Author's response to reviews

Title: Antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: a prospective cohort study

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Author's response to reviews:

Dear Editor,

Please find enclosed a revised version of our article "Antimicrobial resistance predicts death in Tanzanian children with septicemia". We appreciate the work of the reviewers and their highly useful comments. Below follows a detailed point-by-point response to the reviewers' comments. We hope the revision has addressed all reviewer comments appropriately, and that the manuscript may be suitable for publication in Biomedcentral Medicine.

Yours sincerely,

Bjorn Blomberg

Point-by-point response to reviewers' comments:

Reviewer one:
We greatly appreciate the positive feedback on the manuscript from reviewer 1, Dr Thomas F O'Brien.

Reviewer two:
We are very grateful for the highly useful and practical comments from reviewer 2, Dr Shabir A Madhi, and believe the manuscript has improved significantly upon addressing these concerns.

Major Compulsory Revisions

Major comment 1.
This study contributes to the overall literature regarding the importance of septicemia in Africa, however the presentation of the data makes it difficult to appreciate the community-acquired from the nosocomial acquired pathogens. This is important for a number of reasons including: i. the summary inclusion of both undoubtedly would bias the spectrum of pathogens identified. ii. Impact on the spectrum of antimicrobial resistance. iii. Affect recommendations being made as to what the empirical antibiotic therapy should involve. iv. Limit comparisons with other similar studies, the focus of which are on community-acquired infections, v. determine potential of isolate being a contaminant vs. pathogenic, etc. As such, it would be easier to make deductions from the data if the scope of this manuscript is either split into community-acquired and nosocomial acquired; or alternately if only the community acquired aspect of the
The study is analyzed in this publication. In particular, it would probably be best to restrict the study to blood cultures performed prior to antibiotic therapy being instituted at least in the hospital.

Response:
We fully agree with the notion that it is important to distinguish among infections acquired in the community and nosocomial infections for the mentioned reasons. To ensure the quality of the data I have gone through the whole database and double-checked the data related to this issue. We have now re-analyzed the data with focus on the distinction between community- and hospital-acquired infections. As requested, we have presented data on the prevalence of organisms (table 2) and antimicrobial susceptibility-data (table 6-8) specifically for community-acquired and hospital-acquired infections, and compared the two groups. The aspect of hospital-acquisition of infection is also considered in the univariate and multivariate analysis (Table 4-5), and we have added a graph on showing a Kaplan Meyer survival plot for community- and hospital-acquired infections (figure 1d).

We have reanalyzed the data with a strict definition of community acquired infection, including isolates obtained during the first 48 hours, as well as infections in neonates born in hospital within the previous 10 days. However, we advice that there must be some caution with regards to the interpretation of the definition of hospital-acquired infection in this context, for the following reasons: In fact the intention of the study from the start was to focus on community-acquired infections, but as the study progressed, there were indications that a certain part of the study subjects had their blood-cultures drawn at a time (>48 hours) when they could have acquired nosocomial infection. The time to blood culture in our study was recorded as the difference between admission time and the time when the blood culture bottle was received in the laboratory. This definition should be efficient at ensuring that nosocomial infections are not erroneously labeled community-acquired. However, having blood-cultures drawn at a later time does not necessarily mean that the infection cannot be community-acquired if the patient has been sick since admission. For instance, we are aware that, at times, transport of blood cultures from the ward to the lab was somewhat delayed due to logistical issues. Additionally, in some cases, there may, due to high workload, have been delay in obtaining blood cultures. Thus, we think the revised version with a strict distinction between community-acquired and hospital-acquired infection as advised by the reviewer, is appropriate and an improvement over the original draft. However, while the community-acquired infections probably are correctly labeled, for the reasons mentioned above, we caution that some of truly community-acquired infections may have been labeled hospital-acquired.

As for the issue of antibiotic therapy prior to blood culture, we agree wholeheartedly that this is not ideal. In fact, we put strong emphasis on avoiding this in the planning and implementation of the study. However, in the real-life situation when patients were admitted, it turned out that a large part had already tried antibiotics before admission. Some of them had attended other health facilities before, and, sadly, this is a setting where people sometimes have so little money that they even have to prioritize between seeing a doctor and buying medicines, and frequently people opt for buying antibiotics straight away in stead of spending money on seeing a doctor and still needing to buy antibiotics afterwards. We suspect that even more patients than those we identified had used antibiotics prior to admission, as this may tend to be underreported by patients. Unfortunately, it was also unavoidable that a number of patients received antibiotics in the department before blood culture was taken, and this was partly due to the critical state of patients on admission and partly due to logistical issues due to high workload for the clinicians and nurses. All in all, at least two thirds of the patients in the study would be excluded if prior antibiotic treatment would be an exclusion criterion. Thus, we have not excluded all these patients. However, we have analyzed the differences in susceptibility data between those who had received antibiotics prior to treatment and the others, finding relatively minor differences. This information is added in the text, but not in the form of tables, as that would take too much space. We also compared those episodes that were both antibiotic naive and community-acquired, with the other ones, also finding relatively minor differences.

