Author's response to reviews

Title: Pulmonary Melioidosis in Cambodia: a Prospective Study

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Version: 2 Date: 23 February 2011

Author's response to reviews: see over
The Editor,
BMC Infectious Diseases

Re: Revised manuscript

Dear Madam, Dear Sir,

Thank you very much for the review of our manuscript MS# 9503704844854380 “Pulmonary Melioidosis in Cambodia: a Prospective Study”. We found the reviewers’ comments to be very helpful, and have made a number of changes in every sections of the proposed article to address the reviewers’ concerns. Thank you very much for considering our revised manuscript. Please contact me for any additional questions.

Below are our responses to the reviewers’ specific comments:

Sincerely yours,

Sirenda Vong
Reviewer's report

Title: Pulmonary Melioidosis in Cambodia: a Prospective Study
Version: 1 Date: 29 January 2011
Reviewer: Paul Tambyah

Reviewer's report:
This is an important manuscript although it is not entirely novel
There are two very important pieces of data here:
1) the very high mortality which should be highlighted and
2) the fact that only 2 patients completed the recommended course of treatment because of financial reasons.

Response: we made substantial changes in the discussion and abstract to reflect these comments

The authors should be commended for collecting cost data and putting it into perspective in terms of the incomes of the patients and how they had to sell property to pay for their treatment of this deadly infectious disease. This MUST be highlighted and perhaps could be the subject of an accompanying editorial if properly highlighted.

Response: we agree with the reviewer's comment, unfortunately we did not collect detailed information on the incomes of the patients' households. We however expand the discussion to reflect the comment

there are some other less important issues:
1) What proportion of positive cultures were B.pseudomallei

Response: thank you for the suggestion; we added a sentence reporting this information in the results section

2) the comparison between severe and non-severe cases was not helpful. It would be more useful to compare B.pseudomallei with other culture positive cases to help recognise the unique features of melioidosis

Response: we agree with the reviewer’s comment, however, we have reserved this analysis for the main publication which addresses the entire distribution of respiratory pathogens in ALRI.

3) Are there published references to the entire respiratory pathogen study?

Response: please see the previous question

4) How were the sequelae of infection verified?

Response: the lung sequelae were diagnosed based on clinical recovery and radiographic imaging by our clinical experts: BR who is an ID specialist and a pulmonologist, and CM, a Prof. of pulmonology. The sequelae images included bronchiectasis, calcification or retraction.

5) what was the initial treatment used? How does this compare with the WHO recommendations?

Response: the discussion was change to reflect this comment

6) The striking finding that only 2 patients received the recommended course of treatment should be highlighted

Response: we made substantial changes in the discussion to address the reviewer's comment
Reviewer's report
Title: Pulmonary Melioidosis in Cambodia: a Prospective Study
Version: 1 Date: 6 February 2011
Reviewer: Bart Currie

Reviewer's report:

Major Revisions
1. The antimicrobial sensitivity data is problematic. Disc diffusion is recognized as inadequate for B. pseudomallei and there are quite a few publications on this issue. The authors provide no details of how they interpreted disc diffusion results for each of the antibiotics. They state that the finding of substantial amox/clav resistance was a major result of this study and the table also says nearly all isolates were sensitive to quinolones. Literature from other studies, including from neighbouring Thailand make both these findings doubtful. Unless formal MICs (with breakpoints provided) were performed, the antimicrobial results and Table should be removed and the amoxy/clav results not stated as a major finding in the Discussion.

Response: We agree and have removed this statement regarding quinolones and co-amoxiclav in the discussion

2. However the cotrimoxazole results were from E test and so can still be included. Furthermore, the disparity between disc diffusion and E test for cotrimoxazole is also well covered in the B. pseudomallei literature and I suggest the authors note the (false) disc diffusion results that they obtained in comparison to the (correct) E test results. In addition, as it is noted on E Test that up to 15% of B. pseudomallei strains in Thailand have primary resistance to cotrimoxazole, the findings here that on E Test all the Cambodian strains were sensitive is an important difference. This difference between Thailand and the Camodian data here needs brief discussion as it has implications for therapy.

