Author's response to reviews

Title: Salmonella enterica bacteraemia: A multi-national population-based cohort study.

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Author's response to reviews: see over
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Nina Titmus  
Scientific Editor  
BMC-series Journals  
BioMed Central  
Floor 6, 236 Gray's Inn Road  
London  
WC1X 8HL

Re: *Salmonella enterica* bacteraemia: A multi-national population-based cohort study.

Dear Dr. Titmus,

Thank you for your favorable review of our article for consideration for publication in *BMC Infectious Diseases*. We have revised the article along the lines suggested using track changes. A point-by-point response to the reviewer/editor comments is listed on the following pages.

No external funding was received in support of this study. This study was conducted under the auspices of the International Bacteremia Surveillance Collaborative. This is a cooperative group of researchers from Australia, Canada, Denmark, and Finland. All members of the collaborative have made significant contributions to this study. The individuals listed in the primary authorship fulfill all criteria for authorship and the role of the other members is now detailed in the new acknowledgement section. We would like to request that the International Bacteremia Surveillance Collaborative group be listed in the authorship as detailed in the manuscript.

Please note that we have also revised the nomenclature for the serotypes in the results section (second paragraph under clinical and microbiological information) to reflect the most up to date system.

We look forward to hearing from you.

Sincerely Yours,

Kevin B. Laupland MD MSc FRCPC
Reviewer: Khalifa Sifaw Ghenghesh

Reviewer's report:

This work was excellently written and the data nicely presented. The reader will find it easy to grasp the data presented. This work is great and should be accepted for publication without any changes.

RESPONSE: We thank the reviewer for their comments.

Reviewer: Samuel Kariuki

Reviewer's report:
I have enjoyed reading this manuscript. It provides novel data on the low prevalence of typhoidal and non-typhoidal salmonella (NTS) bacteremia in industrialized countries settings compared to the high levels of life-threatening infection rates in most developing countries in subsaharan Africa. One issue of major importance is the fact that these data should be interpreted with caution as there were several limitations (most are already highlighted in the manuscript) the main one being that this was a retrospective study and methods and tools for data collection were not necessarily uniform throughout the study population. Some of the major risk factors for NTS bacteremia in subsaharan Africa include co-morbidity with HIV, malaria, sickle cell trait and malnutrition (especially in young children). Did the authors register any co-morbidities in their study populations?

RESPONSE: We have added further detail to the methods section indicating that we attempted to use uniform definitions and abstracted data from our centres using a standardized template. With respect to the co-morbidity issue, we did not systematically collect that data from all sites and therefore have concerns about presenting data that may be incomplete. We have added a comment to the discussion to address this limitation.

Reviewer: Nuria Torner

Reviewer's report:
Non-typhoidal salmonella is fully recognized as common cause of gastroenteritis which can result in large outbreaks and high disease burden in the community. Although rare, in non-impaired immunity individuals, bacteraemia and severe complications related to extraintestinal focal infections after haematogenous spread such as meningitis may occur. This is a well written and extensive data report on S enterica bacteraemia on a multi-national collaborative setting. Nevertheless, there are some questions of the study that should be encountered.

- Major compulsory Revisions
  Background
  The author states that “all cases of disease occurring among residents of a defined population” are included. This statement needs to be ascertained by providing more information on the availability to health care facilities in all the regions involved in the study. If there are differences in the coverage to hospital
based medical care this can result in an underestimation of the incidence where there is no gratuity for example. Are the health systems in all regions involved fully comparable?

RESPONSE: We have revised the sentence to indicate that this is regarding all cases according to a specified case definition. In our study the case definition involved a positive blood culture. As detailed under the surveillance populations section in the methods, this was greater than 95% overall and likely greater than 99% overall. In all of the participating regions provision of blood culturing is fully funded through public funds such that access to blood cultures is not impeded by financial concerns. We have added further discussion in the second paragraph of the discussion to highlight this point.

