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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Author’s response to reviews:

Point to point replay

Reviewer #1: Dear Editors and Authors,

I read this interesting manuscript and its Supplementary Information.

This work explores the important interplay between demography and vaccination programmes (considering both anti-varicella and anti HZ vaccination).
The illustrated results are of great epidemiological interest and are valuable for Public Health policy-makers, and not only in Germany.

To "parametrize" (in wide sense) their complex model, the authors wisely use/adapt state of the art results for demography and for the contact rate. For example, the modelling of contact rate structure is built on top of the results of the influential POLYMOD study.

Wisely the authors consider three scenarios: 1) stable demography; 2) projected demography; 3) Demography dynamics that includes the unforeseen 2015/2016 "demographic impulse" due to extra immigration (see, however, below).

On the whole, I agree with the authors' approach (apart the caveat notes below), and with their comments on their model and results.

The manuscript is very important and deserves publication, apart minor but very important revisions.
Indeed, due to the very large time-windows of the predictions, authors should far more explicitly include in the "limitation" section the fact that the proposed model is deterministic.

Thank you for your nice comment! We agree that we need to make it clearer that our model was deterministic (and why we chose this approach). We now included the type of the model in the abstract as well as prominently in the beginning of the method section. In addition, we extended the paragraph in the limitation section specifying all factors of uncertainty. The sentence included in the discussion reads now: “Due to the large population size and high prevalence of VZV infection, the multiple runs of a stochastic model will not vary considerably from the deterministic model. The huge uncertainty apart from demography lies in the unknown model parameters (e.g. boosting hypothesis or waning rates of varicella or HZ vaccination), not in random stochastic fluctuations of different realizations of the model. Since we were interested in specific effects of one of the sources of uncertainty (population development) on vaccination impact, we chose a deterministic model where all other parameters were fixed.”
In particular, motivated by the unforeseen 2015/2016 "demographic impulse" (an important practical example of sudden large stochastic fluctuation), which they included in their model, 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.

Thank you for this important comment! We have varied the year of migration with little qualitative effect (see supplement chapter 12). This is the case since the effects of migration are mainly direct in a way that there are more people and therefore more varicella and HZ cases. Respective incidence rates are almost not affected, especially if stratified by age. Moreover, there is almost no change in case numbers in the autochthonous population so that the time point of the stochastic hit (=migration) does not affect model results. The sentence included in the supplement reads now:

“There are only minor effects due to migration which are mainly attributable to the lower VZV seroprevalence in migrants. Directly after immigration there is a small, temporally limited increase of varicella cases followed by a general increase of hospitalizations and deaths associated with varicella. In addition there is a slight increase of HZ incidence, hospitalisation and mortality rates.”

As far as the supplementary information are concerned, I am sorry to say that the description of the mathematical model is largely insufficient. For example, the fact that the model is deterministic can only be inferred thanks to a short observation written at page 12 of the PDF of the manuscript, rows 296-297!

Only a graph plus some scant information are reported, at least in the files I could access. No information at all are given on the simulation methodologies!

In my opinion, the supplementary information of a computational epidemiology work as the submitted ms. ought to have as objective to provide a detailed description of the computational and mathematical details.

We agree that our description of the computational and mathematical details was too concise and not detailed enough. Therefore, we added several new chapters to the supplement, describing in detail the used simulation strategy, the equation systems and the calibration results. In addition we compared our approach with the approach of Marziano et al. in the supplement file With respect to your specific comments, we included the following information in the supplement and the main manuscript. “We used a deterministic compartmental model.” In addition we included
in the appendix: “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 defined as half as infectious as natural varicella which in turn was defined 10 times as infectious as any HZ.”

Kind Regards,

Alberto d'Onofrio

Reviewer #2: The manuscript uses a mathematical model to investigate the joint effects of demographic change and immunization against varicella on the epidemiology of herpes zoster under the hypothesis of exogenous boosting. There is, to my knowledge, only one paper devoted to this subject (Marziano et al 2015 Proc B). The manuscript incorporates the demographic dynamics into the epidemiological model in an accurate manner. It also includes the possible benefits that might results from the adoption of the new subunit recombinant vaccine in mitigating the potential effects of varicella vaccination on herpe zoster (HZ), which is a potentially important aid for current immunization programs. So I believe this research paper worth publishing provided it makes an effort to correctly position the paper in the particular literature on demographic change and infection diseases, and to discuss more carefully the issue of the relationship between changing population structures, contact patterns and boosting, which is the key for the reported results. Moreover, still because this is key for better framing the results of this work, a deeper discussion of the complex matter related with herpes zoster pathogenesis and the modeling of exogenous boosting and VZV reactivation on the light of recent results is recommended.

