Author’s response to reviews

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

Authors:

Dominic Thorrington (domincthorrington@gmail.com)

Nick Andrews (nick.andrews@phe.gov.uk)

Julia Stowe (julia.stowe@phe.gov.uk)

Liz Miller (liz.miller@phe.gov.uk)

Albert Jan van Hoek (albertjan.vanhoek@phe.gov.uk)

Version: 2 Date: 22 Nov 2017

Author’s response to reviews:

Reviewer #1: BMED- D-17-00620

Manuscript Number: BMED- D-17-00620

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)
We thank the reviewer for this comment as this is clearly an issue that needs rectifying in the manuscript. We have amended the methods section starting line 94 as follows:

“We extracted data from HES for the period April 2004 to March 2015 for all admissions with a pneumonia, sepsis or otitis media ICD-10 code in any diagnosis field for individuals in seven age groups: individuals less than 2 years old, 2-4 years, 5-14, 15-24, 25-44, 45-64 and 65+. The main analysis was restricted to admissions with an ICD-10 code of interest in the first diagnosis field as this field indicates the primary cause of the admission.”

Later in the methods section (line after we have described derivation of incidence rate ratios from the pre to post PCV period) we state (beginning line 144) that:

“To assess the robustness of our estimates of the IRRs we performed a sensitivity analysis by calculating the IRRs for each disease endpoint but expanding the number of ICD-10 fields to the first three diagnoses and then using all diagnoses available, while selection of controls remained unchanged.”

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

We are sorry for the confusion. We have amended the diagnoses list in the supplement to remove these respiratory conditions associated with the influenza virus.

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.

We thank the reviewer for this observation. We have altered the text (line 219) as follows:

“Observed trends in incidence among the different respiratory disease endpoints did not consistently follow the reduction observed in the incidence of laboratory-reported IPD (Figure 1). Disease trends for pneumococcal pneumonia were broadly similar to those reported for IPD
for individuals up to 15-24 years of age, though not in older individuals where IPD rates declined but pneumococcal pneumonia admissions did not”

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

§ Not in 65+

We thank the reviewer for drawing our attention to this sentence. First we were incorrect to apply the term “significant” to the ratio of IRRs based on the min and max values. To emphasize this we have adopted square brackets to denote min-max values as opposed to curved brackets for CIs in table 2. While all the ratios of the IRRs compared with the composite control were < 1 for OM with tympanostomy, this was not consistent across all individual control conditions indicating uncertainty. We have redrafted this sentence (line 274) as follows, which we trust is now acceptable.

“Reductions in the incidence of otitis media with tympanostomy were largest in children under 2 years of age (rIRR 0.51, min-max 0.39-0.69). Reductions were also seen at older ages though not always in excess of those seen in all five of the control conditions.”

In view of this we have also redrafted the last sentence in the preceding para (line 268) as follows:

“Compared to the composite control reductions in the incidence of pneumococcal pneumonia and pneumococcal sepsis were seen in all age groups, though not when compared with each control condition individually (as evidenced by a value >1 in the min, max range).“

(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.
We agree that the similarity between the risk/non-risk groups does not go past the 5-14 years group, so we have adjusted the manuscript accordingly.

This section (line 307) now reads:

“The adjusted case ratios in younger age groups were broadly similar between risk and non-risk groups up to the 5 - 14 years group, but there is a marked divergence in the older age groups.”

Row 308: "may have otherwise occured in the 65+ years age group" this is not understandable.

We estimated that the burden of pneumococcal pneumonia from 2007-2015 reduced by 4,969 cases (updated due to inclusion of N10 and N30 ICD-10 codes for UTI control), and that the case burden in the 65+ age group specifically reduced by 2,024 (or 41% of the total estimated reduction for the population).

We have therefore re-written it accordingly (line 313):

“To put the changes in overall disease trends compared to the composite control into some context, we estimated that the total hospitalised burden of pneumococcal pneumonia reduced by 4,611 cases for all ages from April 2007 to March 2015, with large reductions in the 65+ years age group (1,917 cases) and in children under 15 years of age (1,315 cases).”

Row 355: 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
Sorry, our addition was incorrect.

