Author's response to reviews

Title: Prevention of pneumococcal diseases in the post-seven valent vaccine era: A European perspective

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Version: 4 Date: 7 August 2012

Author's response to reviews: see over
Dear Dr. Harris:

We thank you, the editorial staff and reviewers for the careful review of our manuscript. We have considered the reviewers’ comments that we received and are sending you our point-by-point responses as requested.

If you have any additional questions or would like to have further clarification of any of the points in our article, please contact us and we will respond promptly.

Looking forward to your feedback,

Best regards,
Catherine Weil-Olivier

Corresponding author:

MS: 1773851820660268 Debate:
Prevention of pneumococcal diseases in the post-seven valent vaccine era: A European perspective (Revised title)
Reviewer's report

Title: New expectations in the prevention of pneumococcal diseases

Version: 3 Date: 14 June 2012

Reviewer: Orsolya Dobay

Reviewer's report:

The authors of this manuscript have reviewed the effects of the conjugate pneumococcal vaccine PCV7. It addresses a very important and up-to-date issue all over the world, as the wide-spread use of PCV7 has caused many considerable changes in disease spectrum and serotype distribution. The review is taking every aspect into consideration. It is built up to a very logical order, it discusses the important affected infections (invasive diseases, pneumonia, acute otitis media), and finally also the public health benefits of vaccination. The manuscript is based on an overwhelming number of references, so provides a firm background to all statements.

The final conclusion of the manuscript is that there is a strong need for higher valency vaccines. Well, these vaccines are already available for a couple of years, but the data analysed in this review derive from a period up until 2010, so can only see the effects of PCV7. However, it might take some more time to see the effect of the higher valency vaccines, and as a PCV7 review, it is an excellent manuscript.

The manuscript is very well written, it is acceptable for publication also regarding its English. I suggest the manuscript for a definite publication, with only very small changes suggested, as seen below.

My detailed comments, according to the instructed categories, are the following:

1) Major Compulsory Revisions: none.

2) Minor Essential Revisions:

Haemophilus influenzae is incorrectly typed, without the „e” at the end (for example in the Abstract, Discussion / line 11; or in the main text / AOM section, page 12). Similarly, on page 13, line 15: S. pneumoniae is misspelt. These must be changed.

The revisions requested above have been done.

The Hungarian situation, regarding the vaccination situation, is not absolutely correctly indicated. First, on page 6, “Serotype coverage of higher valency PCV vaccines” section, Hungary should be added to the list of the countries where higher valency vaccines have been recently introduced, as also in Hungary, PCV13 replaced PCV7 in August 2010. Second, in Table 2, the date given for Hungary (Apr 2008) is incorrect: PCV7 was made free for children <2 years old in October 2008, and PCV7 was adopted in the NIP as a recommended vaccine in April 2009 (and this is still the situation).

The date of universal recommendation has been added to Table 2
3) Discretionary Revisions:

page 9, the “Aetiology of childhood CAP” section is probably beyond the subject of this manuscript, I suggest it should be summarised instead in just 1-2 sentences.

- Agreed regarding limiting the extent of a discussion of aetiology - however, we would prefer not to condense this section as we would like to highlight the importance of methodology in influencing the outcome of aetiological studies - and surveillance.

In Table 4, the title says: “Pneumococcal serotype distribution in children <5 years old” – but many data cited derive from children <15 years. This might change the meaning of the results a bit, as older children might have different serotypes, as they were mostly not vaccinated yet.

- We have revised the Table title and the article text (page 7) accordingly

Only very small, mostly typing mistakes:

- The mistakes mentioned below have been corrected

Page 4, Background section: in the case of references [5, 6] and [8, 9], there is a dot (”.,”) instead of a comma (“,”).

Page 6, paragraph 2: provide an abbreviation here for the German National Reference Center for Streptococci (GNRCS), as it will be used later, without definition.

same place: at the end of the last sentence, there should be a dot.

Page 7, line 11: “children aged < 2 years of age” should be changed.

Page 7, par. 2, line 3: serotypes 1, 3 and 7 – maybe 7F should be here?

Page 7, par. 2, line 8: “as the” stands twice.

Page 8, par. 2, sentence 3: more commas should be used for a better understanding.

Page 10, line 4: no comma should be here: “between, 1997”.

Page 10, par. 3, line 7: previously it was used as “all-cause pneumonia” (with hyphen), so use it consequently here as well.

Page 11, new section, line 4: “in those from 2-5 years of age”.

Page 11, new section, line 5: “and to approximately…” – “to” should be inserted.

Page 11, new section, line 12: “underestimated” should be written in one word.

