Reviewer's report

Title: Streptococcus pneumoniae Serotype 3 among Costa Rican Children with Otitis Media: clinical, epidemiological characteristics and antimicrobial resistance patterns

Version: 1 Date: 20 March 2009

Reviewer: Amanda Leach

Reviewer's report:

Major compulsory Revisions

Serotype 3 in Costa Rica

1. Is the question posed by the authors well defined?
   The authors wish to describe the epidemiology of serotype 3 OM in Costa Rican children.

2. Are the methods appropriate and well described?
   The group have access to data on OM from clinical trials where tympanocentesis was conducted to collect middle ear fluid and recover bacterial pathogens. This is a retrospective analysis of that data. The trials are not described. For instance it is not clear whether a child was included twice, whether bilateral MEFs were included in the analysis or if double tympanoventesis was performed, and how duplicate isolates were included if they were the same serotype or different. There is no information on how vaccination status was determined.

3. Are the data sound?
   The data are very important as few countries would have performed tympanoventesis over such a long period. There are some gaps in the isolate collection and it is not clear exactly what period is covered (1992 to 2007 or 1992 to 2006) by the isolates versus the tympanoventesis procedures – see comments below. The denominators used are unclear – see Table below. The results presented as %s need to be clarified, particularly as the 1919 tympanoventeses were performed from 1992 to 2007. Of these 511 were positive for pneumococci. Then the there were 511 isolates recovered from 1999 to 2006. This is very confusing and must be clarified. There is no explanation as to why there are such large year to year variations in the numbers of samples collected. The original studies are not described nor cited.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   As the original studies are not described nor citations to publications relating to these original clinical trials are not made in the methods section (Study population), it is not possible to really know if this is the case. The authors may find it helpful to be guided by the CONSORT statement in relation to cross
referencing to the original clinical trials from which this report is derived.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

The document has many typographic, grammatical and spelling errors which make it difficult to read. References are cited inappropriately (see details below) and several important publications are missing. The major omission in the paper is the data relating to serotype 3 immunogenicity and efficacy data from the studies of GSK’s PCV (which was 11-valent and is now 10-valent due to withdrawal of serotype 3). There is no data to show that the serotype 3 in Wyeth’s vaccine is both immunogenic and efficacious.

6. Are limitations of the work clearly stated?

No, limitations are not discussed at all.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?

Yes, it is clear that they have a lot of data.

8. Do the title and abstract accurately convey what has been found?

Given the queries stated above and below, the data will need to be presented more clearly in order to determine accuracy.

9. Is the writing acceptable?

There are many errors in the document.

ABSTRACT

Background – please use consistent terminology

conjugated seven valent antipneumococcal vaccine
seven valent conjugated pneumococcal vaccine

Methods - Participants

Enrolled in clinical trials – Were children receiving antibiotics or placebo? Was recent antibiotic use recorded or was this an exclusion criteria? how could this influence serotype distribution? What class of antibiotics?

Results: 1992 – 1997. 1919 tympanocenteses – in how many children? How many ears per child? Was tympanocentesis performed in both left and right ear? How many were negative? Were any MEFs mixed pathogens? Did any child have mixed pathogens (different in left and right?).

1208 middle ear isolates (1992 to 2007) – From how many children? 511+386+100+54 does not add up to 1208, whereas their percentages add up to 100% (49% + 37% + 9.5%+5%). The denominator used for these %s should be clearly stated. In other words, 511/1208 is 42% (not 49%) etc. As a proportion of 1919 tympanocenteses, these %s would be a lot lower: 27% for S. pneumoniae etc. It would be helpful to have the MEF as the denominator, since this is a greater indication of potential impact of vaccine. When extended further, there were 346 S. pneumoniae isolates serotyped which is 18% of the 1919
tympanocenteses. Of these 346, 34 were type 3 (1.8% tympanocenteses). It is also unclear why the same number of *S. pneumoniae* isolates is listed for the period 1992 to 2007 (511) as for 1999 to 2006 (511)?

These data could be presented most clearly by adding several columns to Table 1. For instance …

<table>
<thead>
<tr>
<th>Year</th>
<th>No. children</th>
<th>No. MEFs (ears)</th>
<th>No. MEFs any pathogen positive</th>
<th>No. MEFs with <em>Spn</em> (%)</th>
<th>No. serotyped</th>
<th>No. MEFs with type 3 (%)</th>
<th>No. children with type 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992-2007</td>
<td>1919</td>
<td>1208</td>
<td>511 (42%)</td>
<td>346</td>
<td>34 (1.8%)</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>1999-2006</td>
<td>?</td>
<td>?</td>
<td>?511 (42%)</td>
<td>346</td>
<td>34 (1.8%)</td>
<td>34</td>
<td></td>
</tr>
</tbody>
</table>

**INTRODUCTION**

The references cited do not seem to match the statements in the text.

(3) is a paper on Diagnosis and treatment, not epidemiology of pneumococcal OM

A reference for the incidence of 1.4 episodes/year/child is needed.

(4) is a Costa Rican study, not including all of Latin America?

(5,6) are papers on resistance rather than the introduction of 7PCV in to NIP programs in different parts of the world – perhaps cite PneumoADIP.

(7) Weekly Epi record No. 12, 23 March 2007. What is the title of this report?

(8) Whitney reports population decline in IPD and herd effects, but not OM.

(9) reports the OM outcomes.