The contribution of the pneumococcus to pneumonia managed as an outpatient is likely to be less than that for pneumonia requiring a hospital admission, so removing the outpatient appointments should see the percentage reduction rise. We have amended the manuscript (line 347) to read as follows:

“The reductions observed in pneumonia admissions in vaccine eligible children post-licensure are greater than suggested by the pre-licensure trial of PCV7 in the US in which clinically diagnosed pneumonias were only reduced by 4.3% [17]. Unlike the US trial our study was restricted to pneumonias requiring hospital admission. As the contribution of the pneumococcus to hospital admitted pneumonias in children is likely to be higher than in those not admitted, the percentage reduction in inpatient pneumonia activity is likely to be higher than 4.3%.”

Row 415: "We were unable to detect a large reduction in admissions for all otitis media diagnoses," Not true with the updated analyses.

We thank the reviewer for pointing this out. The sentence would read correctly if we added “in infants”, as the mean ratio IRRs for <2s and 2-4s were 0.76 (0.58-1.01) and 0.92 (0.74-1.27) respectively for all OM diagnoses. The picture is different for OM diagnoses with tympanostomies.

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.

We looked at this and found that in our dataset the diagnoses of N10 and N30 are much less common that N390. We performed a new extraction of UTI diagnoses by using the N10, N30 and N390 ICD-10s and this only increased the number of cases of UTIs by 249,693 for the study period. This was on top of 3,012,944 cases identified by N390 alone. The reviewer will see in tables 2 and 4 that this does not change our main results. We included the additional ICD-10s in the UTI control for completion.
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.

Thank you. We have added this to the “Identification of cases” section above the “Identification of 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.

Unfortunately, this is not possible in our dataset

Therefore we have changed the text (line 417):

“The analyses from Finland excluded laboratory-confirmed IPD cases but we were unable to do this due to a lack of common patient identifiers in our HES and laboratory-confirmed IPD surveillance datasets. However, removal of laboratory-confirmed IPD cases from admissions with a non-specific sepsis diagnosis should reduce the proportion of such cases attributable to the pneumococcus and thus the potential impact of PCV on this disease endpoint.”

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.

We have re-written the paragraph as suggested. The reviewer is correct in saying that our sensitivity analysis of including more diagnostic fields made identification of cases more sensitive. However this would likely be at the cost of reduced specificity, so the results in terms of estimated impact can be mixed (although would usually mean relative changes are smaller)
depending on the ratio of true to false positive cases included as indeed shown by our analyses. The new results section now reads (line 287)

“The magnitude of the rIRR varied with the number of ICD-10s used to identify each condition of interest. Using only the first ICD-10 code suggests that the incidence of pneumococcal pneumonia for the 65+ age group decreased by 13% (min-max: -34+-3%) relative to the composite control (Table 2), though expanding the number of diagnosis codes to the first three suggests a decrease in incidence of 23% (min-max: 9-41%) and expanding the number of diagnosis codes further to all suggests a decrease in incidence of 25% (min-max: 11-43%) (Table S6). In younger age groups, use of additional ICD-10 codes had little impact (25-44 years) or lessened the relative reduction in pneumococcal pneumonia (<25 years). For pneumonia of unspecified cause increasing the number of ICD-10 codes generally increased the rIRR.”

We have also added a brief comment on the sensitivity analysis in the discussion (line 449).

“The use of additional ICD codes to identify the outcomes of interest should increase sensitivity but would likely be at the cost of reduced specificity. The contribution of additional true positive or false positive cases when the ICD-10 codes are expanded will likely vary with age group, disease outcome and time period so the effect is unpredictable as shown by our analyses. On balance we preferred to restrict our main analyses to outcomes of interest in the first diagnosis field as this is intended to capture the primary reason for admission so should maximise specificity.“

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.

Thank you for this suggestion. We have made further changes to this part of the Discussion and the original sentence is no longer used. Since the non-specific sepsis codes that we used may contain some laboratory-confirmed IPD cases it might be expected that their removal may lessen the impact of PCV (see revised sentence above under 2nd minor comment)

In the discussion, the benefits of the current methodology to time-series analysis should be discussed.
We thank the reviewer for this suggestion, and have added the following to the paragraph in the discussion that addressed other methods for evaluating changes in hospital admissions for pneumonia post PCV (line 456).

“Our method of assessing the impact of the PCV programme in England by comparing the IRR for the outcome of interest with that in control conditions has some advantages over other methods such as time-series analyses that have been used to assess the effect of PCV on pneumonia. The latter method does not take account of factors other than vaccination that may have resulted in secular changes in admission, and the results are sensitive to the model used to fit the pre and post-intervention trend lines [33].”

