Author's response to reviews

Title: High rate of pneumococcal bacteremia in a prospective cohort of older children and adults in an area of high HIV prevalence in rural western Kenya

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

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Dear Editor,

We have reviewed the reviewers’ comments thoroughly and have attempted to address all of their points to the best of our ability. Below is a point-by-point response to all the reviewers’ comments. All coauthors have seen and agree with the revised version of the manuscript.

We apologize for the delayed response. We hope you will still consider this publication for your journal. Please let us know if there is more that we can do. Thank you.

Sincerely,

Daniel Feikin, MD
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Response to reviewer 1. Steve Gordon.

1. The introduction is somewhat surprising in that it offers a limited view of the available literature on bacteremia in HIV infected adults. In both the introduction and discussion, the authors state that pneumococcal infections are the most common infection in HIV infected adults - this rather ignores the published data which suggest that both mycobacteria and salmonellae are very common when sought. This study was set up to offer pneumococcal surveillance and the clinical indications for blood sampling reflect that interest. In my view, it would be appropriate in both introduction and discussion to acknowledge this other literature.

RESPONSE. We appreciate this comment. In the introduction on page 4 and the discussion on page 15 at bottom of page, we acknowledge and reference studies that show that both mycobacteria and salmonellae are common causes of bacteremia, along with pneumococcus, in HIV-infected adults. Moreover, in the discussion on page 15, we mention how our sampling scheme might have biased the results towards finding more pneumococcus and less mycobacteria and salmonellae.
2.. In view of the clinical importance, perhaps there should be some mention of the fact that the study provided a necessary resource in a limited situation for only a proportion of the population. Bacteraemia is common in HIV infected adults; this study provided a sampling strategy but not a clinical service. Best care would provide blood culture facilities when needed. The conclusion about vaccination is valid; so too would a conclusion stating the need for more microbiology provision in this population.

RESPONSE. We have addressed this point in the last sentence of the discussion calling for more microbiology services in parts of Africa with high HIV prevalence (page 16)

Reviewer 2– Zitta Harboe

Some comments:
1. Under “Surveillance methods”, second line: “Three other Ministry of Health outpatient health facilities are in or near the surveillance area." It is not clear from the text if patients attending these facilities are included in the study. Are there any "private" clinics in the area that may lead to referral bias of cases? (selection of patients who attended the referral centre?). There is no statement on the access of patients to HAART. A brief comment on this is important because HAART is known to have an effect in the incidence of IPD in HIV patients and this study reported a very high prevalence of HIV in the population.

RESPONSE. We have clarified that no data is collected on surveillance participants at the 3 other clinics and there are no private clinics in the area -- on page 6, line 4. In the same paragraph, we have given the estimated percentage of HIV-infected persons on cotrimoxazole prophylaxis and HAART at the time of the study.

2. In the limitations, other possible sources of bias and confounding should be discussed. Importantly, socioeconomic conditions, like crowding, alcoholism related conditions, smoking, and other life style variables affect the susceptibility and mortality related to the disease. Some general discussion on this topic in the context of Lwak would be of value. Were also the “first two patients” seen in the clinic selected by the nurses because they were more clinically compromised than the other patients waiting? This may also be a source of bias. I think that one of the main limitations of the study is that the investigators could not adjust the incidence estimates for the HIV-status of patients. In this setting, this may strongly affect the results presented and leading to an overestimation of the crude and adjusted rates in the assumed non-HIV population. This is mentioned in the limitations but should be discussed further.
RESPONSE:

First comment about other possible sources of bias and confounding. We agree with the reviewer that the listed variables are indeed risk factors for pneumococcal disease and mortality. However, it is not clear to us that they are either sources of bias or confounding in the data presented here since we have not done a risk factor analysis of pneumococcal disease or mortality. In relationship to HIV, in western Kenya, HIV is very common among adults and does not strongly associate with other risk factors, like socioeconomic status, crowding, smoking and alcoholism. We have added to methods on page 5 line 6 a sentence about the socioeconomic status of the area.