The figure of “overall 67% vaccine efficacy (9)” appear to be a misinterpretation of the 67% reported by Black for vaccine serotype OM.

The author has not discussed the literature on serotype 3 immunogenicity and efficacy in the POET study, which led to withdrawal of serotype 3 from that vaccine. Is there data from Wyeth to suggest that serotype 3 in the 13PCV is immunogenic and/or efficacious??

No reference is given to support the statement that “OM serotype 3 has been reported as one of the most important MEF replacement isolates…” Reference (8) at the end of this statement refers to necrotizing pneumonia in Utah.

**REFERENCES**

There are numerous typographical errors, including

Inconsistent journal abbreviations

Wkly Epidemiological Report

Weekly Epidemiological Report (no title given)

NEJM

New Engl J Med
Pediatr Infect Dis J
Ped Inf Dis J
Clin Inf Dis

Inconsistent use of et al. after three authors in some, 5 in others or listing all nine in others.

Spelling of Firman should be Fireman in (9)

Title Case is mixed throughout.

(12) Does Serotype Matters? Should be ...Matter?

MATERIALS and METHODS
Another phrase for “Pneumococcal conjugated seven valent vaccine” is used.
Is there a reference for the quoted uptake of 7PCV in Costa Rica of 10% to 20%.
How was vaccination status determined in this study? Was a national register available? Were children’s medical records checked?

Definitions. This is quite difficult to follow at present.
Otitis media: …at least one of ..: otorrhoea ..or at least two ..signs middle ear effusion (…) and at least one indication of acute inflammation (…); AOM,..signs and symptoms …; ROM, history ; FOM, …

Middle ear fluid sampling. Reference (14) is not a reference for tympanocentesis, it is for antimicrobial susceptibility testing. What was the transport medium?

Microbiology. Reference (14) – Is that correct for identification, or just susceptibility testing? Please give manufacturer of Cefinase disk.

Serotyping. Reference (4) is not the direct reference for the Quellung reaction.

Antimicrobial susceptibility. “susceptibility testing for penicillin …..was determined by ..MIC by means E-test.” This does not read well.

“Susceptibility and interpretation from MEF samples was done ...” I think the author means interpretation of MIC breakpoints, not MEF?? Please cite NCCLS correctly and in full and cite reference (14).

RESULTS
The first parpagrpah needs a heading.
2nd sentence (in fact all sentences and for all %s quoted) – what is the denominator? Is this all children with OM, or positive MEFs? See comments on Abstract.

How was vaccination status determined? This should be in the methods.

Serotype 3...characteristics
The first paragraph could have a separate title as it refers to serotype distribution, not just serotype 3.

Figure 1. The labels are %s but this is clear from the size of the Pie section – it would help if the labels were the serotype. The heading is duplicated. In the legend, the Spanish word “otros” should be replaced with “other”.

The peak in 2004 and 2005 is not that convincing in the absence of statistical analysis, no confidence intervals are given, nor trend analysis. What is important is the fluctuation from year to year in the proportion of pneumococcal isolates that are type 3, but also the total numbers typed. A more comprehensive Table as suggested above may be helpful in understanding why one year there are 74 isolates, the next 28 and the next 84?? The graph below is also a suggestion (a bit rough, but a suggestion).

Analysis by age … Again, could the authors provide figures and confidence intervals.

Distribution of … by clinical diagnosis.

The authors could also present this as…The proportion of each clinical diagnosis associated with serotype 3 was 26/347 (7.5%) cases of AOM compared to 7 of 77 (9%) ROM, and 1 of 28 (3.6%) FOM ..note that 95% CIs should be given. For bilateral cases – how were duplicate serotype 3s ‘counted’?

Clinical outcome.

Does cured or improved include bacteriologic cure? i.e. were double taps performed and was serotype 3 eradicated from the MEF?

DISCUSSION

Paragraph 3

The 10% figure for proportion of all pneumococcal otitis episodes is misleading as not all pneumococci were serotyped. Only 346 of 511 isolates was typed. Serotype 3 was 10% of serotyped isolates and 6.7% all pneumococci.

Paragraph 4

The discussion around increasing prevalence of serotype 3 is an over interpretation of the data. Annual proportion of serotypes pneumococci were 9.6%, 15.3% and 10.3% in years 2003, 2004 and 2005, so 10.09% (and it is unclear where this figure comes from) could not be described as a recent increase?? No prospective surveillance was undertaken and participants were enrolled in clinical trials about which no information is given.

The sentence “This serotype now represents the third cause of OM..” should be the third most common .. Although in the context of having serotype data on only 66% isolates. The next sentence needs re-writing “…has also increased in proportions in the USA…” I do not agree that this study shows a trend towards an increase. The data are from a series of clinical trials and are not designed to monitor serotype trends. The next sentence is more consistent with the study –
that yearly fluctuations occur which may or may not be associated with vaccines.
Paragraph 5
“As shown in previous reports ..” please provide reference.
Paragraph 5
Again, the assumption that this study has confirmed an increase in serotype 3
should be removed.
Typographic errors as follows
“This finding suggest that, “ should be suggests
“has increased as mayor OM…” incorrect spelling – but also should be removed
as over-interpretation of the data.
“option to treat this patients.” Should be these
Paragraph 6
In conclusion …with OM, thus any future ..vaccine(2)

**Level of interest:** An article whose findings are important to those with closely
related research interests

**Quality of written English:** Not suitable for publication unless extensively edited

**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’