Thank you for this important comment and also for the literature suggestions in the next point. We added a paragraph to the background section to give a short overview of previous modelling papers applying realistic population approaches.

“However, in the context of childhood infections there are some modelling studies available which analysed the effects of applying realistic population models [1-4]. Due to their increased complexity these models usually need additional calibration data as well as simplifying assumptions. This raises the question when it may be useful to apply a realistic population model and when these additional requirements can be fulfilled.”
Main points

The manuscript repeatedly claims (as e.g., in the Background, L66) that "It is, however, rarely realized that the epidemiology of infectious diseases, which rely on dynamic transmission processes within populations, can also be affected by changing population structures and resulting changes in contact patterns." which is quite not exact. Indeed the field of the impact of demographic change on contact patterns and infectious diseases epidemiology, though seldom cited, has given rise to a number of contributions. In particular after a number of papers by Meredith John and Tuljapurkar (in the 1990s) using however only homogeneous mixing models and no parametrizations from real epidemiological data, a series of papers (Williams JR, Manfredi P 2004, Ageing populations and childhood infections, Int J Epidemiol; Manfredi P, Williams 2004, Realistic population dynamics in epidemiological models etc. Math Biosci; Manfredi P., et al 2005, Measles elimination in Italy: the projected impact of the National Elimination Plan, Epid & Inf) have investigated the issue of the relationship between changes in the age distribution of the population and contact patterns using the standard PDEs models for infectious diseases parametrized by contact matrices. In particular Manfredi -Williams 2004 showed, using the case-study of measles, the same type of effects that is reported here for varicella. One of their approaches was later followed in the paper by Marziano et al 2015 cited here. Moreover, they also attempted at introducing clues for fully disentangle the effects of transient population change on infection circulation, by also looking at longitudinal (or "cohort") trends, as compared to cross-sectional, in key quantities documenting the effects of changes in transmission, such as the average ages at infection. They also supplied a discussion of the limits of WAIFW based models (that was the pre-Polymod matrices epoch) in dealing with the issue of evolving demographics, and suggested that adjusting contact patterns by using the changing age-distribution of the population (as done in the present paper as well by using geometric means of total contacts) is surely appropriate for contacts taking place in the general community, which might be coarsely random, but not necessarily for other type of contacts.

Thank you again for providing these important citations which we added to our manuscript. Moreover, we changed “rarely realized” in “often neglected”. In addition ,we compared our approach with the one of Marziano et al. in the supplement, and discussed published approaches of realistic model population.

“It has to be noted that our model reacts differently to demographic changes than the model proposed by Marziano et al. [2]. In our model the number of contacts are adjusted according to the square route of the ratio of numbers of persons in both age-classes, whereas Marziano et al. balance the contacts of each age-class according to the number of persons in the age-class of the contact. As an example we look for simplicity reasons only at three hypothetical age-classes:

Young children
Their parents

Their grandparents

Let us assume that in case of a demographic changes the proportion of children decreases (for example by 40%) whereas the proportion of grandparents increase compared to a stable population by a factor of 2. The proportion of the total population in the age group of young parents stays about the same. Using the approach of Marziano et al. the contact rates would change when compared to the stable population by a factor of:

<table>
<thead>
<tr>
<th>Contacts to</th>
<th>Child</th>
<th>Parent</th>
<th>Grandparent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>0.6</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Parents</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Grandparents</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

In contrast in our model contacts would change compared to a stable population by:

<table>
<thead>
<tr>
<th>Contacts to</th>
<th>Child</th>
<th>Parent</th>
<th>Grandparent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>1</td>
<td>√(0.6)~0.77</td>
<td>√(0.6/2)~0.55</td>
</tr>
<tr>
<td>Parents</td>
<td>√(1/0.6)~1.29</td>
<td>1</td>
<td>√(0.5)~0.71</td>
</tr>
<tr>
<td>Grandparents</td>
<td>√(2/0.6)~1.83</td>
<td>√2~1.41</td>
<td>1</td>
</tr>
</tbody>
</table>

