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Journal Name:	International Journal of TROPICAL DISEASE & Health
Manuscript Number:	2013_IJTDH_5966
Title of the Manuscript:	VALIDITY OF ACID-FAST SMEAR OF GASTRIC ASPIRATES FOR THE DIAGNOSIS OF CHILDHOOD PULMONARY TUBERCULOSIS AMONG HUMAN IMMUNODEFICIENCY VIRUS-INFECTED CHILDREN
Type of the Article	Original Article

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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.

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PART 1: Review Comments

	Reviewer's comment	Author's comment (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)
Compulsory REVISION comments	This is a cross-sectional study evaluating the diagnostic accuracy of acid-fast bacilli smear of gastric aspirates for pulmonary TB in HIV-infected and uninfected children. The topic is of importance, as there is a growing awareness of the importance of TB and TB-HIV in children. The majority of childhood TB diagnostic research is from resource-rich settings or from a few other isolated pockets, especially in South Africa. There is a need for additional evidence from other resource-limited settings. The study has a number of strengths. It is an appropriate study design for the research objective. It evaluates the diagnostic test among consecutive patients who are at risk for the disease of interest, which is the best design to use for this type of diagnostic question. The authors describe the methodology of the index and reference test in detail. The primary results of the index and reference tests are presented nicely in 2x2 contingency tables, allowing the readers to view it nicely. The authors highlight some important programmatic implications for the study in their discussion – namely the implications for reporting of childhood TB to National TB programmes, and loss of interest in the test. The authors should be commended for undertaking study in this important but challenging field. Despite this, I have a number of concerns which would need to be addressed in my opinion before this manuscript would be acceptable for publication. I would refer the authors to 3 important publications which they should conform to as much as possible or explain why they haven't. (Bossuyt PM, et al. The STARD Statement for Reporting of Diagnostic Accuracy: Explanation and Elaboration. <i>Ann Intern Med.</i> 2003; 138:W1-W12. This article provides guidance on the reporting of diagnostic accuracy studies) AND (Graham, S. M., T. Ahmed, et al. (2012). "Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification	Thanks for the encouraging comments. It is exhilarating to learn about the STARD publications, etc, all aimed at creating a specific place for diagnostic research which I am keen on. Guidelines should be reviewed regularly. These principles described in STARD, are upheld by post-graduate colleges, and they naturally come into consideration if a valid result is the research target. They were largely applied, though not fully documented, in this study. Most of the methodology documentation modifications have been effected. 1. HIV was prevalence 4.1%; TB incidence 133/100,000 per year, as at 2010. I'm happy you specified adult TB incidence. The detection system used by the national TB control programme cannot make a reliable statement on childhood TB incidence. 2. Hospital-based 3. All consenting children/parent who registered in the paediatric dept. and who satisfied the selection criteria. The age range of less than 10 years is a result, not a selection criterion. 4. Any of the criteria was enough for inclusion 5. We did not expect, and did not find significant interobserver variability in