Major comment 2.
The definition of "septicemia" which I suspect refers to bacteremia (?) needs to be clarified. Additionally, what were the specific criteria (other than temperature) used for making a clinical diagnosis of septicemia, which triggered blood cultures being performed. The current definition at the end of paragraph 1 pg 5 is too vague.

Response:
We agree that the definitions used may not have been sufficiently clear. The children were evaluated according to the IMCI guidelines, and the questionnaire used was built up along those lines. The inclusion criterion was a clinically suspected systemic infection, based on evaluation of temperature and various clinical features as detailed in the IMCI guidelines. We have added a section describing the key features used in the evaluation. As for the definitions, we are dealing with two different populations: First, those with
clinical signs and symptoms of systemic infection, equalling all included patients. Second, those who additionally had pathogens grown from their blood-cultures (i.e. bacteremia + clinical signs of infection). In order to clarify the issues, we have now defined the first category as "suspected systemic infection" and the latter as "laboratory-confirmed bloodstream infection".

Major comment 3.
The limitations of using disc-susceptibility testing (vs E-test/MIC) needs to be discussed (pg 6 - 2nd paragraph)

Response:
We have added information on MIC testing, including the fact that it was not routinely used on all isolates, but that MIC determination by E-test (AB Biodisk) was done for certain isolates, most notably enterococci and Gram-negatives.

Major comment 4.
It is unclear as to what criteria were used to attribute "clinical significance" vs "contaminant" - esp as an example for E faecium which was not hospital acquired etc. Similarly, were cultures with multiple isolates considered as contaminants or included in the analysis based on certain predefined criteria

Response:
We have added some more details on this issue in the revised manuscript. In this setting with limited resources, sometimes we are not able to evaluate all aspects of the issue in question. In the case of our study, we did not have resources to do repeat blood cultures, thus, we made a pragmatic choice of excluding all isolates of coagulase-negative staphylococci as probable contaminants, although this means missing some CoNS isolates that may indeed have been clinically significant. Apart from that, Bacillus spp, diphtheroids and micrococci were excluded as contaminants. Enterococcal isolates were included as pathogens as they are more likely to be clinically relevant.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Comment 1.
Pg 5- any reason for the lag in publication- study completed in August 2002

Response:
There has been some delay in the publishing. Reasons for the delay were partly that we retrieved and reviewed a great number of patient records as well as hospital register books in retrospect to assure the quality of the data. Furthermore, we did some additional work on the isolates in Norway, both re-confirming the isolate identification and susceptibilities (finding a high degree of correlation, by the way) and performing various molecular methods to further characterize isolates. We have already published one article on a part of this study in 2005 (JCM, February 2005, Vol 43, no 2, p 745-49) as mentioned in the article. While we agree that it should have been published earlier, it seems not to be very rare with a few years of delay in comparable studies that are published.

Comment 2.
Pg 5: clarify if specific criteria, other than temp used for "suspecting serious bacterial infection"

Response:
Information on this has been included in the "methods" section, under "Location and patients".

Comment 3.
Pg 5: Would be useful to indicate what the empirical antibiotic therapy is for the study site for the treatment of suspected community-acquired sepsis

Response:
Again, a highly relevant comment, and we have added more details on this in the revised manuscript. There was no formally agreed empiric treatment at the site, partly because of the lack of studies on antimicrobial resistance of isolates, and part of the rationale for performing this study was to improve local data to provide a background for developing recommendations for empirical treatment regimens. However, most neonates would receive a regimen with ampicillin + cloxacillin + gentamicin, with 20% receiving ceftriaxone, mostly as a second-line regimen. In older children the regimens used were more diverse, mostly based on a penicillin (penicillin or ampicillin) + either chloramphenicol or gentamicin. To some extent, the choice of regimen was
influenced by accompanying localizing signs, such as signs of meningitis often prompting the use of chloramphenicol and bloody diarrhea leading to erythromycin being used.

Comment 4.
Pg 7: provide data on mean duration between readmissions- and decide on criteria used for considering as nosocomial vs. community-acquired- probably exclude any repeat episodes with ≤30 days if reanalyzing for only community-acquired

Response:
As mentioned above, we have reanalyzed the data using a strict definition of community-acquired infection, and more details have been added both in methods, results and discussion section on this.

