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Journal Name:	International Journal of TROPICAL DISEASE & Health
Manuscript Number:	2013_IJTDH_6809
Title of the Manuscript:	Bloodstream infections and malaria as causes of fever among adult medical patients at a referral hospital in Malawi
Type of the Article	Research Paper

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound.

To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

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PART 1: Review Comments

	Reviewer's comment	Author's comment <i>(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i>
<u>Compulsory</u> REVISION comments	An important study following what was published more than 10 years ago. However the study has major issues in the following areas: 1) The selection of patients based on a single temperature reading leaves out large numbers of patients who may have had either malaria or bacteraemia but with a normal temperature at time of evaluation 2) Authors indicate that those patients that could not give consent because they were too ill leaves a lot of patients that could have changed the results 3) Not recruiting patients during weekends leaves large numbers of potential patients that would have changed	1) Authors agree with the reviewer and are fully aware of the fact that patients having malaria or bacteraemia may have been missed because of the fact being not febrile on the day of presenting to the hospital. This issue is now emphasized in the limitations section. As the study population were patients with febrile illness the authors choose a measurable character to include patients in the study. Including patients based only on self reported previous fever was regarded as vague and the perception and concept of fever may vary widely among patients. 2) Authors agree and highlighted this issue in the limitations. Drawing blood for blood culture is not routinely done. As some patients/guardians might have been sceptical about the amount of blood being drawn, patients were only enrolled if they were able to give consent on their own. 3) Also in this issue authors agree with the reviewer. The weekend could not be covered for financial and logistic constraints. Authors have elaborated this under limitations as well i.e. our findings do rather underestimate the rate of



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	their findings. We know that patient that seek care over the weekend tend to be the sicker ones 4) This may not have been their aim but trying to identify factors that may help distinguish between the two pathologies would have made the paper more interesting 5) Authors should present data better on patients that had dual infection and if possible provide the clinical parameters that would help the clinician distinguish between the two 6) It would be important to know how many of the HIV infected patients WHO stage 3 or 4 conditions on the day of admission. 7) It would be important to know how many patients were admitted with a febrile illness during the study period. This information will put into context the results that are being presented. 8) How did the clinical syndromes correlate with the blood culture and malaria diagnosis	bacteraemia. 4) Authors agree that identifying factors contributing to the different pathologies would be interesting to know. However this was not the aim of this study and data is not available. 5) Only two of the enrolled patients were found to have both malaria and bacteremia. Unfortunately more details including comparable clinical parameters are not available as the clinical examination was left within the routine of the clinicians on duty and not standardized. An SOP might have made findings comparable. 6) Authors agree. However in this study staging was not performed for patients known HIV positive or newly diagnosed. 7) Authors agree that it would be interesting to know the whole number of febrile patients admitted during the study period. Currently the documentation system of Kamuzu Central Hospital does not produce data which are sufficiently robust and reliable. 8) This question highlights an important point. In this study there was no standard operating procedure on clinical examination. Furthermore the clinical examination was performed by different clinicians on charge who might have different ways of interpretation especially as no SOP was available. Therefore the clinical correlates the diagnosis of malaria or bacteremia can
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	9) Some clinical syndromes that would be expected e.g. meningitis, UTI etc are completely missing. 10) It would be useful to know if any of the HIV positive patients on ART? 11) It would be useful to know the effect of cotrimoxazole prophylaxis on the blood culture and malaria test results 12) It would be useful to know the effect of prior antibiotic therapy (amoxicillin etc)on blood culture results. 13) Would the authors provide some insights on how the clinician or nurse verified the information that was provided by the patient on medications that were being taken prior to study enrolment	not be described and discussed. 9)Authors agree. This study focuses on malaria and bacteremia. Other investigations like urine dipsticks or urine culture were not performed as materials are not available at Kamuzu Central Hospital. 10) For already described reasons (documentation system) this data is not available. 11)Also in this regard the reviewer raises an important issue which however cannot be answered by ourstudy. A different study design would be necessary to elucidate the effects of cotrimoxazole on test results. 12)Authors agree. To investigate the effect of prior antibiotic therapy we think testing of antibiotic drug quality and as well as blood levels would necessary to measure all of which could not be done in our study. 13) This information was based on interviews (see methods). The investigator used a standardised list of common antibiotics and antimalarials to ask the patients and ticked the ones which the interviewees mentioned to have taken. 14) "Valid results" used with malarial RDTs and HIV test kits mean that the control line was visible on the test. This means, the test was carried out correctly
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	14) In figure 1, it is not clear what is meant by valid results 15) One would be interested to know what the diagnosis was of those that did not receive a diagnosis of malaria or bacteraemia 16) Statistical analysis will be informed by what the authors decide to do with the revision.	and the result was therefore recorded as correct and “valid”. With regard to blood culture results “valid” refers to “no contaminant “ This is now changed in Figure 1. With regard to blood smears “valid” refers to “done and read”. This is now changed to “available results” in Figure 1. 15) Authors agree. The available resources did not allow to perform any additional tests such as TB culture or virology. Considering the high prevalence of HIV among the study patients Tb may be a frequent cause as potentially other viral or fungal infections. It is important to state that malaria and bacteremia account only for a fraction of the diagnosisamong the febrile patients in this study. 16) As there was no SOP for the clinical examination, clinical findings cannot be set into correlation to the diagnoses. Considering the relatively small sample size of this operational observational study ,no analytical statistical procedures were performed. 17) The discussion section now takes into particular consideration the limitations as highlighted by the reviewer.
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	17) The discussion would be informed by the recasting of the results.	In general we would like to comment that the study was conducted within the usual clinic with all the restrictions and limitations. We still believe that the reported results are informative despite these limitations. As a results of the study there is now a hospital wide initiative for Infectious Diseases surveillance and further attempts are being made to address some of the questions raised
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<u>Minor</u> REVISION comments	1. In the abstract, one of the conclusion they authors present is that the use of malaria RDT has to be carefully supervised and adherence to test results is advisable, but they do not provided information on how malaria RDT underperformed to result in this conclusion 2. The authors need to rephrase line 22 and 23. It does not read well to say bloodstream infections are emerging. 3. In Many places where authors use Africa, they should replace it with Malawi. Most of the information they are quoting pertains to Malawi, 4. Line 32 the words case fractions should be replaced by proportion (I think this is what the authors would like to convey to the readers 5. Lines 52 to 54 belong to the introduction, not the methods 6. There is some confusion with the numbers in the paper. In the abstract and the body of the paper (lines 174 and 176, the number diagnosed with malaria need to be consistent.	1. The respective result is reported in Fig 2. While the discrepant results (RDT positive vs. blood smear negative) seem possible, the opposite result does not seem to be plausible. While these results were reported back to the laboratory a systematicquality control could not be done. However our results support the need for it. 2. Authors agree and rephrased in the manuscript. 3. Authors critically reviewed the manuscript and found the use of (Sub-Saharan) Africacorrect. 4. The term case fraction was replaced by proportion. 5. Authors agree. The sentence was transferred to the introduction. 6. To the best of authors' knowledge numbers are correct.
<u>Optional/General</u>comments	The authors need to reflect on the introduction and how it relates to the key messages they want the reader to take home.	We believe that the introduction reflects the content and key messages of our study