Reviewer's report

Title: Emerging pneumococcal carriage serotypes in a high-risk population receiving universal 7-valent pneumococcal conjugate vaccine since 2001.

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Reviewer: Bill Hausdorff

Reviewer's report:

This paper provides a valuable, detailed description of the nasopharyngeal carriage of pneumococci in a relatively large number of indigenous Australian children in two different years. It is an important snapshot of serotype distribution in the early 7PCV era that will be useful to compare to the pre 7PCV era as well as several years from now.

The presentation of results is oriented around a comparison of 2003 data vs 2005 data, and a number of small differences are presented as being statistically significant and possibly related to slightly greater uptake of 7PCV in these two years. To the authors' credit, they note that the differences appear small and not necessarily related to 7PCV. However, without a more precise analysis, it is difficult to interpret either the validity of this comparison or potential underlying mechanisms of these differences.

Major Revisions

One first wonders how many of these comparisons would survive the Bonferroni test for multiple comparisons.

Beyond that, there are some potentially major confounding issues that could be more precisely addressed by the authors. First, there are the significantly different mean ages of the children sampled in 2003 and 2005, 25 (24-26) months and 35 (33-36) months, respectively. Increasing age has been inversely correlated with the degree of pneumococcal carriage overall and of 7PCV type carriage in particular (e.g., Dagan et al JID 2002;185:927–36). This alone might “explain” some of the apparent differences seen.

By focusing on comparable age groups (<6 month olds) in one paragraph in the results the authors begin to address this, but such paired comparisons (2003 vs 2005) for other narrow age windows (e.g., 6-24 mos; 25-36 mos; 37-60 mos) could be made. Age confounding is also likely at work in the analyses of 23PPV vaccinated (mean 37 mos) vs 23PPV non-vaccinated (mean 21 mos) children.

One additional source of confusion is how 6A/6C are treated. Although in the legends to Figures 1 and 2 the authors note that the proportions of 6A and 6C likely differ in the two years, indicating they have some further serotyping data, all data are presented as if they were 6A only in Table 2 and in the Figures; even more confusingly, the 6A/6C data are combined with 19A data in Table 3, making
it impossible to determine whether the surprising apparent overall decrease in 19A carriage is limited to a single site or truly represents a larger trend. While one appreciates that the sample sizes become very small, the 6A vs 6C distinction is of great interest given US data with 7PCV showing strong evidence of herd protection against true 6A disease, but not 6C (presented at ISPPD in June 2008 and recently published Park et al JID 2008).

Minor revision: Another potentially confounding issue, noted in the last paragraph of the discussion but not integrated into the interpretation of results, is the “epidemic and endemic nature of various serotypes.” While the authors focus on the epidemic serotype 1 and 5, the relative importance of other serotypes can also wax and wane (e.g., Ruckinger S, et al., Vaccine (2008); Lagos JID 2008:198). Thus apparent changes in 19A or 6A/6C (or 16F) reported here could conceivably have nothing to do either with 7PCV or antimicrobial use, and this could be mentioned.

Some of the differences seen among the pooled data in Table 2 disappear when the individual regions are compared, questioning the validity of pooling. This is not just a matter of statistical power because of the smaller sample size—even the trends for the point estimates sometimes run in the opposite direction when one compares Table 3 to Table 2. For example, the overall point estimates for Spn positivity in table 2 appear to decrease from 82% to 76%, but in Table 3 one learns that 2 of the 4 regions the point estimates increase from 83 to 86% and from 85% to 87%. This could be discussed.

Discretionary revisions:

Shouldn’t “penicillin resistant” be “penicillin non-susceptible” given the cut-off used here?

In Methods (Vaccine schedule) it is unclear whether 23PPV was recommended as a booster for aboriginal children in South Australia.

The authors could comment on the influence (or lack thereof) of 7PCV use in non-indigenous populations in these regions on the pneumococcal ecology of the indigenous populations in the same regions.

Finally, if age is better controlled for, it would be of interest to determine whether there are any changes in antibiotic resistance levels by serotype between 2003 and 2005 (i.e., provide 2 bars for each serotype in Figure 2).

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

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

I do not perceive that I have any competing interests, financial or otherwise, that could be affected by publication of this paper or that would influence my interpretation of the analyses presented here. I note that I am employed as Director of Epidemiology at GlaxoSmithKline Biologicals, which is developing a pneumococcal conjugate vaccine formulation.