Author's response to reviews

Title: Clinical aspects and self-reported symptoms of sequelae of Yersinia enterocolitica infections in a population-based study, Germany 2009-2010

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Author's response to reviews: see over
Dear editorial team,

We would like to submit a revised version of our manuscript entitled “Clinical aspects and self-reported symptoms of sequelae of Yersinia enterocolitica infections in a population-based study, Germany 2009-2010.

The authors thank the reviewers for their valuable comments and suggestions. Please see below our response to the reviewers’ points.

A) Reviewer: Mark Riddle

Major Compulsory Revisions

1) Study Design: This does not appear to be a case-control study, but rather a retrospective cohort study among exposed and non-exposed individuals in which they are followed for development of multiple outcomes. Traditionally, a case-control study starts with the selection of the particular disease outcome (e.g. ReA or EN) and a matched control without the outcome and then retrospectively evaluates whether the cases and controls had particular exposures of interest. Suggest re-describing this study using an appropriate methodological design to avoid confusion.

Authors’ response: The methods section has been modified and restructured to clarify our study design (cohort study). The results were restructured accordingly.

2) Control (unexposed comparator group) selection: Controls were selected from population registries at random and frequency-matched to cases by age group (0-4 years, 5-14 years, ≥15 years) and federal state (ratio 3 controls per 1 case). However, for this study design, it would be important to consider patterns of health care seeking behavior. For examples were controls selected based on a non-infectious medical encounter event type (e.g. ER visit, outpatient visit, hospitalization for a different reason?) This is important as you want the unexposed comparator group (non-Y. enterocolitica) to be similar to those who were exposed. Having such selection criteria would assure that they were more similar across variables which could not be adjusted for.

Authors’ response: We addressed this comment by explaining the study design in more detail in the modified version of the manuscript. The frequency matching (by age group and federal state) referred to the original case-control study conducted to identify risk factors of yersiniosis. The control group consisted of persons randomly selected from population registries. Selection was not based on healthcare seeking behavior. We added a short section describing frequency of GI symptoms and health care seeking behavior in the reference group to the results (page 10).

The occurrence of sequelae was studied in a subgroup (=cohort) of participants of the case-control study, originally conducted to determine risk factors of yersiniosis. For the follow-up, the group of yersiniosis patients (the exposed) and the reference group (not exposed to yersiniosis) were no longer frequency matched. The reference group was used to assess the background of self-reported “sequelae-like” symptoms in a population not affected by yersiniosis, because the incidence of some of the symptoms, in particular
musculoskeletal symptoms, was expected to be relatively high in that population as well.

3) Ascertainment of enteric exposures among ‘controls’: Because multiple types of infections can cause ReA, EN, ocular findings, did you query these subjects about recent infectious illness in the preceding month?

Authors’ response: We now address this remark in the results and in the discussion. The reference group was queried about symptoms consistent with gastrointestinal infections in the 7 days before completing the self-administered questionnaire of the original case-control study (see Table 1) and about symptoms resembling sequelae about one month later (see Table 4).

4) Analysis: Authors should justify why ORs and RRs were computed. Since this was event based data (with person-time denominator), it would seem that a Poisson regression that accounts for matched un-exposed individuals should be utilized (see Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004;159(7):702–706.). Authors should justify the appropriateness of their statistical methods used.


5) Results:
   • The finding of appendectomy associated with appendicitis which is associated with Yersinia is not novel. Presentation of the odds ratio is therefore not interesting. Simply describing that you saw it is enough.

Authors’ response: We now present risk ratios of appendectomy in yersiniosis patients compared to the reference group not affected by yersiniosis. The sentence has been modified (see page 9). While it is true that the association is not novel, we still think it is important to present the strength of the association of yersiniosis and appendectomy.

6) • It is strange that one of the main objectives of this study was to identify the relative risk of select outcomes (ReA, EN, conjunctivitis) among those exposed to Yersiniosis and those who were not. Table 4 describes odd’s ratios (Risk Ratios or Incident Rate Ratio more appropriate) of these outcomes between “case-patients” (exposed) and ‘non-case patients) (unexposed) however these are nowhere mentioned in the results.

Authors’ response: Table 4 now presents risk ratios. We modified the results and describe the association of yersiniosis and the outcomes ReA, EN, and conjunctivitis in the text in more detail (page 11). We also hope to have clarified that the reference group was important in order to estimate the background incidence of “sequelae-like” symptoms
because we assessed self-reported symptoms in the group of yersiniosis-patients (see page 5: “An unexposed reference group was used because…”)

7) Discussion: (see control selection above) Authors should comment on how control selection and assessment of outcomes (and antecedent preceding GI illness/STD exposure), may have affected the estimates derived from this study.

Authors’ response: A section addressing the reviewer’s comment has been added to the discussion (page 15; “Selection of the reference group…”). Most of the respondents (68%) of the reference group reported no symptoms in the 7 days before completing the questionnaire. Therefore, we think that preceding GI illnesses in the reference group may have affected our estimates only slightly.

8) Minor compulsory Revisions:
Introduction: For completeness, authors should be aware of the scope of post-Y enterocolitic infections that have been shown to occur (see Porter CK et al., Pathogen-specific risk of chronic gastrointestinal disorders following bacterial causes of foodborne illness. BMC Gastroenterol. 2013 Mar 8;13:46. Finding: Yersinia enterocolitica risk of functional bowel disorders, particularly IBS.)

Authors’ response: We thank the reviewer for this hint and included the information in the introduction (page 4; “Furthermore, chronic GI disorders…”).
Reviewer: Maria Fredriksson-Ahomaa

Reviewer's report:
This manuscript is interesting and brings some new information about sequelae, hospitalisation and antimicrobial treatment of Yersinia enterocolitica infections. I have only two minor essential revisions:

1) In the abstract, the conclusions should be rewritten. They should be focused on the results obtained in the study. The second conclusion is not based on the results and should be omitted.

Authors’ response: The conclusions of the abstract have been rewritten to better reflect the results obtained in the study.

2) In the conclusion part, the authors should add some more conclusions from the own study. The two last sentences fit better in the discussion part.

Authors’ response: The conclusions have been rewritten. The last two sentences were moved to the discussion as suggested.