Author's response to reviews

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

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Author's response to reviews: see over
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Dear Editor,

RE: Manuscript ID 1976914097304906  
*Dynamic models of pneumococcal carriage and the impact of the Heptavalent Pneumococcal Conjugate Vaccine on invasive pneumococcal disease.*

Thank you for your kind consideration of our revision of this manuscript. We have made changes to the text in response to the comments from the Reviewer 3.

The revised manuscript and our response to the comments raised by the Reviewer 3 are enclosed. The changes made to respond to reviewers’ comments are marked in bold in an Additional material file, “Melegaro 2009_resubmission_Changes.doc”.

We look forward to hearing from you.

Yours faithfully,

Alessia Melegaro  
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MINOR ESSENTIAL REVISIONS

Q1. 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: - 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

A1. The text in the paragraph has been changed as follows:

The model consists of 100 cohorts of individuals (0, 1, 2, 3,..., 99) each corresponding to one year of age and each of equal size (nc=0.01), with a total stable population (i.e. births equal deaths) which adds up to 1 [24]. Individuals are born into age cohort 0 at the start of the year and live to the age of 99 years, at which point they die. Aging is thus modelled at the end of each year, with individuals in age group i moving up to become age group i+1. Each age cohort goes through the transmission cycles according to the infection process outlined in the following paragraph.

Q2. 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.
One critical aspect of the current work is that the model categorises pneumococcal serotypes as either vaccine-type (including 6A) or non-vaccine type and assumes that the characteristics are homogeneous within each of these two categories. Firstly, the inclusion of serotype 6A in the vaccine group was implemented due to existing evidence that the 7-valent pneumococcal conjugate vaccine induces cross-protection against 6A [52,53]. However, the newly identified serotypes 6C and 6D [54,55], which do not benefit from cross protection [54,56-58] should be excluded from the vaccine group in future modelling work. Secondly, there is considerable heterogeneity between individual serotypes in, for example, their transmissibility, duration of infection, ability to co-colonise, ability to prevent co-colonization with other serotypes, and potential to cause disease [59-61]. All these factors may influence the response of individual serotypes and the pneumococcal population as a whole to the introduction of infant PCV7 vaccination. Studying these effects would require an individual-based model in order to incorporate many circulating serotypes. 

Within such a framework it would also be possible to begin to investigate the impact of acquired immunity on pneumococcal transmission by incorporating a mechanism for generating type-specific and/or type-independent immunity [62-65].

Q3. 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.

A3. The sub-index for the FOI for non-vaccine serotypes has been changed in the text and made consistent with Figure 4. The arrows in Figures 4 have been fixed.

Q4. 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)?
There were three stages to the analysis. First, a steady state pre-vaccination model estimated age-stratified values for the forces of infection and case:carrier ratios for VT and NVT. Second, a dynamic post-vaccination model estimated key vaccine parameters, interaction between VT and NVT and the level of assortativeness of mixing pattern from US surveillance data. Third, the dynamic model was used to assess the impact of alternative vaccination strategies in England and Wales.

The pre-vaccination model was programmed in Excel to estimate forces of infection for VT and NVT and for the following age groups: 0-1, 2-4, 5-9, 10-19, 20-39 and 40-99 using the carriage prevalence data available for England and Wales and a given value for the competition parameter ($c_N$). The fully assortative and fully proportionate mixing matrices between the six age-groups were also generated and later used as two extremes in the transmission model. Age-specific case:carrier ratios were then derived fitting the model to the age distribution of IPD cases caused by, respectively, vaccine and non-vaccine serotypes in the pre-vaccination era. The procedure, which required the minimisation of a Poisson deviance using the SOLVER in Excel, was run for both England and Wales and the US to calculate the risk of developing disease when colonised.

The transmission dynamic model was programmed in Berkeley Madonna (R. I. Macey & G. F. Oster, UC Berkeley, CA, USA) and fitted to the pre- and post-vaccination IPD data from the US to estimate degree and duration of protection of the vaccine against invasive disease, and the mixing parameter ($\varepsilon$) for different values of the competition parameter ($c_N$). The forces of infection, case:carrier ratios and extreme mixing matrices were updated for each value of $c_N$. The estimate of $c_N$ was derived by finding the value that minimised the deviance.

