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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Reviewer: Arto Palmu

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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 manuscript describes an observational ecological study on the impact of pneumococcal vaccines on pneumonia and several other disease syndromes with pneumococcus as a major causative agent in England. The topic is important as most of the research has focused on laboratory-confirmed IPD. Furthermore, the manuscript includes novel method development further contributing to the research field.

The manuscript is well-written in native English, but needs clarifications in some places. Additionally, there are a number of points I want to comment on.

MAJOR COMMENTS

1) The criteria for selection of the control conditions remain unclear.

   a. Were these selected a priori and on what specific criteria?

   b. Was there any exploration that the control conditions would behave similarly compared to the outcome diseases during the pre-vaccine period?

   c. was any control condition similarly seasonal compared to the outcome diseases?

   d. Some of the control conditions are recurrent (similarly to the outcome diagnoses), but e.g. the thyroid disorders probably not, although repeated hospitalizations may occur to
receive repeated treatments. I assume the use of rate ratios should take into account most of these differences (assuming that there are no secular changes).

2) 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.

3) In the elderly age group (65+) age standardization should be considered to control residual confounding due to age as the follow-up periods are quite long apart, and changes in the age distribution within this age group may occur.

4) Table S7 should be included in the manuscript itself to show the changes in absolute numbers. This table should include the laboratory-confirmed IPD as a reference.

5) Non-specific sepsis increased in all age groups. This should be analysed more (by risk group strata) and discussed in detail. In case the authors consider the results valid for IPD, pnc pneumonia and any pneumonia, then also the significant increases re. non-specific sepsis should be considered valid. So the ultimate question is: Does the PCV programme increase the number of sepsis admissions? Could this be due to replacement? If regarded as true, this would be considered a major safety issue and would decrease the cost-effectiveness of PCV programmes.

6) 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.
MINOR COMMENTS

1) Intro: pls give the estimated coverage for PPV23 in the elderly.

2) Intro: move the second last column to the methods. "Episode" defined now differently in the intro and the methods.

3) Methods: I guess ER visits are not included in this evaluation. This might be better clarified.

4) Methods: Identification of cases. Pls describe first the data collection. Now starts with "Our analysis…" See previous comment on all pneumonia codes.

5) H65 (=secretory otitis media) should be included in the otitis diagnoses. Tympanostomies are now included only, if associated with purulent otitis media or otitis associated with some other specific disease (=H66-H67). However, as most tympanostomies should be due to some form of otitis (including H65), the addition of a diagnosis criterion may result in losing outcome cases due to lack of proper coding.

6) Risk groups: Pls clarify how identified. Any prior admission within a specified time range or the admission with the outcome diagnosis? If latter, will probably result in low sensitivity of risk group identification?

7) The follow-up periods were not season-matched (=2-year periods starting from different months). Probably no bias, but please check that the age distributions are similar, especially in children as the outcomes are strongly age-related.

8) Results: Table S4 gives results by age, not annual.

9) Page 11, row 184: "7% of all pneumonia" first dg or all?

10) Page 13: word "activity" difficult to understand/unfamiliar in this context, also in table2 title.

11) Table 2: Ratio IRR disease endpoint not given for IPD?
12) Page 17: there is some repeating in the text as the results compared to composite reference are given separately. Consider merging this with the pre-post comparisons.

13) Sensitivity analysis: add the result on 3 codes also in the text and clarify that the first ICD-10 was the main analysis. Reference should be to the table 2 not 3.

14) Table 3: clarify (with footnotes?) the "Adjusted" and the results given in parentheses.

15) Page 22, first line: the 4.3% reduction includes outpatient pneumonia cases, thus the comparison is not fully valid.

16) page 22, row 311: the development of the indirect effect will increase the reduction observed also in the vaccinated age groups (as the VE approaches 100% due to the disappearance of the vaccine types).

17) page 24, row 355: reduction in the vaccine-eligible children reported also after the introduction of PCV10 in the national vaccination programme (Palmu et al Pediatrics 2015).

18) page 24: "Some reductions in non-specific sepsis were observed in older age groups" Really? Not shown in table 2 or in figure 2??

19) page 24: lung abscess rare with low numbers, thus, evidence not expected to be observed?

20) Incidences of the control conditions to be given in a supplement figure?
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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AAP is an employee of the National Institute for Health and Welfare, which has received research funding from GlaxoSmithKline Vaccines for the conduct of a nationwide effectiveness trial of the 10-valent pneumococcal conjugate vaccine. AAP is a co-investigator in this study.

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