Author's response to reviews

Title: A Changing Picture of Shigellosis in Southern Vietnam; Shifting Species Dominance, Antimicrobial Susceptibility and Clinical Presentation

Authors:

Ha Vinh (vinhh@oucru.org)
Nguyen TK Nhu (nhunk@oucru.org)
Tran VT Nga (ngatvt@oucru.org)
Pham T Duy (duypt@oucru.org)
James I Campbell (jcampbell@oucru.org)
Nguyen VM Hoang (hoangnvm@oucru.org)
Maciej F Boni (mboni@oucru.org)
Pham VT My (myvpvt@oucru.org)
Christopher Parry (cmparry@liverpool.ac.uk)
Tran TT Nga (ngattt@oucru.org)
Pham V Minh (minhpv@oucru.org)
Coa T Thuy (thuyct@oucru.org)
To S Diep (tsdiep@oucru.org)
Le T Phoung (ltphtp@oucru.org)
Mai N Lanh (mainl@oucru.org)
Bui L Mong (monglbui@oucru.org)
Vo TC Anh (anhtcv@oucru.org)
Phan VB Bay (bayvb@oucru.org)
Nguyen VV Chau (chaunvc@oucru.org)
Jeremy Farrar (jfarrar@oucru.org)
stephen baker (sbaker@oucru.org)

Version: 4 Date: 3 November 2009

Author's response to reviews: see over
Dear Editor:

Enclosed is the modified manuscript entitled “A Changing Picture of Shigellosis in Southern Vietnam; Shifting Species Dominance, Antimicrobial Susceptibility and Clinical Presentation” by Ha Vinh et al. We wish this edited article to be considered for publication in your journal.

Shigellosis is ongoing public health problem in many parts of the world, including industrialized and none-industrialized countries. Our data presented in this manuscript demonstrates a shift of species dominance over a period of 14 years in Southern Vietnam. This shift is combined with a change in antimicrobial susceptibility patterns and a change in the clinical presentation. These findings are important for the development of future vaccine and treatment policies in South East Asia and other places where Shigella is endemic. We have answer all the required points raised by the reviewer and we have dealt with each point in turn below.

Comments from editors at BMC infectious diseases

The abstract should include Background, Methods, Results and Conclusion sections. In addition, the last section of the abstract should be Trial Registration: listing the trial registry and the unique identifying number, e.g. Trial registration: Current Controlled Trials ISRCTN73824458. Please note that there should be no space between the letters and numbers of the trial registration number.

This has been changed in accordance with BMC guidelines

In addition to paying careful attention to the reviewers comments, the authors should take care to ensure that the reader is not swayed to infering causation from association. For example, in their abstract (and again in the results section), the authors write that their findings suggest that "the clinical presentation of shigellosis...may be related to the antimicrobial resistance profile". The data are insufficient to make this conclusion. However the worsening of clinical presentation was associated with increased resistance.
To ensure the data is not misleading this has been edited and we note a concurrent change in disease syndrome with a change in serotype and antimicrobial sensitivities.

The figure legends need to make it clear what each bar and line represents on the graphs.

The required information has been added to figure legends

Reviewer 1

The authors present a comprehensive combined epidemiological and microbiological data of shigellosis from three studies in Ho Chi Minh City Southern Viet Nam over 14 years period. The manuscript appear to be well written, however there are minor essential revisions required. Line 183: "defined as" is repeated

This has been edited appropriately

Lines 188 - 190: White and red blood cell count was examined microscopically and scored on scale from zero to four, being zero without and four with the most. It is not clear how many cell correspond to score four. I would suggest to present the scale in quantitative way, e.g. scale 1 = xx to yy cells / HPF

This has been edited in the methods and now reads “A white blood cell count was performed on all patients and stools were examined by microscopy (HPF (x 400)) to identify white and red blood cells, these observations were scored on scale from zero to three, scale 0 = 0 cells / HPF, scale 1 = 1 to 10 cells / HPF, scale 2 = 11 to 20 cells / HPF and scale 3 = >20 cells /HPF”

Lines 232 - 235: The sentence “These observations are consistent .......3 years of age” it seems more discussion than results.

