Reviewer's report

Title: Dynamic models of pneumococcal carriage and the impact of the Heptavalent Pneumococcal Conjugate Vaccine on invasive pneumococcal disease.

Version: 2 Date: 11 January 2010

Reviewer: Kari Auranen

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Minor Essential Revisions

Model

• p. 7, section ‘Population’. It is still not clear to me what the age structure of the population in the model was. The fact that IPD incidence in each age group was based on knowledge of the size of the age groups seems irrelevant to mention here. My specific questions thus remains:

  o Did you solve for the stable population, given the current birth and/or death rates? Or, after all, was the population initialised with the current age structure + birth & death rates? In this case, the population would undergo a transition phase towards equilibrium. Or something else? Please try to clarify.

Structure

• p. 7, 2nd paragraph: Reference [39] (Eskola et al.) does not include data about the vaccine effect on carriage of serotype 6A (or any other serotype for that matter). Instead, it does report a reduction in the incidence of otitis media due to 6A. Please remove the reference when addressing the vaccine effect on carriage.

  You may also want to discuss the inclusion of 6A as a ‘vaccine type’. Not all previous literature speaks for protection against 6A. In fact, it may be that a substantial effect on 6A depends on the particular vaccine and/or administration of the booster. Another factor is that the newly discovered serotype 6C has previously not been distinguished from 6A, with potentially different direct vaccine effects on these two types confounding inferences.

• p., 8, line 2: The symbol of the force of infection for the non-vaccine types has an erroneous subindex. According to the notation used in Figure 4, it should read \( \lambda_{N_i} \). The same mistake repeats at least on the following line (p.8, line 3).

• Figure 4: The arrows between compartments \( V_i \) and \( B_i \) still point to the same direction (towards \( B_i \)). The arrow denoting clearance should be reversed.
Parameterisation

- p. 9, Section ‘Forces of infection’. It is not clear which age classes were used in deriving the force of infection and the mixing matrix (‘beta’). Could you give the age categories here or perhaps in the 2nd paragraph of section ‘Model analysis’ (where it is mentioned that 6 age groups were used)?
- Table 1: The text at the bottom of the table: The proper interpretation would be clearer if you wrote: “Duration and degree are correlated, i.e., …”

Discretionary Revisions

Structure

* It is somewhat confusing that ‘V’ is used to denote (the status of) vaccine type carriage and ‘v’ those vaccinated with PCV7. In addition, it is still not clear whether the latter is ‘v’ or ‘\nu’ since different symbols are being used (see e.g. the last line on page 7, and the equations for the forces of infection on page 9).

Parameterisation

- Table 1: The text at the bottom of the table: The proper interpretation would be clearer if you wrote: “Duration and degree are correlated, i.e., …”

Model analysis

- This section is a considerable improvement to the earlier version of the manuscript. However, I think it is too vague to write “… identify steady state values for model parameters” (p. 11, line 2). Could you not mention that at this stage the “model parameters” that were identified were the forces of infection (as I understand this stage)?
- Related to this, in Appendix A2, you write that “Given values of the pneumococcal transmission parameters (in particular the competition parameters c_V and C_N), …”. When calibrating the transmission model to the UK carriage data, did you assume specific values for c_N (and c_V)? And then, at the next stage, these competition parameters were estimated from the US IPD data. Could you clarify this somehow?

Results

- p. 12, line 4-9. You write that “The decline in the … was best captured …”. This
sentence seems to refer to the results obtained for parameters c_N and epsilon, irrespective of the assumed level of vaccine coverage. Is this interpretation correct? If so, it could be written out more clearly.

• The estimated value of the degree (relative reduction in the rate of acquisition for a vaccine serotype) appears quite high, regarding data from vaccine trials (see e.g. Rinta-Kokko et al, Vaccine 2009). This is just a comment, since it can certainly be argues that the strength of the current approach is that this parameter is estimated from data in the actual context of the transmission model.

• Table 3. Add ‘years’ as the unit of age in the table.

• Figure 7: The title of the x-axis (‘Vaccine years’) seems odd. It must mean ‘Years after PCV7 introduction’ (see the title you use in Figure 8!)

• Is Figure 8 really necessary? It seems that this information is at least somehow given already in Figure 7 on an annual basis. Only the split of IPD cases in age classes <15 and 15+ is not described by Figure 7. Then again, this split is given in Figure 9 for the new steady-state.

Also, although I think I now understand how the annual reduction in the number of IPD cases (2,300), as given on page 13, line 4, relates to the appr. 20,000 cases in the new steady-state (i.e. ~5x(6,200-2,300)), Figure 8 does not seem necessary.

Discussion

• p. 16, line -10: What does it mean that “Vaccine trial and other vaccine studies were used to inform vaccine parameters”? I understood that in this study in particular, the degree and the rate of waning immunity were inferred from the post-surveillance data in the US, within the context of the current transmission model.

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.