It is stated that the aim of the study was to evaluate temporal and regional differences in the occurrence of Salmonella enterica bacteremia, yet they should clarify the statistical significance of these differences.

RESPONSE: In population-based studies, sampling by definition, is not performed. The number of cases identified is considered a fact, and any variance from the ”true” population value is a bias (ie misidentified cases for example) and not a random error. There is considerable debate among population-based investigators as to how such data should be reported. However, most are of the opinion that incidence rates should be reported without statistical measures such as confidence intervals. If incidence rates are to be compared statistically (ie null hypothesis is that the incidence of salmonella bacteremia is the same in Australia, Denmark, and Canada) then one would need to consider each of the regions as a random sample from the countries involved. This certainly is not the case. We believe that the incidence rates are best left reported descriptively and not formally compared using statistical tests. We would however, be willing to concede this at further reviewer and editorial request and perform the tests in question.

Methods
Was it through a systematic process or through a protocol implemented specifically for the study that the microbiological processing was carried out?

RESPONSE: Microbiology testing was performed locally using their own procedures. We have added this detail to the methods and it is further discussed as a limitation in the discussion section.

Results
Page 8 : Providing % values for cases in different regions and serotypes might be more informative.

RESPONSE: These have been added as suggested.

Incidence:
Adjusted incidence rates were markedly different among the regions and by salmonella group. Shown on Figure 1…I would suggest setting up these results in a Table showing values and statistical significance values and hence deleting Figure 1. Figure 2 could include a correlation for trend line showing correlation index to assess increasing trend for non-typhoidal salmonella
RESPONSE: Please see discussion above re statistical testing. It is our opinion that the data should remain as presented. The other two reviewers seemingly also support our approach. We disagree with trying to fit a linear trend line across the data in figure 2 as the data are clearly not linear.

Clinical and microbiological information:
Bacteremia was defined as either hospital onset (>2 days after admission) or community onset (in community or within 2 days of hospital admission) yet on page 9 2nd paragraph the 18 hospital onset cases were isolated during the first 5 days of admission ... this should be clarified, because only from the 3rd day on after admission the cases can be classified according to the methodological definition as hospital onset.

RESPONSE: This has been revised as recommended.

Results on the 252 cases with added details written out in the text are tedious to go through, a table including this information as well as susceptibility data would be more clear and concise.

RESPONSE: We disagree. There are many serotypes that are isolated in very small numbers. These would result in a table with a very large number of rows that would be equally tedious to read, or alternatively lead to a large footnote related to an “other” category. In addition, providing susceptibilities for single isolates would not be useful. We maintain that the text presentation should be used but would be willing to reformat this data in a table upon further reviewer/editorial request.

Discussion
Page 12
At the end of the first paragraph the author state that excess population risk in males for non-typhoidal salmonella bacteremia may be due to agricultural or diet exposure in males. Could this statement be supported by other studies or is it just a perception of the author. What does agricultural or diet exposure relate to? And why should this be different for men and women? Further on in the same paragraph: Typhoidal salmonella in younger adults with no differentiation in gender is considered a reflection of a greater rate of foreign travel to endemic areas and in younger immigrant population. Has the variable immigration been considered and analyzed in the study? If so it would be convenient to include this data, if not, why wasn’t it included? the rate of immigrant population is a relevant factor to take into account due to the increasing flow especially in high income countries such as those included in the study.

RESPONSE: These are solely speculation and we have now emphasized this as such in the discussion.

Editorial requests:
- Please clarify and document, within the Methods section of the manuscript, whether each site received approval by the local ethics committee.

RESPONSE: This was the case and the sentence has been added as requested.
- We strongly encourage you to include an Acknowledgements section between the Authors' contributions section and 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 their source(s) of funding. Please also acknowledge anyone who contributed materials essential for the study. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements. Please list the source(s) of funding for the study, for each author, and for the manuscript preparation in the acknowledgements section. Authors must describe the role of the funding body, if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

RESPONSE: This information has been added as requested in a new acknowledgments section.