Author's response to reviews

Title: Bacteriological methods as add on tests to FNA cytology in diagnosis of tuberculous lymphadenitis: Can they reduce the diagnostic dilemma?

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

Subject: Re-submission of Original Article

Dear Editors,

We, Ketema Abdissa, Mulualem Tadesse, Mesele Bezabih, Alemayehu Bekele, Ludwig Apers, Leen Rigouts, Gemeda Abebe, hereby re-submit our original article titled ‘Bacteriological methods as add on tests to FNA cytology in diagnosis of tuberculous lymphadenitis: Can they reduce the diagnostic dilemma?’ to BMC Infectious Diseases for possible publication. We have attached the line by line responses to the comments by reviewers in the following pages.

Regards,

Gemeda Abebe (PhD), Associate Professor.

Corresponding author.
We appreciate the reviewers for their constructive comments which we have used to improve the quality of the paper. We have accommodated the comments line by line. We have re-written some portions of the article.

**Reviewer #1**

**Comment 1.** The diagnostic dilemma of tuberculosis in Africa, Ethiopia included, as stated in this article, remains a real problem for clinicians and pathologists. While this article might present a very simplistic and overworked problem to an environment where the prevalence is not so high and the facilities and funds to diagnose it better equipped, in many countries even culture is beyond reach. Therefore the ability to diagnose TB on FNAC becomes paramount

**Response.** We strongly agree that FNAC has paramount importance in the diagnosis of tuberculous lymphadenitis. As we tried to indicate in the introduction part, Ethiopia is ranked 7th among the 22 high TB burden countries and placed 3rd in terms of extra pulmonary TB of which 80% are due to Tuberculosis lymphadenitis (TBL). This indicates that the country is facing high burden of TBL. However according to the existing diagnostic algorithm in Ethiopia (Reference no.3, line 7), and in real practice the diagnostic approach relies on clinical grounds due to lack of professional experts and facilities. Most of the patients are referred to district hospitals and above, where FNAC and biopsy is the main diagnostic tool for TB lymphadenitis.

**Comment 2.** The major problem I foresee with this article is the assumption that TB (or mycobacterial disease) can be diagnosed on cytomorphology alone. TB has many mimics and in this era of HIV an even more diverse presentation on cytology and therefore to make a diagnosis – positive or negative without including a stain such as ZN or Kinyoun is not advisable. The diagnosis of mycobacterial disease (NOT TB) on cytology should always include identification of the organism. This is relatively inexpensive and simple and within the ability of most laboratories expertise. This should be emphasized in the article and the figures recalculated. The specificity of cytology will increase markedly although the sensitivity will drop. It ensures that patients are treated appropriately.
Response. We strongly agree that TBLN cytomorphology has many mimics and also has diverse presentations. We have clearly stated in background part of the abstract and introduction, and discussion part. However in the setup where this study was undertaken and in Ethiopian context at large, FNAC and histo-pathological examination of excision biopsy (where applicable) are the sole method to rule in or rule out TBLN after clinical suspicion. Patients are put on treatment if FNAC is suggestive for tuberculosis. Other supplementary methods like ZN are given less attention. This was the main driving problem, which led us to hypothesize that supplementation of FNAC with bacteriological methods including ZN stain (where facility allows) could improve the specificity and reduce the dilemma of the diagnosis, which we proved it with our evidenced data. We have discussed in the discussion part that bacteriological methods (culture) can help species identification. This is in agreement with our finding that out of four NTM, three were categorized as tuberculosis by FNAC. However culture facility is not available in remote settings and we recommended its usage where applicable. We believe this study helps as baseline to develop more comprehensive TBLN diagnostic algorithms. The added value of ZN was stated in the result part table 3 to indicate its paramount importance. We have stressed its importance in our conclusion part of the paper. However, due to its low sensitivity, even though it improves the specificity of FNAC, relying on ZN microscopy would lead to high chance of missing true positive cases (page 12, Table 3). Hence we suggest its importance as supplementing test.

Comment 3. The references are incomplete/incorrect, particularly 1,2,4,5 and 9

Response: We have now corrected the references

Comment 4. The language /grammar needs attention. As this is a PDF document I could not do the corrections in track. They are too many/too significant for current publication

Response. We have edited grammar and spelling checks

Reviewer # 2

Comment 1: Is there any background data on the level on culture confirmation of lymph node TB in Ethiopia?

Response. Now we have included data on the level of culture and PCR confirmation in the background part. We indicate on page 3 line 12-15 of the text “A study conducted in four different sites reported that only 78% of TBLN cases were culture positive[6]. Diagnosis by PCR revealed
that 87.5% of TBLN cases identified by clinical and cytological criteria, were positive for mycobacterial DNA[7].”

**Comment 2:** Is there any background data on current diagnostic accuracy and outcomes for lymph node TB in Ethiopia?

**Response.** We found only one report with treatment outcome and included in the background part (line page 3 line 15-18). We now indicated in the text “According to study conducted in Northwest Ethiopia, successful treatment was achieved in only 24% of TBLN patients with total death rate of 5.2% [8].”

**Comment 3:** Were any drug resistant cases identified?

**Response.** We did not do drug resistance testing in this study. But according to our finding in one of our ongoing project we found 4% rifampicin resistance in TBLN cases.

**Comment 4:** Most cases of lymph node TB will be diagnosed in remote clinics or district hospitals not a tertiary center. How can the techniques identified here be of us if remote settings?

**Response.** According to Ethiopian context, most of patients suspected of having TBLN are referred to institutions were skilled professionals and facility for FNA cytology is available. In those settings, at least one of the methods we reported here exists. In addition ZN microscopy is available in most of health institutions in peripheral settings which will have positive impact on diagnosis.

**Comment 5:** Would it be sensible to conclude that the place for FNA is diagnosing pathology other than TB?

**Response.** We focused on the use of FNAC for TBLN and we do not have evidence for other pathologic conditions.

**Comment 6:** Is the outcome for the group of patients known and does this differ from the outcome of historical controls?

**Response.** We did not have any data on the outcome and we put as recommendation for future studies.