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

We apologise for this and have now added information to the supplementary figures. All figures now have the colour key in the figure caption or in a figure legend.

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)

We thank the reviewer for these observations and we apologise that our results tables in the manuscript and supplementary material were unclear. We did not analyse pneumonias with J14–J17 codes as these are mainly attributed to other non-pneumococcal pathogens (for those sub-
categories with unknown aetiology the numbers are small) nor any of the codes J09-J12 as these specifically mention influenza or viruses causing pneumonia. We have now made this clear in the methods section.

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.

We thank the reviewer for this observation. However, we feel that this additional sensitivity analyses is not warranted and would add even more length and complexity to the paper. As mentioned above the diagnoses we excluded all had other pathogens mentioned and together comprise only a small percentage of the total diagnoses from J09 to J18. Together J13 and J18, on which our analysis is based, comprise 96.7% of all the diagnoses from J09 to J18. Even in children less than 2 years J13 and J18 comprise 90% of all diagnoses from J09 to J18.

We can add a table to the supplementary material to show the numbers and percentages of cases by age with a primary diagnosis from J09 to J18 if it is felt important to justify the exclusion of respiratory conditions attributed to non-pneumococcal pathogens. We have included a draft (Table S9) for this reviewer’s consideration.

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.

We thank the reviewer for their comment on the illegibility of the figure margins. We hope that our changes have made the margin labels easier to read.

The incidence of pneumococcal sepsis is indeed low in comparison to IPD. We’ve now commented on this in the manuscript in the results section and in the discussion. IPD will include pneumococcal pneumonia (J13) as well as pneumococcal sepsis which includes meningitis and arthritis and it is true that together these two pneumococcal-specific ICD-10 codes still have a lower incidence than laboratory confirmed IPD. We now point this out in the results (line 240) as follows:

“When added together the incidence of pneumococcal pneumonia and pneumococcal sepsis was lower than that of laboratory-confirmed IPD in all age groups (Figures 1 and 2)”

Furthermore we comment on it in the discussion (line 389) as follows:

“The incidence of pneumococcal sepsis when added to pneumococcal pneumonia was considerably lower than the incidence of laboratory-confirmed IPD in all age groups. This is consistent with a previous study in which we linked laboratory-confirmed IPD reports with HES admissions and found that only a minority of laboratory-reported IPD cases had a specific pneumococcal sepsis or pneumonia code in HES [23] thus highlighting the limitations in documenting pathogen-specific causes of admission in HES.”

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.

The laboratory reporting system for IPD is quite different to HES and secular trends have been shown to reflect blood culture practices and laboratory reporting practices so we do not think it valid to use HES controls for laboratory-reported IPD. We have however expended the rationale for not using hospitalised control conditions to derive the ratio of IRRs (line 184) as follows:

“We did not compare the IRR of laboratory-reported IPD to the control conditions from HES because the IPD data from laboratories are not subject to the same secular trends as the HES data and were already corrected for trends in ascertainment of laboratory confirmed pneumococcal bacteraemias [7,8].”

Reviewer #2: The authors have spent some time in responding to the reviewers, but have not addressed the comments "within" the manuscript.

Explanations are given, but no changes/improvements to the manuscript. Please will the authors assume that for many if not all the queries, not only the reviewers but also other readers will want to know how/why they did things…what they found if additional analyses were done.

Say if the reviewer missed it and the detail is there, or add detail to make the manuscript better.

For example:

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

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

Thank you for pointing out that we had not addressed this crucial point in the manuscript. We have amended the Methods section to include more information on rationale for the selection of the controls (line 148):
“To account for biases arising from potential secular trends in admission practice over the study period the IRRs of each disease endpoint was compared to the IRRs of five control conditions that should not be affected by changes in the introduction of the PCV programme [11]. These were urinary tract infections, infections of the skin and subcutaneous tissue, disorders of the thyroid gland, diseases of the blood and fractures. These conditions were selected a priori with the criteria that they were not caused by the pneumococcus; not the focus of other public health interventions; and with a large case-burden with a similar age-distribution of cases to the pneumococcal disease outcomes.”.

b. Related to another reviewer's comments: The use of 5 control variables is a major strength of the work. However, it would further strengthen the findings if the authors could show/discuss how the control variables were related to the main diseases of interest in the pre-vaccine years through plotting or modeling. Ideally, the 5 controls would have similar pre-vaccine behavior to the main diseases (in addition to being unaffected by the vaccine) but then differ post-vaccine if there was an actual PCV effect. If the controls never showed much association with the main diseases then it may suggest that they are less informative about the potential PCV impact, and additional controls should be obtained.