The approach by Marziano et al. is motivated by the idea of random mixing of persons. If the frequency of one age-group changes over time, all contacts to this age-group change by the same factor whereas the contact behaviour of the respective age-groups does not change at all. Our approach is motivated by the idea of balancing desired contact rates according to wishes of both contact partners by correcting resulting inequalities with the geometric mean. Compared to Marziano, our approach predicts smaller changes due to demographic effects. For example, in our model the age-specific varicella incidence will not change considerably due to demographic changes since the number of contacts is usually highest to persons of the same age and these will not change in our approach. With Marziano’s approach, contacts of young children with each other would be halved resulting in an age-shift of the epidemiology of varicella towards older age-groups. Boosting contacts for the elderly (to children) would however decrease in both models at almost the same magnitude. ”

On the different issue of the modeling of exogenous boosting and VZV reactivation, which is key to assess the effects of ongoing processes of population change and vaccination, the manuscript follows the assumption of full boosting plus reactivation along the specification first adopted by Mark Brisson et al. Given its key role for the results of the manuscript, this part
should perhaps be better detailed in the Supp Mat. More important, on the topic there has been a number of recent advances suggesting that things might be quite more complicated. In particular in Poletti et al, PONE, 2013, it was suggested that the estimates of key parameters (such as the level of 20 years typically assumed for the duration of protection against reactivation after each re-exposure to VZV), are dramatically variable between countries and therefore caution should be used in borrowing estimates from elsewhere. Moreover Guzzetta et al (2013) showed that much more stable estimates of reactivation parameters can be obtained under the formulation of reactivation they termed "progressive immunity". This formulation yields larger increases in HZ incidence following mass childhood varicella vaccination (Guzzetta et al 2016) compared to the formulation popularized by Brisson et al. In addition, there have also been attempts to consider the role of endogenous boosting (e.g. Ogunjimi et al Elife 2016, Van Liers et al 2016), a typically neglected factor whose importance is basically unknown. On top of this there is the complication of the equivocal (or hard to measure, as it seems to be the case for Germany) trend in herpes zoster in settings where mass childhood varicella vaccination has been ongoing for years. All this should be carefully discussed in the manuscript.

We included a comparison of our model and the model of Marziano et al. and Guzetta et al. in the supplement an added an overview of applied boosting assumptions in the supplement.

“Indirectly associated with the question of contact patterns are the boosting assumptions. Most previous VZV models followed the simplified approach of Brisson et al. in which boosting is only possible if protection against HZ has already waned [9] and in which boosting leads to a temporal immunity against HZ. In Karhunen et al. and Guzzetta et al., boosting events do not lead to immunity, but reduce the reactivation rate. To which extent the reactivation rate is reduced depends in Karhunen et al. on age and time since last contact with VZV, in case Guzzetta et al. also on the total number of boosting events of each individual so far [28, 29]. For simplicity all models use in their base case analyses the assumption that all contacts which would lead to an infection in case of a susceptible person will lead to a boosting event for a person susceptible to HZ. Furthermore, as most of the calibration data comes from the pre-varicella vaccination era, the estimated baseline reactivation rate is estimated based on these model assumptions”

Other points

Another strictly related paper in the field is the paper on measles by Merler and Ajelli Proc R Soc B, 2013.

We have now included the paper of Merler and Ajelli in the background section.
A population defined by a time invariant number of births per year and a time-invariant age-specific mortality rates is termed "stationary" in correct demographic jargon.

We changed the term stable population into stationary population.

Can you add details on to whom is administered the second dose in the model (with respect to first), i.e. they administered independently, or those who had the first have a higher chance of being administered the second dose? Do you have evidence about Germany on this?

Recommended age at varicella vaccination in Germany is 11 to 14 month for the first dose and 15 to 23 month for the second dose; both are given simultaneously with mumps, measles and rubella vaccination. We were able to use annual vaccination coverage rates of children at the age of 24 months including the number of doses, but not the exact time of vaccination. For simplicity, vaccine protection starts in the model at the age of 1 year (first dose) and 2 year (second dose) with the observed coverage reported for at least one dose and two doses respectively.

Text included in the manuscript reads:

"Vaccination coverage was set to observed rates until 2010 and assumed to be constant afterwards (86.9% one dose at 12 month / 64.1% two doses at 24 months; recommended age in Germany is 11 to 14 months first dose, 15 to 23 second dose)"

We provide to our knowledge the first analysis etc…. The paper by Marziano et al 2015 does this for Spain, studying the effects on HZ trends of an evolving demographics first, and then superimposing the effects of vaccination.

We agree that the Marziano paper already went in the same direction; however, it does not include zoster vaccination. To avoid any misunderstandings we changed the sentence into “We analysed the expected changes of varicella and HZ epidemiology due to combined effects of demographic changes and vaccination against varicella and HZ.”

Figure S3. Why the left panel shows such an unsmooth trend under the case of a constant population?
We added the following sentence in the supplement in order to clarify this subject to the reader.

