Author’s response to reviews

Title: Varicella susceptibility and transmission dynamics in Slovenia

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

Please find enclosed the revised manuscript entitled Varicella susceptibility and transmission dynamics in Slovenia (MS: 20162607183302499) along with the Appendix.

We tried our best to reply to the queries and the comments of both reviewers. The answers are in attached document and clearly marked (track the changes) in the text.

We are not sure whether or not we cited the references as they ought to be. One reference is cited in the Appendix only other three appear both in the main text and in the Appendix. We decided to cite all references which are in Appendix from 1-4 regardless the number they have in the main text.

If we made a wrong decision, please let us know how to correct the order of the references and how to cite the reference which is in the Appendix only.

The text was corrected by native English speaker (from UK).

Best regards,
Maja Socan
Reviewer 1

We would like to express thanks to the reviewer for his comments.

Point-to-point answers to the reviewer’s questions and comments are:

311 Two new references covering broader geographical locations from tropical area were added to the text:


312 The text has been changed to:

Also, the VZV-specific antibodies seem to appear much earlier in some European countries than in the others – the differences which are difficult to explain [16]. Dissimilarities in environmental determinants (e.g. climatic factors) and distinctive social structures may affect the seroepidemiology of VZV.

31 We completely agree with reviewer's comment. The mathematical modeling studies suggest an increase in herpes zoster after introduction of the universal varicella vaccination which was confirmed by some observational data (e.g. Civen R et al. The incidence and clinical characteristics of herpes zoster among children and adolescents after implementations of varicella vaccination. Pediatr Infect Dis J 2009;28:954-9).

The following text and references have been added:

The reason for not implementing routine varicella vaccination programmes might be the lack of recognition of varicella as a serious disease. A concern has been raised that widespread childhood varicella vaccination will shift the peak incidence of the disease from children to young adults and result in higher numbers of severe cases [20]. Mathematical modeling suggested that routine varicella vaccination might generate an upward trend in herpes zoster incidence at least in the short to medium term [22, 23].


4 The definition of force of infection was cited and the paragraph changed accordingly:
The force of infection is a central parameter in assessment of an infection within a population. The force of infection is the rate at which susceptible individuals become infected by an infectious disease because it takes account of susceptibility. It can be used to compare the rate of transmission between different groups of the population for the same infectious disease. It depends on a variety of age-dependent factors, is thus itself age-dependent and, therefore, provides the key information regarding childhood vaccination schedule.

6 The “European” has been added and reference 16 quoted.

7 The reference 16 has been cited as suggested.

8 The text has been modified as suggested and (a simplified) explanation of both parameters (a and b) has been included.

11 “then” has been changed to “than”

11 The mandatory case-based reporting system for varicella has been assessed recently and the results of the assessment will be published in Central European Journal of Public Health in near future. In short, significant changes in reporting system were not found therefore we believe that the increase in varicella cases in small children is real and not an under- or over-reporting artefact.

The following explanatory text has been added:

These changes could theoretically derive from modification in reporting e.g. an increase in under-reporting over time. The obligatory notification system has been assessed for completeness and consistency recently [38]. The average rate of notified cases was 76.2 % in last ten years when compared to health statistics data. The mandatory notification system in Slovenia provides enough information to survey age/sex-specific varicella trends in the prevaccine era [38].


Appendix A

All suggestions have been followed and supplementary material (Appendix A) has been modified accordingly.
Reviewer 2

We would like to thank the reviewer for his valuable comments.

Point-to-point answers to the reviewer’s questions and comments are:

Continuous antibody levels and their distribution are not shown in the paper. The data were classified as positive or negative (according to instructions of the manufacturer of the diagnostic kit and as described in the text) reporting antibody protection in patients. Antibody protection in patients is key information in the study. Results presented in the paper were therefore obtained using qualitative information (positive or negative). Therefore we considered that showing continuous antibody levels and their distribution was not necessary or relevant.

p6 The number of equivocals in the study was very low (approximately 1%) and equivocals were uniformly distributed amongst age groups. As explained in the paper, specimens with equivocal results were retested using the same test kit and those few that remained equivocal were classified as negative, not deleted. FAMA test, as golden standard method for varicella serology has not been performed in order to resolve equivocal results (due to technical limitations). Our rationale has been done on the basis of reference (added to the text): Heininger U, Deshgrandchamps D, Schaad UB: Seroprevalence of Varicella-Zoster virus IgG antibodies in Swiss children during the first 16 months of age. Vaccine 2006, 24:3258-3260.

The text has been modified as follows:

The sera were stored at -20°C before testing with a commercial enzyme-linked immunoassay (ELISA; Enzygnost Anti-VZV Virus/IgG, Dade Behring, Marburg, Germany) that was used for determination of specific IgG antibodies against VZV in accordance with manufacturer's instructions. Optical density measurement was performed and results were calculated using an automated system (Dade Behring BEP III System, Dade Behring, Marburg, Germany). All tests were evaluated using adequate positive and negative reference controls according to the manufacturer's instructions. Results were classified as positive, negative or equivocal. Specimens with equivocal results were retested using the same test kit and those few that were equivocal again were classified as negative [26].

p7. As the tested sera were residues of specimens taken for routine diagnostic tests, they do not represent a random sample, which is an inherent weakness of many seroprevalence studies. However, varicella is so prevalent disease that the estimates of seropositivity based on either systematically collected or residual samples yield similar results [34].

p8. The age groups chosen enable the comparison to ESEN2 study and study done by Mossong. The findings are related to the Slovenian educational system as children start with primary education at the age from five to six.

p8, p9: The required details/values have been included as suggested.
Figure 1: We are aware that inclusion of the requested additional information in Figure 1 would help summarize overall findings, but we believe that it would make Figure 1 difficult to read, as two age groupings have been employed for the semiparametric method, both consistent with the Slovenian educational system (see the comment above). The FOI values for both cases are summarized in the Table 2, and the tabulated form might prove more informative than the inclusion of FOI step curves (with corresponding prevalence estimates) in Figure 1. Should the actual appearance of Figure 1 seem less than appropriate due to the inclusion of the parametric FOI curve, we might prefer to consider removing the latter and leaving only the representation of the data with their corresponding error bars.

p12. We agree with the reviewer comment that the ambiguous results regarding the possible increment in herpes zoster incidence in non-vaccinated individuals provided by mathematical modeling must be taken into consideration when implementing universal varicella vaccination.

The following text and references have been added to the Background section to point up the problem:

The reason for not implementing routine varicella vaccination programmes might be the lack of recognition of varicella as a serious disease. A concern has been raised that widespread childhood varicella vaccination will shift the peak incidence of the disease from children to young adults and result in higher numbers of severe cases [20]. Mathematical modeling suggested that routine varicella vaccination might generate an upward trend in herpes zoster incidence at least in the short to medium term [22, 23].