Regarding comment on first two fever patients of the day. On page 5 line 21, we have added that the first two patients of the day were selected without regard for diagnosis or severity. Therefore, there should be no systematic bias in who these two patients are.

Regarding the third point, although we did not have the HIV status of some patients, we did adjust the incidence estimates for the HIV-status of the patients as described in methods on page 8, line 15. We state the following: “To estimate the pneumococcal bacteremia rate in HIV-infected persons, we calculated the numerator by applying the same proportion of HIV-positivity among patients with pneumococcal bacteremia in whom HIV status was known to those whom the HIV status was unknown.” We do raise this as a limitation in the discussion and feel that it is adequately addressed. To address the reviewer’s comment that this is the main limitation of the study, we have moved this limitation to the first to be discussed in the limitations paragraph on page 15, line 6 of the discussion.

Some Minor Essential Revisions:
1. In the Results, first paragraph: “Of these, 1,301 (8%) had blood cultures done”.
   In the abstracts it is stated that 1,342 blood cultures among persons > 5 years were taken", this information is missing in the results.
   RESPONSE. The correct number is 1,301. This was corrected in the abstract.

2. Page 13, in the first sentence in the paragraph referring to MIC results, the word “isolates” is missing.
   RESPONSE: Page 11 bottom. We have added the word isolates to this section on MIC testing. We think this is what reviewer is referring to here as there is no MIC discussion on page 13.

3. The median age of the 51 patients, IQR would be nice to see.
   RESPONSE: IQR has been added on page 10, 2nd paragraph.

4. Persons > 5 years old or persons # 5 years old? – lack of consistency
   RESPONSE. This has been changed to “> 5 years” throughout the paper.

5. The name and manufacturer of the vaccines should be mentioned.
   RESPONSE: This has been added on page 14.

6. Statens Serum Instituts – remove the last s.
   RESPONSE: This was corrected on page 7.
7. The titles of the tables should be more accurate, since data are presented for patients included in the study and not only for PB patients. Also the number of decimals should be the same for all the proportions (%) presented in the tables.
RESPONSE. The titles to tables 1 and 2 have been changed. We go to one decimal place throughout.

8. Table 1 and 2: in “Pneumococcus recovered (% cultures)”, consider instead "Pneumococcus recovered (% of positive cultures)"
RESPONSE: We prefer to give the % of total cultures that are pneumococcus as this is a figure given in other places in the literature for comparison. The % of positive cultures that are pneumococcus can be calculated from the numbers given in the tables.

9. Consider in Table 3, to do the ranking of serotypes according to their prevalence. Also, “PCV7 vaccine specific" it should say: "PCV7 serotypes", also for the other two vaccines.
RESPONSE: This has been changed as recommended.

10. Table 4: It would be of interest to see the 95% CI of the estimates of crude and adjusted incidence and also for the HIV rates.
RESPONSE: 95% confidence intervals were calculated for crude rates using Fisher’s method (Computer Programs for Epidemiologists, PEPI, version 4.0x) and for extrapolated rates using the delta method. See page 7 last line of methods and table 4.

- Discretionary Revisions
1. Abstract: in the results, clarify how many blood cultures have positive findings (for any bacterial species) among the 1,342 blood cultures taken from 1,301 patients. Maybe the authors can describe already here that the pneumococcus was the most common bacterial spp. obtained from blood cultures.
RESPONSE. THE NUMBER OF BLOOD CULTURES IS 1301 AND THIS HAS BEEN CHANGED IN THE ABSTRACT. IT IS NOW STATED THAT PNEUMOCOCCUS WAS THE MOST COMMON BACTERIA SPECIES ISOLATED.

2. Community interviewers visited enrolled households every two weeks to inquire about illnesses. It is not clear from the text how many households were actually enrolled, and how these households were chosen. A brief comment on this would be important because it has to do with the validity of the data collected and possible sources of bias.
RESPONSE. THIS IS NOW CLARIFIED IN THE FIRST SENTENCE OF THE METHODS ON PAGE 5 first paragraph. ALL PARTICIPANTS LIVING IN THE AREA WERE ELIGIBLE AND PARTICIPATED, THEREBY MINIMIZING BIAS.

