Author’s response to reviews

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

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Editorial comments:

1. Please include a list of 3-10 keywords

We added now five keywords in the manuscript:

Varicella, herpes zoster, mathematical model, demographic change, vaccination

2. In accordance with the preferred reporting guidelines for observational studies (STROBE), the role of the study funder(s) needs to be stated explicitly; e.g. 'The funder had no role in [e.g.] the design of the study'
We added the following statement to the manuscript:

“The coauthors from the funding organization (Robert-Koch-Institute) were involved in the interpretation of the findings and participated in writing and revising the manuscript.”

3. With regards to your revisions, it seems that some of the changes made in response to the reviewers’ previous comments do not appear in the manuscript text. Examples are your response to Reviewer 1’s final comment (you mention that you have added text to the appendix, but I could not find the quoted paragraph) and your response to Reviewer 3’s third point about assessing the effects of demographic changes in other countries (again, I could not find the quoted paragraph in the manuscript text not the supplementary material).

We apologize for these omissions and corrected them now. In addition to several smaller changes we added the following paragraphs:

Paragraph revised in the supplement (1st paragraph)

“Transmission of the virus as well as boosting of protection against HZ or extension of varicella vaccine protection was modelled dynamically using contact matrices provided by the POLYMOD project. Breakthrough varicella was assumed to be half as infectious as natural varicella [8, 9] which in turn was 10 times as infectious as HZ. Depending on infectivity, contact with an infectious individual (I, IB, IZN, B, V) will lead to new varicella infections in susceptible individuals (S, SB, SB) as well as to boosting of protection against HZ (SZN, B, V, V1V, V2V) or boosting of varicella vaccine protection(V1, V2, V1V, V2V).”

Paragraph revised in the conclusion of the manuscript

“Due to reimbursement issues there is an overall trend to higher hospitalization rates with shorter durations in Germany. This is also true for HZ, complicating the analysis of trends in hospitalization rates, which already started to increase before introduction of varicella vaccination. In most countries, just as in Germany, HZ incidence and hospitalization rates increased considerably in the last decades. In the US for example, most studies suggest an increase of HZ incidence; however, its exact extent varies between studies. Similar to Germany, it occurred independently of the introduction of varicella vaccination. This indicates that there must be at least one additional factor explaining the variation. Effects of demographic changes on HZ resulting from the boosting hypothesis would be expected to be weaker than those of vaccination. Therefore, even with both factors, demographic change and varicella vaccination, in
place, the observed patterns in HZ epidemiology could not be explained completely. In addition, this trend is not consistent across studies focusing on hospitalization rates.”

Reviewer comments:

Reviewer 1:

The revised manuscript is very good apart a point, maybe for my fault!

Indeed I explicitly asked to the authors " in my opinion the authors ought to explore a fourth scenario where a SECOND similar pulse is included in a random year between 2018 and 2060, let us say in 2030. Even better, the impact of the year of occurrence of such an impulse should be analysed".

It seemed to me quite clear that I was requiring a second simulation of a *** second *** (thus, additional) virtual immigration influx in a year T, where T is a parameter for sensitivity analysis.

However, maybe my final phrase ("even better...") was ambiguous and the authors read it as follows: "perform the simulation of a single migratory flux in two or three time points, in order to see what changes".

Thus, on the one hand I ought to ask that the author perform also the simulations of the second immigration influx. On the other hand I am very sorry that my ambiguous writing mislead the authors.

As a consequence, my final suggestion is "optional minor changes"

Regarding the comments from referee#3, I think that you captured the essential of the “scientific message” sent by my colleague and that, according to it, you also adequately modified you work in many points and with good detail. Thus I confirm my positive evaluation of your paper.

We thank the reviewer for this comment. We indeed misinterpreted the reviewer’s wording and apologize for that. We added now additional sensitivity analyses with regard to time-period and extent of migration, and also added a second pulse of migration. This did not change our findings qualitatively, so that we added it only to the supplementary material.

“The increased short-term migration had only temporary effects on varicella epidemiology but also minor long-term effects on HZ. Directly after the immigration impulse, there was a small, temporally limited increase of varicella cases followed by a general increase of hospitalizations and deaths associated with varicella. In addition, there was a slight increase of HZ incidence,
hospitalizations, and mortality rates. Both effects can be attributed to the lower VZV seroprevalence in migrants, especially in adults when compared to the autochthonous German population. Changing the year, the extent of migration, or adding a second period of increased migration did not change this finding qualitatively, but almost linearly shifts the effects in time, changes the extent of the effects, or adds a second similar effect of migration, respectively.”