Reviewer’s report

Title: Molecular epidemiology of pneumococci obtained from Gambian children aged 2-29 months with invasive pneumococcal disease during a trial of a 9-valent pneumococcal conjugate vaccine

Version: 1 Date: 1 November 2007

Reviewer: Bill Hausdorff

Reviewer’s report:

General

This is potentially an important study with some very careful analyses, and I'm convinced that clonal analyses of this type can potentially be very meaningful. Unfortunately, after a few readings I found myself uncertain as to what are the major conclusions from the study. Were there any driving hypotheses behind it or was it simply purely descriptive? To remedy this, I think more hypotheses could be easily tested (see below) to make it a more interesting and valuable study.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. In line with the above general comment, it is not clear to me how the conclusion as listed in the abstract follows from the results. To play the devil's advocate, what did we learn from the present study that leads to the conclusion that it's important to monitor clonal distribution?

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

2. Suggest “herd protection” instead of herd immunity—p.4

3. p.4: 131 isolates; p.5 127 isolates—I think it is only in discussion where it finally become explicit why only 127 isolates were selected.

4. Were the IPD serotypes shown from the per protocol or ITT analysis?

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Discretionary Revisions (which the author can choose to ignore)

5. p.7: “There was no particular association of clones with specific presentations of invasive pneumococcal disease (data not shown)”—demonstration of lack of an association is also important considering continuing controversy about whether different clones of the same serotype may have different disease presentations (or invasiveness). Can this be shown more explicitly?
6. In addition, is there any difference in clone distribution by age?

7. Similarly, is there any difference in vaccine or non-vaccine type clones BETWEEN the vaccinated and unvaccinated populations? For example, for a given serotype—1, 14, 9V—do vaccine failures represent different clones than the clones in the unvaccinated? It is not clear from p.7 last sentence that this was examined. Although the carriage clonal distribution is not shown, it would very much strengthen the paper to know if there are differences vis a vis IPD clonal distribution. But I realize this might be a separate paper.

8. The metanalysis mentioned on p.8 is likely not an appropriate method to assess results from only two, highly discordant studies. Given the results obtained in the South African trial, with 5 cases in the control group and only 1 in the vaccine group for serotype 1 IPD (Madhi et al Vaccine 25 (2007) 2451–2457), I don’t understand the basis for the conclusion that the metanalysis “shows no evidence of protection.” It is in the Gambia study only where serotype 1 efficacy was not demonstrated, and so to me the most fruitful approach is to search for potential methodological or epidemiological differences vis a vis South Africa—e.g., relative ages of serotype 1 patients in the two trials, any differences in clinical presentation or immune or malarial status etc. Also, reference 26 presumably should refer to a specific chapter in that book.

What next?: Accept after discretionary revisions

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

Quality of written English: Acceptable

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

Declaration of competing interests:

I don’t see any potential financial or non-financial competing interest for my review of this particular paper, as it focuses on descriptive epidemiology of the pneumococcus itself. However, since the analyses were being undertaken in the context of a vaccine study, it is relevant to provide further details:

I am currently an employee with GlaxoSmithKline Biologicals, which is developing a pneumococcal conjugate vaccine designed to be effective against many of the serotypes whose molecular epidemiology is being characterized here. Previously, I had been an employee of Wyeth Vaccines, and was involved in the original design of the Gambia vaccine efficacy study, and am a co-patent applicant for their 13-valent vaccine (of which the 9-valent vaccine here was a predecessor). Please note that as a former employee I will receive no financial
compensation from that patent if awarded.

Because the focus of this paper is descriptive epidemiology, and not to assess the characteristics nor efficacy of the vaccine (which has already been published), I don't perceive any potential competing financial or non-financial interest that could be affected by the results of the study here. In addition, Wyeth has publicly stated that this vaccine formulation will not be commercialized.

In addition, I should clarify that I had absolutely no involvement or knowledge of the design or analyses of the present study.