We thank the reviewer for pointing out that our previous response to this question did not fully address the issue.

We have added some charts to the supplementary material (see Figure S2) to plot monthly incidence of J18 pneumonia in each age group along with the monthly incidence of each control condition. One of the issues in our dataset is the availability of only two years in the pre-PCV period, so there is limited analysis that can be done here to determine the relationship between the controls and the diseases of interest. However, we hope that these plots demonstrate a lack of any significant changes to incidence for each control condition, indicating these conditions were not subject to any factors that might cause them to behave differently to J18 pneumonia in the pre-PCV period. We reference Figure S2 in the Limitations section. We have also added this section to the discussion (line 523):

“However, we were unable to extract data for more than five control conditions due to resource limitations, and with data from only two pre-PCV years available to us in HES we were unable to conduct further investigations into the similarities between the control conditions and the disease outcomes of interest beyond the age-distributions of cases and not being subject to other
public health interventions (see Figure S2). Furthermore, we did not assess the seasonality of the control conditions. However, we minimized the impact of seasonality by averaging over a 24 month period and including the same months pre and post PCV (April to March) for both outcomes of interest and control conditions. Despite being restricted to five controls our analysis is an improvement on impact analyses that use no controls, or the use of a single control condition which can be sensitive to changes in secular trends unrelated to the introduction of the PCV programme and therefore a source of bias in programme impact estimates [34].”

2. was any control condition similarly seasonal compared to the outcome diseases? Related to comment b below.

a. financial years (also mentioned earlier) are ok related to the winter seasonal disease in the northern hemisphere? And are almost like the epidemiological years often used (end of June to beginning of July) - it would be good to make the case that using the years in this manner makes sense for this disease (and then just to consider if any summer seasonal diseases were used in the control that may have affected the year-on-year comparisons)

We have amended the manuscript to include Fig S1 which displays the monthly incidence in the pre-PCV period for the each of the controls. There is some evidence of seasonality for some control conditions in some age groups. However, using a 24 month period that encompasses two the winter and two summers seasons and should mitigate any seasonal effects in the controls.

3. Non-specific sepsis increased in all age groups. This should be analysed more (by risk group strata) and discussed in detail

We added some additional figures to the supplementary material (Figure S5) to address this point and have amended the para of the discussion dealing with the sepsis results beginning line 403 to provide a fuller discussion of our results.

“Mixed results were obtained for the other non-specific disease endpoints. No reductions for non-specific sepsis were observed with increases both in raw IRRs and IRRs relative to the
composite control in all age groups. This suggests that these codes do not contain many cases of occult pneumococcal sepsis, at least not with a predominance attributable to vaccine-type serotypes. With the exception of children less than two years old the increase in incidence was greater for the risk groups than the non-risk group (Table S5, Supplementary Material). The reasons for this difference are unclear but they reflect our findings in Table 3 showing that the greatest increases in incidence for pneumonia were also in the risk groups”

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

We thank the reviewer for pointing out that our previous explanations and the text in the manuscript did not fully address the previous comments. We have amended the methods section starting line 94 as follows:

“We extracted data from HES for the period April 2004 to March 2015 for all admissions with a pneumonia, sepsis or otitis media ICD-10 code in any diagnosis field for individuals in seven age groups: individuals less than 2 years old, 2-4 years, 5-14, 15-24, 25-44, 45-64 and 65+. The main analysis was restricted to admissions with an ICD-10 code of interest in the first diagnosis field as this field indicates the primary cause of the admission”

Later in the methods section after we have described derivation of incidence rate ratios from the pre to post PCV period we state (beginning line 144) that:

“To assess the robustness of our estimates of the IRRs we performed a sensitivity analysis by calculating the IRRs for each disease endpoint but expanding the number of ICD-10 fields to the first three diagnoses and then using all diagnoses available.”