“In the model, contact patterns are modelled according to age-stratified contact data from the Polymod survey. Whenever a person moves into the next age-class, contact frequency and patterns are adapted which can lead to a considerable different risk of varicella infection.”

In passing, I am worried by the predicted increase in varicella deaths following vaccination in Fig2. That means Germany is going to suffer huge perverse consequences from current varicella immunization.

We agree that our modelling study suggests that varicella deaths will increase considerably on a relative scale. To emphasise and explain this aspect in detail, the following sentences were added. “The impact of vaccination is opposed by with age strongly increasing lethality hospitalization rates reduction of hospitalizations leading to only a small overall reduction of hospitalizations and even an increase of deaths. It must, however, be noted, that while deaths associated with varicella will be increasing considerably on a relative scale, they are still very small in absolute numbers (in average below 10 deaths per year for all of Germany). In addition, the estimation of number of deaths due to varicella (or HZ) is quite difficult as most deaths associated with varicella occur in multimorbid patients where a unique definition of exact cause of death is usually not possible.“

Reviewer #3: 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.

Thank you for your important comment. We now included the model fit regarding varicella seroprevalence as well as HZ incidence in the supplement; furthermore, a paragraph about the availability of calibration data for varicella and HZ was added.

“The general problem is a lack of incidence data before the introduction of varicella vaccination. The only publication with varicella and herpes zoster incidence data before introduction of varicella vaccination [26] recorded in outpatients medical practices in a small town (1992 - 1993) suffers from methodological problems. Physician reported varicella incidence was only half of the rates necessary to fit observed seroprevalence data. Moreover, reported HZ incidence was less than half of the rate reported in later studies. Most available data after vaccination is not processed, analysed or published. Current surveillance started after introduction of vaccination; health insurance data in Germany is only consistent since 2004, the year of introduction of varicella vaccination.

Nevertheless annual hospitalization rates and mortality rates were recorded for varicella and herpes zoster since 2000, thus including time-periods before as well as after the introduction of varicella vaccination. However, these data are prone to time-dependent biases and provide inconsistent results. For example, the two sources of mortality rates for herpes zoster show different trends (A: principal diagnoses of all persons which die in hospital (strong increase), B: reason of death according to death certificate (constant)). In addition, similar to other countries there is a strong continuous increase of herpes zoster hospitalization rates across all recorded years (2000 - 2015) which does neither fit to an possible impact of varicella vaccination nor to demographic changes, indicating that there must be additional causes.”

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.
In a previous paper using the same modelling approach in a stationary [5] we varied in a sensitivity analysis duration and probability of boosting. Independent of the values of both parameters a good fit to observed HZ incidence data could be achieved when calibrating unknown reactivation rates of herpes zoster. A calibration of boosting parameters can therefore not help in determining the most likely parameter set.

The main problem with calibrating boosting parameters is that there is almost no data about HZ incidence before and after varicella vaccination which is directly comparable. Without a matching pair of data however calibration of boosting parameters is not feasible.

With a realistic model the same problem remains. As there are almost no interactions between these parameters and the choice of the population or vaccination we did not present all sensitivity analyses for these parameters of uncertainty again. To further complicate the subject varicella seroprevalence and HZ incidence in Germany do not come from the same time period; resulting in a calibration process with fitting (seroprevalence varicella, incidence HZ) at two different time points without using any simplified assumptions.

* 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.

Thank you for your comment which helped us to find several weaknesses in the reporting of our study. We indeed extensively assessed the effect of assumptions on the duration of protection (1 to 60 years) as well as the proportion of contacts which lead to boosting of protection (20 to 100%) against herpes zoster in an already published general modelling study for Germany which was based on the same model [5]. We found there that only when both the majority of contacts lead to boosting and the derived duration of protection is longer than 10 years considerable effects of boosting (temporal increase up to 30 %) were evident after the introduction of varicella vaccination. We found out in this paper that the effects of demographic changes and boosting are almost independent of each other and do not affect vaccination impact estimates for varicella and HZ.
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.

We totally agree with these comments. Further limitations were included in the discussion:

“To model demographic changes we used the geometric mean to balance changing population proportions. For simplicity and lack of available data we do not model changes in demographics before 1990 or potential changes over time in age-specific mixing rates due to behavioural changes like for example the establishment of day-care centres in Germany or the population movements after the reunification of Germany.”

However, these aspects are mainly relevant for HZ.

