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: 10 Jun 2017

Reviewer: Piero Manfredi

Reviewer's report:

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 herpes 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.

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.

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 complicate. 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.

Other points

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

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?

"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.

Figure S3. Why the left panel shows such an unsmooth trend under the case of a constant population?

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.

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

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable
Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests'

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal