Author’s response to reviews

Title: Bacteriologically confirmed extra pulmonary tuberculosis and treatment outcome of patients consulted and treated under program conditions in the littoral region of Cameroon

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Author’s response to reviews:

Dear Editor in chief

I count it a privilege to have had Giuseppina De Iaco and Nathan Kapata review this work.

Their contributions were so remarkable. View the pertinence of their remarks, we have tried to address all the points and suggestions they raised.

Find below our responses to their concerns.

We have copied their commend and provided response to each point in red.

we remain entirely at your disposal for any other needed clarifications.

(Reviewer 1): General considerations

Giuseppina De Iaco

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Here, as follow, I will number my comments and refer to section, page and line numbers in the manuscript.
Background

Line 13 tuberculosis is the second cause of death related to…. please specify if worldwide and add a reference for this sentence. We could not lay hands on this reference, I have modified it to read Tuberculosis (TB) is a leading cause of morbidity and mortality worldwide, accounting for about 9.6 million new cases and 1.5 million deaths annually and a reference is included.

2) Line 19 extra pulmonary TB is already used as abbreviation in line15, d no repeat extended form – We have replaced it with EPTB

3) Line 22 "bacterium from the lung" the plural form has been used “Bacteria”

Methods

1) Line 30-31: here you write that 145 non sputum specimens were collected: it is not clear if are all from EPTB? From all form of TB? We have specified that these were EPTB suspects.

2) Line 35: revise punctuation in the sentence, may be divided the sentence in two parts. Second part concerning the participants younger than 15 ys. The sentence was divided in to two parts.

3) In this section you should add the policy followed for HIV testing. Yes, it was review to read “HIV screening was done by testing serum from coagulated blood collected in dry tubes on Determine HIV 1/2 strip test. Positive samples were confirmed on rapid SD Bioline HIV 1/2 3.0 cassettes.”

4) Line 1 (following page of method section): "specimens obtained … were …: It is not clear if are all specimen (pulmonary and extra pulmonary sites? They were all from extra pulmonary sites.

5) Line 6: "the other half…: it is not clear to me what half does it means? Half of specimens? The sentence has been changed to read “The aliquoted specimen was decontaminated using …”

6) Line 10-11: "participants were declared positive for TB…” Please try to better clarify: the meaning is ambiguous to me. It has been reviewed to read “A positive diagnosis for EPTB was declared when direct Gene Xpert MTB/RIF and or culture results were positive.”

7) Line 12: "Confirmed EPTB were administered with… It has been reviewed to read “Bacteriologically confirmed EPTB cases were treated following the …. “

8) Line 14: Rifampicin (R) yes, (R) was added
9) Line 18: please write treatment outcome in a fully clear manner. It was reviewed to read “At the end of treatment, treatment outcome was categorized as cured, completed treatment, lost to follow up, failure and died based on the standard criteria(7)”.

10) Harmonise fonts and capital letters in this section, Yes, it was done

Results

1) Line 34: characteristics “corrected to the plural form”

2) Line 34: median could be used instead of mean age because of not homogeneous population It has been reviewed to read “The median age of study participant was 40.0 ± 19.23 years with females being relatively younger (35.5 ±20.0 years) than their male counterparts 45.0 ± 18.3 years).”

3) Line 36: please specify if are microbiologically confirmed EPTB or just EPTB: It has been reviewed to read “The prevalence of bacteriologically confirmed EPTB”

4) Line 38: it not correct to say "the most infected age group.." May I suggest to say "the most represented…" it not correct to say “The most affected age group”

5) Line 39 please correct 318-34 years with 18-34 it was corrected to read “18-34..”

6) Line 1(following page): it not correct to say "those who had no retreatment history were more infected .." May I suggest to say "represented the 66.6%....." Corrected to read “Though those who had no treatment history for TB represented 66.6% of the study population”

7) Line 11: I think there is not significant difference in treatment outcome among males and females (22 /26 among males and 16/19 among females give very similar percentage): Yes, we said there was a difference but not significant. Line 21-22 results section “Overall, 84.4 % of these participants had a therapeutic success with males responding better 22 (57.9%) as oppose to females16 (42.1%) (p=0.442).

8) Line 12 : here the author mention HIV for the first time (see previous comment in the general recommendation of my revision: This issue has been addressed in the method section were we have described HIV diagnostic methods. In the result section, we have also included the prevalence of HIV in the study population [36 (33.6%)] as well as the EPTB/HIV co-infection rates [13 (28.9%)].

