Author's response to reviews

Title: Health-Economic evaluation of vaccination strategies for the prevention of herpes zoster and postherpetic neuralgia in Germany

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Author's response to reviews: see over
Dear Dr Shackley,

I wish to submit in the name of all authors the 2nd revised version of the manuscript entitled “Health Economic evaluation of vaccination strategies for the prevention of herpes zoster and postherpetic neuralgia in Germany” for re-consideration for publication as a research article in BMC Health Services Research.

We thank the two reviewers for their helpful comments. We believe that after consideration of these comments the quality of the manuscript has further improved.

Please find below the point-by-point responses to the reviewer’s comments. In addition, we highlighted all changes within the manuscript and tables yellow.

All authors have seen and approved the revised version of the manuscript.

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Sincerely yours

Bernhard Ultsch
Reviewer’s report:

Review of the revised manuscript

I want to thank the authors for the great number of changes they made to the manuscript. However I am still not satisfied with the investigation of the uncertainty around the vaccine efficacy and the discussion, and I realise I should have articulated my problems perhaps more extensive in the previous round, my excuses. The authors should be more upfront about the large uncertainties. Lines as “The model demonstrated high robustness in PSA” (in the abstract) and “the validity of our results considering the German health-care setting can be considered very high” are too strong. This because the authors have a good estimate of the incidence, however it does include the immuno compromised (an important risk factor) and therefore there is an overestimation of the incidence (for which they could have corrected but they didn’t). The duration of PHN does not change by age and the duration of protection is not really known, and does not change by age. Also the model of a fixed duration of no-waning followed by a period of waning is based on an assumption and not on data, around which is actually a lot of uncertainty, as is nicely discussed in reference 54 by Bilcke et al. And although also not included, I guess the optimal age of vaccination will change when different waning scenarios are tested in this context. Therefore there are enough reasons to be a bit less curtain about “high validity” and “robustness”.

Especially the suggested robustness of the PSA is misleading. In figure 5, where the results go from doing harm (which is actually a very suspicious outcome of the model) to preventing costs. Therefore figure 5 is almost the definition of an outcome not being robust! Again, this uncertainty is perfectly fine, as there is a lot of uncertainty, but please don’t suggest it is robust. (on page 14 there is a very narrow CI around the median, I don’t how this was calculated but it does not seem to reflect the large cloud in figure 5c). Uncertainty means that we don’t really know, and that it is important what you believe. For example the duration of protection – this is estimated (based on the clinical trial data – the main trail had a median follow-up of ~3.6 years) in the literature between no waning until an average protection of just over 3 years (lower bound). The optimal age of vaccination and the value for money change hugely between these extremes. The authors say that the protection is fixed for 10 years before waning sets in. This assumption only, which again is based on a believe rather than data (again see reference 54), changes the cost-effectiveness from 28,146 to 53,702 (as can be seen in table 4). And how strong is this believe? The authors do believe that there is a recurrence. Which perhaps implies that there is a short lived immunity after natural infection. However they believe there is a long protection by the vaccine. Is this consistent? Will natural infection not boost as good as the vaccine? And hence a model with quicker waning is more consistent? Or is this recurrence among a group of immune compromised people who should be excluded from the incidence in the first place? A lot of these questions can be asked, but perhaps a few answers can be given.

I find it hard to translate the above into a specific revision,

Only that I hope that the authors can change the tone of the manuscript towards uncertainty rather than suggesting a robustness.
Thank you for this advice. After re-reading our manuscript we agree that a change in tone towards a less certain argumentation is needed. Accordingly and as suggested above, we have performed changes in the following lines: 37, 42-43, 44 (last sentence deleted), 48, 322-323, 327 (last sentence deleted), 330-331, 343 (last sentence deleted), 407, 411, 427, and 432.

I requested the authors to integrate a sensitivity analysis around the duration of protection and the optimal age of vaccination. And I will do this again. Because, as the waning is not really known the authors should investigate the impact of this uncertainty on the optimal age, as it is likely that this has an impact.

In the old version of the manuscript we presented already results of the univariate sensitivity analysis (in which we measured the impact of a varying waning immunity rate) and a structural sensitivity analysis, in which we investigated the impact of a variation in the duration of stable VE. As suggested by the reviewer, we now included in the revised version also a combined sensitivity analysis, in which we investigated the impact of varying the duration of stable VE and annual waning immunity rate on the optimal age at vaccination. See: lines 200-202, 278-284, 333-335, 416-418, and figure 5 (new). We renamed Figure 5 in the old version of the manuscript into Figure 6 in the revised version of the manuscript.

The authors can still be a bit more to the point, for example there is still a page long comparison with other CEA-models followed by a statement in which is said that you cannot compare them (“Country specific issues.....to make results more comparable”), if you cannot compare them, you cannot compare them. And I think the authors are right, you cannot compare them. Eyeballing the referenced papers there are listed ICERs which use a much lower vaccine price as the price used by the authors. And as the price is a very important parameter this “validation” is misleading.

Following the reviewer’s suggestion we changed the paragraph of ‘external validation’ in a more precise, compact and less ‘validating’ way. Hence, in the revised version of the manuscript the respective paragraph is about 50% shorter now and is rather in the tone of a comparison with international literature. See lines: 232-233, 350-359.
Reviewer 2:

Reviewer's report:

I would like to thank you the authors for their report. The responses to my comments were sufficient and I have no further questions.

We would like to thank the reviewer for this comment.