In contrast the epidemiology of varicella reacts very fast to possible changes. For example, in a theoretical sensitivity analyses we modelled a possible stop of varicella vaccination. After only 10 to 15 years the epidemiology was not considerably different to the pre-vaccination area in the stationary population scenario. The main reason for starting the model in 1990 was that we have no access on annual age-stratified population data from the former German Democratic Republic which is necessary for our model. Therefore we started our model with the German reunification in 1990.

* 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.

We added the following paragraph in the discussion:
“In most countries (just like in the US), HZ incidence increased considerably in the last decades almost independently of if or when varicella vaccination was applied indicating that there must be at least additional factors. Effects of demographic changes on herpes zoster according to the boosting hypothesis alone would be expected to be weaker than those of vaccination. Therefore, even if both effects would be fully in place patterns could not be completely explained. In the US, most studies propose an increase of herpes zoster incidence; however its exact extent varies between studies. In addition, this trend is not consistent across studies focusing on hospitalization rates. In Germany, hospitalization rates increase stronger than it would be expected due to either demographic changes or varicella vaccination. Whereas short time hospitalization rates more than doubled, long term hospitalization rates decreased over time, a development which also could be seen for other diseases and is caused by changes in the health care system.”

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).

We have performed sensitivity analyses on the effectiveness and duration of protection for the currently available and for the new HZ vaccine. As there are almost no herd effects, the impact of effectiveness and duration on reduction of HZ cases, hospitalizations and deaths is linear for the currently available vaccine [6]. Only if the duration of vaccine protection is considerably longer than the average life expectancy, the additional duration of protection is getting less and less beneficial. The predicted duration of protection for the new subunit HZ vaccine exceeds residual life expectancy for individuals at age 60 considerably so that even under very conservative assumptions no major changes of vaccination impact could be detected. This, however, raises the point on the best age of vaccination for the new vaccine. Since HZ incidence, complication rate and hospitalization rate increase with age, vaccine protection is most important at the end of life. Despite the with age decreasing effectiveness, we have shown that an age of vaccination of around 60 is the best age of vaccination for the currently licensed vaccine with respect to overall case reduction; regarding reduction of hospitalizations or post-zoster-neuralgia the best age would be 70 years. In case of the new subunit vaccine and the estimated duration of protection of 56 years, the best age of vaccination would be much lower. We decided, however, to set for the purpose of comparability the age of vaccination for both vaccines at 60 years,
potentially underestimating the protective effects of the new vaccine. At this age of vaccination, there is, however, almost no effect of varying duration of which will be in most cases lifelong. We think that our approach is sensible with respect to the overall aims of our study (which does not focus on the new HZ vaccine), but we agree that we need to discuss this point in more detail.

Sentence included:

“For the purpose of comparability, age of vaccination was set for the new subunit HZ vaccine at 60 years which has been shown to be the best age of vaccination regarding the reduction of overall HZ cases for the currently licensed vaccine. However, due to its longer duration of protection a younger age at vaccination would be even more efficient for the new subunit vaccine since a vaccination age of 60 years would even under conservative estimations for protection duration result in a lifelong protection. For a decision on the best age of vaccination, however, more information about the loss of vaccine protection over time would be necessary.”

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.

One of the conclusions of our study is that in our case it is not necessary to use a realistic population if the aim is to evaluate cost-effectiveness or relative reduction of burden of disease due to vaccination. Boosting, however, will be affected by both vaccination and demographic changes. Therefore, research questions focusing on the prediction of future cases (for example in the context of providing resources in the health care sector), still require including boosting and demographic changes independent of if there is vaccination or not. Our study indeed indicates that it is usually not necessary to include vaccination in a demographic model with boosting for the prediction of future cases as these effects can be derived from separate stable models. We therefore agree that your proposed strategy of combining a stable vaccination model with changes in the population structure would be a feasible way of getting to (almost) the same results. However, we do not think that it is more efficient since almost the whole complexity and
uncertainty is attributable to boosting and demographic changes; therefor adding vaccination to such a model, which would be necessary to be run due to the dynamic process anyway, is very simple and does not increase uncertainty or limitations.

We added the following sentences to the discussion:

“Our study indicates that there are only small differences in model predictions when age-standardizing results so that one potential alternative approach could be to simply apply predictions of a stationary demographic vaccination model to predicted changes in the population age-structure. However, this approach would not be more efficient since almost the whole complexity and uncertainty in our model is attributable to boosting and demographic changes; therefor adding vaccination to such a model, which would be necessary to be run due to the dynamic process anyway, is very simple and does not increase uncertainty or limitations”

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

Thanks for spotting this error! We corrected it accordingly.