Page 12, line 8: microbiological

Page 12, new section, line 6: “serious”(the “i” was left out)

Page 12, new section, line 7: the abbreviations “SOM” and “CSOM” are unnecessary, as they are not used elsewhere.

Page 13, line 5: “etiology”, or “aetiology” earlier – use it uniformly!

Page 14, line 11: instead of “compared to control”, it should be “versus”, as “comparing” stands already earlier in the same sentence.

Page 15, new section, line 1: “The PCV7 vaccine, is licensed” – no comma is needed here.- page 15, new section, line 12/13: “than before” – something is missing here.
…”than it was before…”
Page 16, line 1: “have a strong effects” – no “a” is needed here.
Page 16, line 3: “in the US, the..”
Page 16, par. 3, line 4/5: “sequellae" or „sequellae" – use it uniformly.
Figure 2: everywhere throughout the manuscript PCV is used, but here Prevenar. Maybe this could be changed.

- Figure 2 has been changed from “Prevenar” to “PCV7”

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.
Reviewer's report

Title: New expectations in the prevention of pneumococcal diseases

Version: 3 Date: 22 June 2012

Reviewer: Jo MC Jefferies

Reviewer's report:

This is a well-written review of current literature and unpublished evidence regarding pneumococcal disease in the post-PCV7 era, as it stated in the closing paragraph of the introduction. However, the title of the article does not accurately reflect the content and may confuse potential readers – the words new expectations convey the idea that this article will discuss future pneumococcal vaccines, for instance those serotype independent vaccines that are currently in clinical trials.

Major Revisions

Title
I suggest the title is changed to better reflect the content of the article and to reflect the fact that data included in the review is largely taken from developed countries with a strong European perspective.

- We take this point concerning the title and have changed it to:
  “Prevention of pneumococcal diseases in the post-seven valent vaccine era: A European perspective”

Abstract
The abstract should also state that the review is based on presentations made at ESPID

- The statement has been included in the Abstract

Page 9, line 15:
The authors state that S. pneumoniae was identified in” 47 of them”. Is this 47 of 292 patients? If so how does this correlate with 45 PCR identifications plus 11 culture identifications when 45+11 = 56? Please clarify numbers of patients, samples and tests here.

- We have clarified this to state that S. pneumoniae was identified in 47 of the 292 patients by one or both of the methods; in 45 by PCR and in 11 by culture (Page 9, 3rd paragraph, last sentence).

Minor Revisions

Main Text

Page 6, Line 1:
Reference 13 is not the primary source of data regarding changes in vaccine type and non-vaccine type IPD, the article cited is a review and this should be made clear.

- Now indicated – last paragraph, page 5
Page 7, Lines 6-8:
The section on AOM sits uncomfortable in the middle of discussion of invasive disease. I suggest this paragraph be moved to the AOM section. The source of the data on severe AOM is unclear, is this also from Germany? As in many settings the majority of AOM cases have no pathogen identified, it would be informative if the country, number of AOM cases making up the denominator for the percentages presented and the percentage of AOM cases that yield serotype information were presented in order to provide information regarding the validity of these estimates.

- The AOM data for which the pathogens were identified was Germany, during the same time as the reported IPD cases, and that is now stated in the manuscript.
- We would prefer to keep this surveillance data together as it shows that in Germany the etiology – the serotype distribution or vaccine coverage of PCV7, PCV10 and PCV13 – differed depending on the site and type of pneumococcal infection.
- We have now included the numbers of reported cases of children with AOM with efflux and the percentage of the cases that yielded serotype information.

Page 9, line 7:
It is not clear what clinical specimens were used in the PCR to confirm pneumococcal CAP – was this sputum? If so a brief discussion of the potential contamination of this sample with URT flora, including pneumococci should be inserted.

- The cited study used real time polymerase chain reaction on blood samples to diagnose and serotype pneumococcal infection in children with community acquired bacteremic pneumonia. This and the source of the specimens i.e., blood, is now included (2nd paragraph, page 9).

Page 12, line 19 (Last line):
Please provide a reference for the statements “Recurrent cases are increasingly likely to involve NTHi” and “Some of these cases respond to treatment, but others become chronic with increasing likelihood of NTHi involvement”

- References have been inserted here (Page 13, line 2) for studies that have shown NHTi to be associated with AOM recurrence, persistent clinical course and lowered efficacy of antibiotic treatment (Refs 43-45: Barkai 2009; Leibovitz 2004; Moriyama 2009)

Page 13, line 1:
What data was the “expected rate” based on? Page

- We simply did not expect to find as high a percentage of mixed pneumococcal plus NTHi infections as we did. The sentence has been re-worded to indicate only the frequencies of occurrence (Page 13, lines 5 & 6).