5. 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?
We thank the reviewer for pointing out that we had no clarified this in our manuscript. We have added to the paragraph on risk group identification:

“Risk groups were identified using ICD-10 codes for comorbidities found to increase the risk of pneumococcal infection in any of the 20 diagnosis fields [2] (immunosupression; cochlear implants; asthma; diabetes; alcoholism; chronic diseases of the lungs; heart; liver; kidneys; all ICD-10 codes are listed in table S2).”

We have also added the following paragraph to the Limitations section of the Discussion to address the issue of sensitivity in our risk group identification:

“We identified risk groups using only the information available within the selected admissions, rather than examining prior admissions for individuals in the years before the outcome diagnoses. This may have resulted in a lower sensitivity for risk group identification. However, we performed a sub-analysis (unpublished) where more information from the HES dataset was extracted from previous years on a patient-by-patient basis for a random sample of 1000 patients. However, despite being much more work, adding information from previous years increased the risk group identification only from just below 80% to just over 90%, which we deemed acceptable given the purpose of this analysis.”

6. Table 2: Ratio IRR disease endpoint not given for IPD?

The laboratory reporting system for IPD is quite different to HES and secular trends have been shown to reflect blood culture practices and laboratory reporting practices so we do not think it valid to use HES controls for laboratory-reported IPD. We have however expended the rationale for not using hospitalised control conditions to derive the ratio of IRRs (line 184) as follows:

“We did not compare the IRR of laboratory-reported IPD to the control conditions from HES because the IPD data from laboratories are not subject to the same secular trends as the HES data and were already corrected for trends in ascertainment of laboratory confirmed pneumococcal bacteraemias [7,8].”
7. Line 128: related to comment for line 125 above, what I then do not understand is why 1 Sept 2004 to 31 August 2006 is compared to an April March period for post vaccine?

We have now changed the pre-PCV period in our analysis to cover 1st April 2004 – 31st March 2006, rather than the September – August period as used before. The reason for the original choice of September – August was this 24 month period ended just before the introduction of PCV7. Given that the main burden is in the winter month this change had only a small impact.

8. Line 274: why are these data know presented from 2007 vs 2015? I may have missed this, but this result has no method in methods?

The use of April 2007 as the starting point for this part of the analysis was because this was the first full financial year after the introduction of the PCV programme. As the incidence data were reported in financial years we were unable to begin this part of the analysis from the beginning of the PCV programme. We acknowledge that this is a limitation in this part of our analysis and may have underestimated the potential changes in the disease burden for each outcome diagnosis. We have added this to our Limitations section of the Discussion (line 515):

“Our analysis of the potential change in the case burden for each of the diagnoses of interest may have underestimated the reported changes in Table 5 as the initial period from September 2006 through April 2007 was missed due to the use of HES data years.”

9. comment on whether the authors examined separately the impact of PCV 7 using relevant time periods prior to PCV 13 reduction viz a viz post PCV 13 and if not some rationale as to why this was thought unnecessary. Most of the other studies the authors reference (and the attribution is by no means comprehensive) were evaluating PCV7 impact and this difference would be worthwhile to highlight
We have added a line to this in the Limitations section of the Discussion (line 509):

“Another potential limitation is that we did not try to estimate the impact of PCV7 and PCV13 separately. We did this because our laboratory confirmed IPD analyses showed that the impact of serotype replacement post-PCV7, particularly in relation to 19A and 7F, which offset some of the benefit of PCV7 was mitigated by the subsequent introduction of PCV13 [8] and thus it was more informative to focus on the impact of the sequential PCV7 and PCV13 programme as a whole than each separately”

Reviewer #4: Statistical Review #2: The authors have addressed each of my original points regarding the statistical methods being used; although I do believe the Bonferroni correction (or some other type of correction) is needed when a large number of confidence intervals are being analyzed (i.e., you are more likely to identify an interval that incorrectly excludes one if you analyze a large number of intervals without some correction). However, this is a minor point and the authors can determine if any changes are needed.

Following the comments of the reviewer we have added the following statement to the discussion:

“We have reported disease trends for many age groups and many diagnoses of interest, so it is possible that our results may include some IRR estimates for which the upper 95% confidence is less than one by chance. However, a formal correction for multiple comparisons is not straightforward in this instance given the method that we have used. Furthermore use of only 5 controls in deriving rIRR values precluded any formal statistical comparison such as computation of confidence intervals so uncertainty in this measure could only be depicted by showing maximum and minimum values across the control conditions.”