPD-outcomes: adjusted IPD and raw IPD data.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review
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the same as in the previous review.

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