Once the parameters were generated, the epidemiological model was used to assess the impact of alternative vaccination strategies in England and Wales. The system was solved using the Euler method to integrate ordinary differential equations with fixed time steps of 0.001 years. The model simulated 50 years (five years pre-vaccination and 45 years after vaccination).
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., …”

The text under Table 1 has been changed

**DISCRETIONARY REVISIONS**

Q5. 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) to denote both the vaccine type (or vaccine type carriage) and those vaccinated with PCV7. See e.g. notations for V_v (vaccinated).

A5. We have changed the (Sv, Vv, Nv, Bv). We have kept the notation V for vaccine serotype carriers, N for non-vaccine serotype carriers and little v for the vaccinated groups.

Q6. p. 8, line 7: There is a subtle assumption that double carriage is cleared (in the sense that one of the carried serotypes is cleared) with the same rate as single carriage. Because it could be conceivable that double carriage is cleared at a higher rate than single carriage, this assumption could be worth mentioning.

A6. We added some text in the ‘Model structure – Infection paragraph’

This happens at an age-dependent rate r, which is the same whether or not the individual was in the colonised state (V or N) or in the co-colonised state (B)

Moreover, a discussion point of the competition mechanism assumed here as opposed to the alternative of increased clearance rate has been added in the ‘Discussion’

**The mechanism of competition incorporated in the model may influence the projected outcomes [49]. Here, the mechanism assumed was of a reduction of the acquisition rate of other serotypes when already colonised. This mechanism is supported by a recent Danish longitudinal study of pneumococcal infection [50], which preferred it to a mechanism of competition through an increase in the clearance rate for co-colonised**
individuals. Our exploration of alternative hypotheses for competition is limited by a lack of co-colonisation data. Clearly, more work is needed in this area and laboratory techniques that enable detection of carriage of multiple serotypes will facilitate studies of the interactions between different pneumococcal serotypes.

Q7. 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., …”

A7. We changed the text at the bottom of Table 1

Q8. 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)?

A8. We changed the text according to reviewer’s suggestion. See A4.

Q9. 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?

A9. Some changes have been made to the text to include details of the estimation procedure for the competition parameter. See A4.

Q10. 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.

A10. We want to make two points with this paragraph. 1. Increases in the coverage level produced reduction in the degree and duration of protection and vice versa as expected; 2. When coverage levels lie within the realistic band (80-90%), the decline in the number of VT cases as well as the increase in the NVT cases strongly suggests that some level of protection against acquisition of NVT when already colonised with VT exists and that mixing pattern is closer to assortative than proportionate.

We have changed the paragraph as follows.

The sensitivity of estimates of the degree of vaccine protection and duration of protection to the assumed PCV7 coverage was investigated. Increasing the vaccine coverage assumed may account for some protection derived by individuals who were only partially vaccinated; reducing the vaccine coverage assumed is equivalent to reducing the take of the vaccine to less than 100%. Parameter estimates are presented in Table 2 according to six vaccine coverage values from 80% to 90% and show that increases in the coverage level produced some reduction in the degree and duration of protection as expected. However, for coverage levels within this range, the estimates of the competition and mixing parameters were not sensitive to the assumed vaccination coverage. These results suggest that individuals who were carrying VT were partly protected against NVT acquisition ($c_N=85\%, 15\%$ protection), and that population mixing was closer to assortative than proportionate ($\varepsilon = 0.87$) in line with a recent European contact study [46].

Q11. Table 3. Add ‘years’ as the unit of age in the table.

A11. Table 3 changed accordingly

Q12. 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!)

A12. We changed the X-axis according to the suggestion.

Q13. 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.

A13. Figure 8 has been deleted

Q14. 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.

A14. We have changed the sentence as follows

Surveillance data on IPD cases pre- and post- PCV7 introduction in the US were used to estimate vaccine parameters, mixing patterns and to infer the degree of competition between VT and NVT.