Author's response to reviews

Title: The 7-valent pneumococcal conjugate vaccine elicits cross-functional opsonophagocytic killing responses to Streptococcus pneumoniae serotype 6D in children

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Author's response to reviews: see over
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Editor, BMC Infectious Diseases

Dear Editor,

Enclosed please find a revised manuscript by H Lee et al. (Title: The 7-valent pneumococcal conjugate vaccine elicits cross-functional opsonophagocytic killing responses to Streptococcus pneumoniae serotype 6D in children). We made revisions on the manuscript according to the reviewers’ comments, and we feel that the manuscript has improved with these changes. Responses to the reviewers’ comments are attached to the cover letter.

I hope that this article is now acceptable for publication in your journal. This study was funded by RP-Grant 2011 of Ewha Womans University to HL and KHK and by the Korea Food and Drug Administration (11172KFDA360) to KHK. University of Alabama at Birmingham (UAB) owns intellectual property rights on the various reagents used for pneumococcal vaccine studies, and MHN and RLB are UAB employees. The authors declare they have no other conflicts of interest.

This manuscript was reviewed by all authors, has not been published before and will not be submitted for publication elsewhere. If you have any questions, please feel free to contact me.

Sincerely,

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Response to reviewers' comments

Reviewer's report (1):

The study by Lee and colleagues is a well conducted study addressing the important issue of cross protectively of the 7 valent pneumococcal conjugate vaccine against serotype 6B. I suggest to accept the paper for publication with minor revisions.

Major comments:

1. Are there any data about preexisting infections (e.g. pneumococcal infections) in the studied groups? This may alter the OPA levels. Especially as there were differences in the mean ages of the groups (19 months, 14 m, 15 m) and therefore the older subjects had a higher probability of previous infections.

⇒ None of the subjects included in the study had previous history of known pneumococcal diseases, including invasive pneumococcal diseases. However there is always the possibility of pneumococcal infections which were not documented by culture or were unknown to the subjects. Also, exposure to pneumococcal antigens in carriage is possible. The authors agree on the reviewer’s comment that this could affect the OPA levels, especially in the differences in the mean age of the groups. We have included this speculation in the manuscript (page 11-12, line 188-192).

2. There seems to be a marked difference in the prevalence of ST 6D in the Korea vs the US. The authors should discuss if there can be differences regarding susceptibility and genetic determined levels of vaccine response between this two different ethnic groups.

⇒ There is a difference in prevalence of serotype 6D in Korea and the US, with serotype 6D being more prevalent in Korea. However, the authors do not feel that this difference is due to genetic determinants of vaccine response between these two ethnic groups. According to
previous studies on immunogenicity of the 7-valent pneumococcal protein conjugate vaccine, Korean infants had a higher (not lower) response compared with other ethnic groups, including the US, European or Taiwanese infants. The authors think that this difference in epidemiology of serotype 6D could be more related to the characteristics of the strain and environmental issues, rather than a response to the vaccine. For example, Oliver et al recently discovered new serotypes within serogroup 6 (J. Biol. Chem. 2013 Jul29), raising the possibility of additional heterogeneity within this serogroup. However there is no definitive evidence to support this speculation yet and this issue has to be further studied.

3. I find the reverse cumulative distribution curves misleading (Figure 2) and hard to interpret. As a suggestion I would only display ST 6B and 6D and display them in only one panel.

⇒ Thank you for the comment. The figure is revised according to the reviewer’s comment.

**Reviewer’s report (2):**

The ability of pneumococcal conjugate vaccine to elicit cross-reactivity and by implication cross-protection has been an intensely studied area. It is important to describe the implications for individuals countries and, in particular, for their vaccination policy. As a discretionary comment, a little information about the history of serotype 6D in Korea would be helpful along with any known clinical implications.

The age group studied (12 to 23 months) is of interest, as this is still a period of high risk. However, the numbers are relatively small. Despite this, the serology is convincing - it appears that there is cross-reactivity across serogroup 6, especially after a booster dose. For countries with a 2+1 schedule, the applicability is less certain that for countries with a 3+1 schedule.
1. One possible component of bias could be the reasons that the subjects sought "medical examination" - this implies that they may not have been entirely "healthy volunteers". One would expect that if the subjects had anything other than a minor illness, that this would have been mentioned.

⇒ Thank you for the comment. The subjects included in the study were mostly sampled for minor illnesses and there were no subjects with significant illnesses. We have described exclusion of subjects with major medical illness or history, which could affect the immune response towards pneumococcal conjugate vaccines, on p. 7 line 91-93.

Reference