3. Regarding recurrent cases: "(One patient had bacteremia with serotype 6B pneumococcus in February and August 2007.)”. Is this the only patient with a recurrent IPD? It is interesting because 1/51 cases corresponds to approx. 2% of
recurrent cases, which is similar to the rate reported from populations with low prevalence of HIV, and much lower than what could be expected in a population with the HIV prevalence that is described in the methods section. This should be discussed in the discussion section.

RESPONSE. WE ARE INTERPRETING THIS DIFFERENTLY THAN THE REVIEWER. THE RATE OF PNEUMO BACTEREMIA IN HIV POSITIVE PATIENTS WAS APPROXIMATELY 2% PER YEAR (2399 PER 100,000 PYO). THIS IS SIMILAR TO THE RECURRENCE RATE SEEN (2%). FOR THE NON-HIV INFECTED PERSONS, THE RATE WAS APPROXIMATELY 0.12% PER YEAR. THEREFORE, THE RECURRENCE RATE IS HIGH. ALSO BECAUSE OF THE SMALL NUMBERS, WE FEEL WE CAN’T DRAW CLEAR CONCLUSIONS ABOUT RECURRENT DISEASE AND SO CHOOSE TO NOT DISCUSS IT.

4. In page 13, the authors should underline that the results regarding serotype distribution and coverage of the vaccines in HIV-infected individuals must be interpreted with caution, because of the relatively small number of patients with known HIV status in the study. Also, a reference to published data on HIV from the surveillance population obtained from the home-based HIV testing initiative would be appropriate.

RESPONSE: WE ADDED THE SMALL NUMBER OF PATIENTS WITH HIV TEST AS A LIMITATION ON PAGE 15, LINE 12. THE HOME-BASED HIV TESTING PROGRAM HAS NOT BEEN PUBLISHED YET.

5. In the abstract it is stated that “Nineteen (61%) of 31 patients with HIV results were HIV-positive”, also in the tables. It seems that these 31 patients were tested after inclusion? Maybe the authors can state more clearly which HIV data you are using for doing the extrapolation and which for doing the estimations on serotype coverage of conjugate vaccines.

RESPONSE: AS STATED IN THE METHODS ON PAGE 7, SECOND PARAGRAPH, THE ONLY HIV TESTING DONE ON PATIENTS WAS DONE AS PART OF THE HOME-BASED TESTING PROGRAM. WE DID NOT TEST MOST PATIENTS IN THE CLINIC. THESE ARE THE HIV RESULTS USED TO DESCRIBE THE SEROTYPE DISTRIBUTION IN HIV VS. NONHIV INFECTED PERSONS AND ALSO USED IN THE RATE EXTRAPOLATIONS.

6. You report a 7.7% 30-day case fatality which is actually quite low compared with other studies from industrialized countries reporting mortality from PB in adults - even in studies that do not include pneumococcal meningitis patients. The authors could discuss the reasons behind this finding.

RESPONSE: THIS OBSERVATION IS ALREADY ADDRESSED IN THE DISCUSSION ON PAGE 13. THE FOLLOWING SENTENCE IS RELEVANT. “Studies of invasive pneumococcal disease in Africa have yielded case-fatality proportions averaging 14-16%; the lower case-fatality proportion we found (7.7%) likely results from inclusion of outpatients, as well as not collecting cerebrospinal fluid on higher mortality meningitis cases.”

7. Data on antibiotic resistance are presented in the results and abstract but are not discussed. It appears from the text that data on antibiotic consumption before culturing were also retrieved, however not presented. The low res to beta lactams and macrolides in contrast to high trim-sulfa should be discussed.
RESPONSE. THIS POINT IS NOW DISCUSSED IN DISCUSSION ON PAGE 14 IN THE FIRST PARAGRAPH.