Reviewer’s report

Title: Influence of demographic changes on the impact of vaccination against varicella and herpes zoster in Germany - a mathematical modelling study

Version: 0 Date: 15 Jun 2017

Reviewer: Marc Brisson

Reviewer's report:

The authors examine the potential influence of demographic changes on the predicted impact of varicella vaccination on varicella and herpes zoster incidence, and the predicted impact of herpes zoster vaccination. This is a very important question, as the introduction of varicella vaccination has been delayed in some countries due to concerns about the potential influence it may have on herpes zoster incidence. In countries where varicella vaccination has been introduced, herpes zoster incidence has increased but the increase started before the introduction of the program. This has lead researchers to question whether varicella vaccination has an impact on herpes zoster incidence. Finally, 2 herpes zoster vaccines (only 1 is currently licensed) will soon be available, which could mitigate increases in herpes zoster incidence.

I think this is a very good and interesting paper. See below for my comments, which can be easily addressed.

Major comments:

1. Model fit to observed data should be presented:

   * The authors conclude that models incorporating realistic population structures allow a direct comparison to surveillance data. However, the authors do not show the model fit to surveillance data under their 3 demographic scenarios. The fit to pre-vaccination (and ideally post-vaccination) data should be presented.

   * Calibration and model fit discussed in the supplement but figures not presented.

2. Herpes zoster boosting parameters (duration of boost & probability of boost) should ideally be calibrated and sensitivity analyses should be presented:

   * The authors only use 1 scenario for the herpes zoster boosting parameters (% boosting, and duration of protection following a boost) in their base case, and the values were not determined through calibration.
* Herpes zoster boosting parameters have an important impact on model predictions of herpes zoster increase following varicella vaccination (and thus potential benefit of the HZ vaccines) and should be varied in sensitivity analyses.

* The authors state in the discussion that they have examined different boosting assumptions but I am unclear what exact parameters were used (only a very limited number of sensitivity analyses seem to have been performed), and results are only generally described (without numbers or figures). Figures and number should be presented rather than described.

3. Limitations section should include a discussion on potential impact of including changes over time in age-specific mixing patterns due to societal changes, and including demographic changes before 1990:

* To my understanding, the authors do not model changes in demographics before 1990 or potential changes over time in age-specific mixing rates due to behavioural changes. For example, in many high income countries the rate of varicella increased in 0-4 year olds likely due to higher proportion of children in child care. These types of changes to mixing patterns are not included in the analyses (rather contacts vary due to changes in age structure).

* The current epidemiology of varicella and herpes zoster is likely dependent of pre 1990 demographic and behavioural changes. The authors should acknowledge, in the limitations section, that they do not model pre 1990 changes in demographics (unless I am mistaken and they do), and that they do not take into account possible changes to age-specific mixing due to societal changes.

* It would have been really interesting and useful if the paper examined whether changes in demographics could explain the magnitude of pre varicella vaccination increases in herpes zoster seen in countries such as the US.

4. Sensitivity of results to assumptions of the duration of protection of the new subunit HZ vaccine should be presented (and discussed):

* There is great uncertainty around the duration of protection of the new subunit.

* The authors should conduct a sensitivity analysis on the duration of protection of the new HZ vaccine, and include caveats to their strong conclusion regarding the potential benefit of the new HZ vaccine if their results are sensitive to vaccine duration of protection (both in the results section and in the abstract).
5. Authors should discuss whether it is necessary to include demographic changes in the model, or simply apply predicted age-specific rates of varicella and herpes zoster incidence from a stable population model to predicted changes in the population age-structure:

* To the naked eye, it seems that there are very small differences in model predictions when age-standardizing results. This may mean that the changing demographics have very little impact on the age-specific post vaccination dynamics of varicella and herpes zoster. That is, differences are mainly due to size of the population in each age group.

* If this is the case, modellers could simply apply predictions of the stable demographic varicella dynamic models to predicted changes in the population age-structure, without complications of including demographic change in their dynamic models.

Minor: Table S1 - I think the reference for the Duration of vaccine protection for the new subunit should be Supplement 10.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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