Comment 5.
Pg 7: Useful to show if any difference in spectrum of isolates between 1st and readmissions

Response:
The isolates obtained during readmissions were few (1 klebsiella, 1 salmonella, 1 E. coli, 3 Acinetobacter, 3 enterococci and 1 S. aureus), and there was no significant difference in resistance rates between first admissions and readmissions (probably the numbers were too small).

Comment 6.
Pg 8: suggest incorporating footnote at end of table 1 into "antimicrobial therapy" text section.

Response:
This has been done.

Comment 7.
Pg 8: 1st sentence- unclear where the figure of 1 402 comes from- should the denominator not be 1 557?

Response:
The one may be as correct as the other. For the patients missing in between 1402 and 1557, we knew the treatment given, but the timing was unsure, so that we could not establish whether it was given before or after blood cultures were taken. In order to make it less confusing, we change according to the reviewer suggestion. The sentence is still correct if we change to "... AT LEAST 67% (1046/1557)".

Comment 8.
Pg 10: duration of hospitalization comparing inappropriate antibiotic therapy should exclude children who died from the analysis- as this would bias result toward showing no difference between the groups. Also, if there are many children who survived without adequate antibiotics- raises questions of the pathogenicity of the isolates- which would need to be discussed.

Response:
We agree with this suggestion. We have now recalculated times to discharge accordingly, and found that, indeed, the difference was significant. We have also added some more detail in the 'Methods' section about the methodology used for comparison of medians of time variables, i.e. Wilcoxon rank-sum (Mann-Whitney) test.

Comment 9.
Pg 10: the comparison of "clinical TB" is artificial- since the signs and symptoms of AIDS and TB overlap- resulting in a lower threshold of HIV infected children being treated for TB

Response:
We agree with the comment and have removed the statement.

Comment 10.
Discussion: this would need to be tailored in relation to nosocomial vs. community acquired infections

Response:
We have added considerations regarding community- and hospital-acquired infections in the discussion.

Comment 11.
Pg 13: 3rd last line- evidence from South Africa (Clin Infect Dis 2000) that HIV does impact on outcome of bacteremia and association with antibiotic resistance
Response:
Thank you very much for the reference. We have included the reference and rewritten the section accordingly.

Comment 12.
Pg 14: 2nd paragraph: low yield of MTB from blood culture- same as observed in children in Malawi (Graham S et al.)

Response:
We agree and have rephrased the statement accordingly. Thank you again for the reference.

Comment 13.
Pg 14: 1st sentence -speculative - based on post mortem studies- septicemia contributes to mortality- but major problem in 1st two years in HIV infected children PCP, CMV etc.

Response:
Upon rereading the paragraph, we agree that this statement appeared to overstate the importance of bloodstream-infections. The statement has been rephrased appropriately in the revised version.

Comment 14.
Pg 23: table 2: indicate what the percentages reflect

Response:
Table 2 and other tables have been revised, and hopefully the percentages appear more recognizable now.

Comment 15.
All tables- suggest splitting between comm.. acq vs nosocomial acquired

Response:
We have revised the tables with that aspect in mind in line with the response to the major comments (above). The data in tables describing the frequency of organisms, and the resistance tables have been split to allow for comparison of community-acquired and hospital-acquired infections. The tables showing univariate (Table 4) and multivariate analysis (Table 5) takes this aspect into consideration. We also added a Kaplan-Meyer plot on community- vs hospital-acquired infection.

Comment 16.
Figures 2 and 3- limit analysis to proven case of septicemia- unclear if this is the case

Response:
This was already the case with the previous figures, but was not clearly stated to the reader. In the revised version both Figure legend and figures should clarify the issue.

Additional comments.

Number of tables & figure:
Due to the focus on community-acquired versus hospital-acquired infection, the number of tables has increased. If there should be any problem with regards to the number of tables, please advice, as we may consider removing a table (no 7). Similarly, we have expanded the figure to include six panels in order to visualize some further important information.

Updated numbers:
As mentioned, in response to the reviewer’s comment, we have gone through the database with the intention to quality-assure / recode the variable for hospital-acquired versus community-acquired infection. During this exercise, based on revisiting various registry books and questionnaires, we managed to complete some missing values in the database, particularly with regards to age and sex of the patient. We have recalculated all statistical analysis in the paper accordingly, and this has also slightly affected the logistical regression modeling. Thus, there is a slight change in some of the numbers in the current, revised version of the manuscript as compared to the previous version.