Response: the discussion was corrected to reflect this comment

3. The major conclusion of this study must be that the very high mortality seen reflects both diagnostic issues but, equally importantly, the non availability of ceftazidime for treatment of presumed or confirmed melioidosis in Cambodia. The high mortality in the context of a lack of ceftazidime needs noting specifically in the abstract and at the beginning of Discussion (as a major finding) and in the concluding remarks at the end of the Discussion. Ref 8 (White Lancet 1989) needs repeated referencing at the end of the Discussion at least.

Response: the discussion and the abstract were corrected to reflect this comment

4. Further discussion on making ceftazidime available is required in the context of decreasing costs of that drug and the potential fro generic ceftazidime to be impoted from Thailand, where it is now manufactured.

Response: the discussion was corrected to reflect this comment

Minor Revisions
1. In the context of the final statement on improved diagnosis using Ashdown broth, a more recent reference from the Thai or Australian literature could replace the current ref 26.

Response: we added a more recent reference

2. In the Introduction and Discussion, the clinical findings and mortality and access to therapy issues could be better discussed by comparing to the 2 latest publications on similar data from Thailand and Australia.


Response: The first article was actually already referenced. Thank you for these suggestions.
**Reviewer's report**

**Title:** Pulmonary Melioidosis in Cambodia: a Prospective Study  
**Version:** 1  
**Date:** 17 January 2011  
**Reviewer:** Brenda Ang

**Reviewer's report:**

Major Compulsory Revisions (please see attached Comments)

Inclusion criteria:
in the beginning, authors included only patients with ALRI <14 days. This would result in missing those with sub-acute or chronic presentation. Thus in questionnaire, they had cases with symptoms longer than 14 days, but we would not know how many other cases are missing.

**Response:** The study was based on the follow-up investigation of cases that were detected through a surveillance of ALRI. With careful interrogation during the follow-up investigation, many of the cases that were admitted for an acute infection actually had symptoms that started before 14 days prior to hospital admission. We made changes in the results section to clarify.

Exclusion of cases with known TB, HIV, chronic steroid use, cancer would also mean missing out on other potential cases. Authors do not explain why they excluded these.

**Response:** the present melioidosis was based on the follow-up investigation of cases that were identified through surveillance. Inherent to the initial design of the surveillance project, known TB, HIV and cancer were excluded.

Follow up with questionnaire - why not apply this during hospitalisation as well. Doing it after discharge is good to look at long-term outcome and relapse, but there would be recall bias.

**Response:** we fully agree with the reviewer’s suggestion; however, implementing a follow-up investigation of all ALRI cases detected via surveillance would go beyond the scope of the surveillance project and its cost.

Treatment : :"chloramphenicol would be interrupted" - do authors mean "stopped".

**Response:** we meant “chloramphenicol would be discontinued". Sorry for the confusion

Follow up at Takeo hospital - were all pt, even from Kampong Cham followed at Takeo hospital?

**Response:** The follow-up investigation relied on home visits of patients admitted either in Takeo or Kampong Cham hospital. A follow-up consult was set in each hospital. We made corrections accordingly

"The main clinical features did not differ from a common pneumonia" - needs clarification.

**Response:** this sentence was speculative based on observations shown in Table 1. We did not show any analysis between melioidosis and non-melioidosis cases. Therefore, we have removed this statement from the text.

Radiological features
Difficult to be sure if other patients would have CXR changes or sequelae as there is no mention of whether there is a protocol for repeating CXR.
Response: The present study was designed piggybacking on the surveillance project. The latter did not account for repeated CXR during hospitalization and at discharge. However, we included systematic control of CXR for cases that were found during the follow-up investigations. We made correction in the methods section to reflect this comment.

Discussion
Presence of DM and co-morbidities. Authors contradict themselves—“the prevalence of DM in our population seemed to be low.” “Our findings confirm results...reporting higher prevalence of DM in bacteremic pt. 5/7 DM patients had positive blood culture, but total number of bacteremic pt was ?24.

Response: Sorry for the lack of clarity. We corrected the sentences to reflect this comment.

The discussion in the last paragraph unfortunately becomes quite jumbled and needs to be re-written.

Response: We changed substantially the discussion to hopefully address the reviewer’s concerns.

Well designed prospective study should have protocol that stipulates at which day of illness patients have labs, CXR’s, and other assessments. This was very clear for Blood and respiratory samples collection, but not so for radiology, or clinical assessments.

Response: We are well aware of the limitations and have addressed the reviewer’s concern in the methods.

Thank you

Sirenda Vong