This has been edited appropriately

Lines 238 - 240: Again as the previous

This has been edited appropriately

In figures 2 & 3 there is missing the labels of red and grey bars

This has been edited appropriately

Reviewer 2

These are listed below:-
Line 57.....it is disease,… Should be……it is a disease
Reviewer 3

The authors should make the points clear, and should provide only the essential results. There are a plenty of data presented in the manuscript, which include interesting points. However, the contents of some of Figures and Tables overlap. Please try to reduce them. I think at least Figures 4 and 5 are not necessary.

This work was written to represent an overall picture of shigellosis in Southern Vietnam and therefore combines all our epidemiological data. The authors feel that all the data is presented with a specific aim in mind and we have tried to avoid overlapping data in any great detail. Each figure and table answers specific questions that microbiologists and epidemiologists working in this field may ask. We wished to show that any change, either was, or wasn’t related to the isolation of differing species, which may add huge bias into each data period. We have removed one of the elements of figure 5, yet feel that figure 4 and the remainder of figure 5 are essential for the presentation of our argument and are the most interesting part of the manuscript. The article has been edited somewhat (by 800 words) to ensure that the points are more concise and that there is no overlap between the text and figures/tables.

I do not think that it is important to explain each of the three studies in detail. Alternatively, they should explain how relevant the combined usage of three period data is. And more epidemiological information should be provided; are all the patients in this study sporadic? are there any outbreak of Shigellosis during the periods? These factors could affect distribution of species and resistance. Namely, one large outbreak can change the distribution.

The questions have been answered appropriately in the discussion to ensure that there were no reported epidemics during this time. This reads “The change is species and antimicrobial resistance pattern reflects a change occurring in the Shigella population over time in this setting. Locality and time of isolation data suggest that entrance to all
studies was sporadic and there was no evidence of transient epidemics”. Regarding the explanation of the three studies in detail, this recommended on editorial review after the initial submission of the article. Rather than a direct epidemiological study, it was a number of studies combined, therefore, we highlighted the study outlines to be transparent and to show any change is unrelated to study enrollment criteria.

The term of “Study” seems to be confusing as this study used data and isolates from three collections of previous studies. “Period” or “Group” should be preferable.

This has been edited to period, were appropriate

Line 255-, I think Table 2 is enough, and it would be better to analyze data of S. sonnei and S. flexneri in separate since trends in resistance, especially for traditional antimicrobials, seemed to be different from one another. Change of species distribution may account for that of resistance. For example, resistance to chloramphenicol became high in S. flexneri and low in S. sonnei though the periods. Increase in resistance to nalidixic acid seemed to be common for both, which may have something to do with usage of fluoroquinolones in treatment as discussed in the manuscript. Ampicillin resistance among S. sonnei seemed to increase transiently in period B. I wonder if the authors could have any suggestions for it.

I appreciate the point of the reviewer and to demonstrate that resistance changes are dependant not only on time but also on species variation we felt it necessary to include figure 5, which demonstrates a change in total change over the three periods and also how the change may be species specific. Ampicillin resistance may have increased due to the use of oral cephalosporins, although this is purely speculative.

Line 288-, changing in severity of clinical features is interesting. But it is difficult to evaluate it because no control can be provided. Is the change specific for shigellosis? How about other food- or water-borne diseases? Economic and/or social changes in Vietnam may have to do with the change. I also wonder if the results of Table 4 were consistent when comparing the data of the species in each period.

This is one of the most interesting findings of the study, we have no data on other enteric infections on which to relate, and which we appreciate there are limitations, the data is real and recorded consistently by the same research team, allowing consistency, but there may be secondary factors we cannot control for. We did analyze the data to see if such changes were true during each period, however due to the number of each serotype the sample size was insufficient to suggest a significant variation.

Line 176, quality control strains such as ATCC25922 should be declared.

This has been edited appropriately
Line 204-216, can be integrated into Methods.

*This has been edited appropriately*

Line 237, is the wet season May and September, but not from May to September?

*This has been edited appropriately*

Fig 2 and 3, what do red and gray bars and curved line indicate?

*This has been edited appropriately*

10. The name of species, dysenteriae, flexneri, boydii, and sonnei, should be written in small letters.

*This has been edited appropriately*

This manuscript has been read and approved by all co-authors in its current form. We think you will find that the concepts of this article are novel, entirely consistent scope of your Journal and will be of significant interest to your readership. All authors have no competing interests and we hope you will consider publishing this article.

Thank you for your attention to this matter.

Yours truly,

Dr Stephen Baker