A) The issue of HIV and TB co-infection is not clearly addressed. HIV testing and prevalence in the population study is not well described nor in the method neither in the results. This issue has been addressed in the method section were we have described HIV diagnostic methods. In the result section, we have also included
the prevalence of HIV in the study population [36 (33.6%)] as well as the EPTB/HIV co-infection rates [13 (28.9%)].

9) It should be mentioned at this point that all patients died were HIV positive and it could be important to verify if the one with heart involvement was HIV Ab positive or not (it looks like this reading table 4). All five patients who died were all HIV positive.

Discussion

Line 2: please revise English; it was revised to read ‘This study was aimed at determining the prevalence of bacteriologically confirmed EPTB; to determine the most affected organs and to evaluate the treatment outcome of EPTB patients’.

Line 6-7 and Line 8-9 are redundant: reviewed

Line 19-23: same comment than before. I may suggest to write «male gender was more represented than female gender». It could be interesting to address possible explanation for this. More limited access to health services for women? Suggestion taken into consideration to read “The male gender was predominantly more represented than the female gender.”

Conclusion

Line 39: it is still unclear to me if 45 (41.3%) is a prevalence of bacteriologically confirmed EPTB among suspected cases? Clinically diagnosed and then microbiologically confirmed? The conclusion has been reviewed both in abstract and conclusion sections

References

I suggest to exhaustively check the reference section for accuracy and format and also to mention more recent studies (for instance: WHO Global TB report edited in 2017 or 2018 instead of the one listed as Ref. N°1 edited in 2015, articles on GenXpert vs Standard culture recently published instead of Ref N° 12 which focus on Imaging and TB..). : we have reviewed the references as requested

Finally, I hope my comments can be considered useful and constructive by the authors and taken in account in order to improve the quality of the manuscript. The topic addressed can be inspiring for the Cameroon National TB program to revise national guidelines and allocate available resources on GeneXpert implementation especially in EPTB TB where diagnosis and treatment can be really challenging.
Nathan Kapata (Reviewer 2): This is a cross sectional and important study that addresses a topic that has not been well documented in Cameroon and many other TB programmes in the region. Extra pulmonary TB is usually reported without confirmation in most TB programmes and therefore estimating the actual prevalence of EPTB has been challenging. This article adds to the body of scientific and programmatic knowledge with respect to TB.

I have some few comments concerning the article that I feel can help to improve the manuscript.

General: The article is well written, however, there are a number of typographical errors that the authors need to address.

Introduction

In paragraph 4 and line 23-24, the authors indicate that there were no national guidelines on EPTB diagnosis and management. How were patients diagnosed? What guidelines were being followed? Did WHO guidelines exist? If so were they applied? In Cameroon, EPTB is diagnosed mostly clinically with or without bacteriological confirmation. In this study we used both Gene Xpert and Culture to establish bacteriological confirmation of EPTB

Methods

The authors should provide some details about the study population (TB Burden/ HIV burden/ diagnostic and treatment facilities…etc.) and justification as to why the Littoral region was chosen for the study. We reviewed it to include “The littoral region was chosen because it harbours about 20% of all TB diagnosed cases in Cameroon and also because it is the economic head quarter of Cameroon and Douala the regional head quarter is the largest city in Cameroon with a population of 1,338,082 people. It harbors many referral diagnostic and treatment institutions that pulls many persons from the regions in search for better health service.”

Results

How was the therapeutic success rate determined? Was it evaluated as in routine programmatic settings or was this done differently considering that in this case EPTB confirmation was done? Therapeutic success rate was determined using routine programmatic settings given that it was not easy to obtain the same sample from persons who were no long sick.

Discussion

The authors may includes some discussion on the therapeutic success rate in these study participants and try to show how this compares with routine programmatic therapeutic rates: This has been done and reads “EPTB treatment success rate in this study was high and identical to the nationwide pulmonary TB therapeutic success rate of 75% to 84% reported in 2006 to
This finding was in line with the stop TB strategy united nations millennium development goals to cure at least 85% of sputum smear-positive TB patients (21). This study established that treatment success of EPTB patients co-infected with HIV was lower (28.1%) compared to TB-HIV negative patients (71.7%) and this is in line with Atekem, et al (22) in the South West region of Cameroon, but contrary to that of Mekonnen et al. (23) in North Eastern Ethiopia. Therapeutic success in this study attained the WHO stated target of 85% because we assigned a staff to call our patients very regularly to ensure that they all complied to their treatment even when they no longer felt sick. All the patients who died in this study were HIV positively co-infected, but the numbers were too small for a proper analysis. We thing that these patients may not have been compliant to their treatment and turned to neglect the regimen as they thought having HIV is the end of life. Furthermore, a weaken immune system may justify the death cases recorded in these HIV positive cases. There was no significant different between males and females and across the different age groups.”