Author's response to reviews

Title: HHV-8 seroprevalence: a global view

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Author's response to reviews: see over
Dear Dr Moher

Thank you very much for the constructive feedback on our manuscript. Below we address each comment point-by-point. In addition, we took the opportunity to thoroughly revise our manuscript for the sake of readability and comprehensibility. All changes made are highlighted in the attached document with track changes.

Yours sincerely

Eliane Rohner and Julia Bohlius

Editorial requests

1) Please include an acknowledgement section at the end of the manuscript before the reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for all authors. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements. Please state clearly whether or not you have funding in the acknowledgement section. If there is no funding, please state this.

Answer: We added an acknowledgement section at the end of the manuscript stating our funding sources. There is no person to acknowledge at this point.

Reviewer’s comments

1) This is a very sound protocol using appropriate methods. I just have a few comments/suggestions, noted by page number.

Answer: Thank you very much!

2) PAGE 6: Suggest just citing PRISMA (redundant to use both checklists).

Answer: Thank you for your suggestion. We deleted the reference to the guidelines promoted by the MOOSE group. Please find the changed sentence below:

“We will conduct a systematic literature review and meta-analyses following state of the art methods [43]. Reporting will be in accordance with the PRISMA statement [44].”

3) PAGE 6: Case series will be excluded but what will be the minimal sample size for inclusion?
**Answer:** We plan to include studies with a minimal sample size of 50 participants. Please note that this cut off is set arbitrarily. We have clarified this in the protocol as follows:

“We will include cross-sectional, cohort and case-control studies as well as clinical trials documenting the seroprevalence of HHV-8 with a minimal sample size of 50 analyzed participants in total.”

4) **PAGE 7:** Tense is reversed to past tense (we searched...) – need to review for consistency.

What will be the dates for the search?

**Answer:** Preliminary literature searches have already been conducted and we plan to update the searches in the future. We have changed the wording and the tenses as outlined below:

“Electronic searches: Preliminary electronic literature searches for relevant studies have already been conducted in December 2012. We searched Medline and Embase without language restrictions for published reports from 1994 to 2012. An update of the literature search will be conducted in 2014. All literature searches are restricted to studies in humans. The following search strategies are being used: [...]”

5) **PAGE 9:** I query the appropriateness of including results (even preliminary ones) in a protocol.

**Answer:** Thank you for your concern. We deleted the paragraph on the preliminary results.

6) **PAGE 12:** I would recommend limiting the number of covariates for meta-regression.

**Answer:** We agree that only a limited number of covariates should be used in the meta-regression and that it might be more appropriate to only present subgroup estimates, but no overall pooled estimate. For clarification we added the following statements to the statistics section:

“Therefore, we aim at exploring differences in prevalence across studies in subgroup analyses and if feasible in random-effects meta-regression. Depending on the degree and
nature of heterogeneity identified we might not present a single overall pooled estimate, but rather provide subgroup estimates. We will explore the following factors that might explain between-study heterogeneity: geographic location of study, rural versus urban sites, calendar years of recruitment, age, gender, ethnicity, HIV status, different risk groups for sexually and parenterally transmitted infections (MSM, sex workers, haemophiliacs, intravenous drug users), other reasons for immunosuppression such as solid organ transplantation, study design and size, study quality (sampling) and type of HHV-8 test used. Based on epidemiological and biological reasoning we will assess a limited number of these factors in random-effects meta-regression.”