Page 13, line 4:
Use of the word “because” implies causality – suggest, “Presumably because of” Page

- The sentence has been revised to state “possibly because of..” (Page 13, line 9)

Page 13, line 14:
Why not cite the Hall-Stoodley paper (ref 49) in this section, as it provides stronger evidence of the role of biofilms in AOM than reference to other otorhinolaryngological infections.

- We would prefer to retain the current organization (Page 13, line 19; ref 49 is now 53): In this section we are saying that the clinical picture in some children with complicated or chronic AOM is suggestive of an etiology that includes biofilms, also
known to be associated with other otorhinolaryngological infections (ref 50). We then cite evidence in the next paragraph that *S. pneumoniae* may be associated with NTHi in complicated AOM – i.e. Hall-Stoodley (refs 52-54).

Page 13, line 24:
Please cite a reference for the statement that PCV vaccination reduces pneumococcal carriage
- We have included a reference for this statement (Page 14, line 6; Ref 55: Dagan, et al 1996).

Summary:
Please include a statement in the summary that highlights the facts that the majority of the data is European and that findings may therefore not be generalizable to less developed settings.
- Done (Page 17)

Discretionary Revisions
Page 12, line 24:
Some would argue that children with AOM do not “require” tympanocentesis – suggest this is replaced with “underwent”
- Done (Page 13, line 5)

Page 16, line 3-10:
It would be useful to discuss that the use of life years saved does not take into account quality of life, which may well be reduced following serious pneumococcal infection, particularly if sequelae were suffered
- The paragraph has been revised to expand mention of the influence of QALY – i.e., consideration of reduced morbidity in addition to reduced mortality on overall public health benefits (Page 16, 2nd paragraph).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I have received consulting fees from GSK and have received financial assistance from pneumococcal vaccine manufacturers to attend conferences. All honoraria were paid into University accounts and I have received no personal payments
Reviewer's report

Title: New expectations in the prevention of pneumococcal diseases

Version: 3 Date: 5 July 2012

Reviewer: Massimiliano Don

Reviewer's report:

The paper by Weil-Olivier et al. is a complete review on the known topic of pneumococcal vaccination and its implications on invasive (IPD) and non-invasive pneumococcal diseases, in particular community-acquired pneumonia and pleural empyema on one side and acute otitis media (AOM) on the other side. Important topics have been discussed by the Authors. As for IPD, in more parts of the text it has been clearly stated how, after the introduction of PCV7, the circulation of non-PCV7 vaccine pneumococcal serotypes and the incidence of infections due to such serotypes increased in countries with routine vaccination. Moreover, the Authors underlined the potential of higher valency vaccinations to decrease the burden by non-PCV7 serotypes. The implications on non-invasive pneumococcal diseases such as AOM are discussed exhaustively, too. The paper is clearly written and easy to follow; its Abstract, size, references and English language are proper.

MINOR ESSENTIAL REVISIONS

- These revisions have been done accordingly. See the explanatory notes below for revisions not done exactly as requested.

Page 2, Discussion paragraph, line 7: “…occurrence of pneumonia…”-->
“…occurrence of complicated and not complicated pneumonia…”;
  - Done

Page 7, last but one line: “…as the as the…”-->
“…as the…”;
  - Done

Page 8, line 11: “(Farha et al, 2005)”-->
to be adapted to the other references;
  - Done: Farha et al, 2005 is reference 23.

Page 11, last but two line: “…19A; accounting…”-->
“…19A accounting…”;
  - We have revised the sentence to read "…19A; which account for…"

Page 15, last but two line: “…vaccines. Most…”-->
“…vaccines. Most…”
  - Done
Page 16, line 3: “… US, The vaccine…” --> “… US, the vaccine…”
  ● Done

Page 16, line lust but six: “…52.4%for…” --> “…52.4% for…”
  ● Done

Page 17, line 3: “…to 60 000 to 70 000…” --> please clarify
  ● Done – “from 60 000 to 70 000.”

Page 28, Table 2: the present reviewer though the introduction data of PCV7 in Italy was prior to 2006 (look at reference 29, at page 10); please, check again all data in Table 2.
  ● The table summarises the various times at which PCV7 was included in the NIP of various countries or when a recommendation for universal vaccination was made. The data from reference 29 is from a regional program that began before NIP adoption. The table has been modified (via footnotes) to indicate that is the case.

Page 30, Table 4: please, correct Title that overlaps the first line of the Table itself
  ● The table did not overlap on the file that we have. It must have been a computer “artifact.”

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.