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	of intrathoracic tuberculosis disease. Consensus from an expert panel." <i>J Infect Dis</i> 205 Suppl 2: S199-208. AND Cuevas, L. E., R. Browning, et al. (2012). "Evaluation of tuberculosis diagnostics in children: 2. Methodological issues for conducting and reporting research evaluations of tuberculosis diagnostics for intrathoracic tuberculosis in children. Consensus from an expert panel." <i>J Infect Dis</i> 205 Suppl 2: S209-215.) 1. Please add additional information about the study setting. What is the HIV-prevalence? What is the adult TB-incidence if known? Is this a primary, secondary, or referral level hospital? 2. Is this a hospital-based (inpatient) study or a community-based (outpatient) study? This is quite important for generalizing the results. 3. Please be more specific about the study population. Children were considered between what ages? 4. Please clarify regarding the inclusion criteria – Was the presence of any one criteria sufficient to be included, or 2 criteria were necessary, or some specific combination of criteria, etc.? 5. The smear results are the key outcome variable in the study. Since it is somewhat objective and their may be operator-dependence, please describe the expertise and training of the persons reading the slide. How many persons were involved in the reading of the smears? Was each slide read by a single person or by multiple people? If they were read by multiple people, how were disagreements handled? If each smear was read by multiple people, what was the between reader agreement (kappa)? 6. Please describe if the readers of the smears were blinded to the culture results and if multiple readers were used, to the other readers result? Presumably the culture results would be available much later than the smears, so this would not be an issue, but it should be clearly described. If the smear readers were aware of culture results that could introduce bias. Were the readers blinded to clinical information? I.e. were they aware of whether the child had been started on TB treatment, or why they had a sputum, etc.? 7. Line 118-120 says "specimens were collected from each patient every morning..." Can the authors clarify how many specimens were collected	detecting AFB. 6. Thanks. Blinding protocols described 7. Issue of number of specimens have been restated for clarity purposes. Increased number of per-child samples were, by our observation, influenced by inadequate compliance by mothers who fed their children few hours before 6:00am Nigerian time. It did not seem very interpretable comparing number of specimens required for AFB detection in the two groups. 8. Chi-square was used to compare smear positivities. On assumption of Central limit theorem, Z-test was used to compare the proportions(sensitivity, specificity and predictive values) 9. & 10. Thanks. Much modification has been done to the presentation of the findings. 11. Figure 1 is off 12. Thanks for raising my consciousness of flow diagram. The recommendation will be implemented in another study. Records were not created <i>ab initio</i> 13. Radiological classification of childhood TB as a yardstick for severity assessment in the sub-Saharan African environment is a conundrum. This is because of the various endemic childhood respiratory illnesses that have eroded the validity of all the diagnostic criteria including
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	from each patient and for how many days? Was this standardized? If not, the number of specimens should be reported in the baseline table, and some effort made to determine if this may have impacted the results – i.e. were HIV-infected patients more likely to have more specimens? Or were patients who ultimately had smear+ results associated with the number of specimens taken? 8. What specific statistical test was used to compare the diagnostic accuracy of smear in the 2 groups (HIV pos and neg)? Please specify. 9. In the results section some of the clinical and demographic characteristics are presented, but it is usual to present in a single table. Characteristics should be reported as number and percentage (i.e. not just %HIV pos, but number and %). Probably would be useful to include these characteristics stratified by HIV status (i.e. two columns – HIV-neg and HIV-pos). 10. I did not see any of the clinical characteristics presented, such as reason for eligibility (cough vs TB contact vs suggestive x-ray). 11. Please remove Figure 1 – it doesn't add anything to the description of the HIV results in the text. 12. A flow diagram of the patients would be very helpful and is strongly recommended. Do you know how many patients were screened for study eligibility? Were any patients eligible who were not enrolled in the study and why? Were any patients enrolled who do not provide specimens? Study results could also be shown in the same flow diagram. 13. The proportion of smear and culture positivity for TB will depend greatly on the severity and type of disease. Can you please specifically report on the severity and type of pulmonary TB in you study patients, stratified by HIV status? What proportion had cavitating disease? What proportion had extensive radiographic changes? Miliary TB? This is a very important piece of information. It may be that disease severity could be confounding the impact of HIV-status on smear-positivity, or alternatively could explain the impact of HIV-status on smear-positivity. This is very important for interpretation of the study results. 14. I don't think Table 4 adds much to the results and I would remove it. What statistical tests were used to determine the differences in sens	radiology and tuberculin tests. The diagnostic relevance of "history of contact" is also eroded by this environment. In our discussion, we recommended wider scale studies. Objective parameters for assessment of the effect of severe disease on the diagnostic yield of acid-fast smear in children could be built into the design from the onset. Since all the HIV-infected had clinically severe disease; and almost all of them had typical radiological signs, disease severity may well be the reason behind the effect of HIV, rather than a confounder. 14. Table 4 is off 15. Confidence intervals provided 16. Results and discussions separated. 17. That aspect of the discussion has been addressed. 18. Noted. see my introductory comments above 19. The spirit of this research design is strictly to assess the accuracy(sens and spec) of acid-fast smear in detecting culture-confirmed TB cases(HIV-infected vs HIV-uninfected)
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	and spec between HIV-pos and neg groups? 15. 95% confidence intervals should be provided for the calculation of sensitivity and specificity, as the presented values are only estimates which may differ from the true population value based on chance. 16. Please separate the discussion from the results with a section heading. 17. The detailed discussion of immunologic response to TB among HIV-infected persons from lines 303 to 359 should be substantially condensed and summarized in 1-2 sentences maximum. This part of the discussion is too long. 18. The authors should generally conform to the recommendations in the 2 articles from Journal of Infectious Disease referred to above wherever possible. Since these are relatively new recommendations that have come out since after the time this study was implemented, it may not be possible to conform to everything. The authors should state where they haven't been able to conform to these recommendations and why. 19. When referring to sens and spec of smear in this paper, it should be clear throughout that this is sens and spec of smear compared to culture-confirmed TB, as this will be much different compared with sens and spec of smear for all TB (culture-pos and culture-negative combined (i.e. probable PTB in children).	
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<u>Minor</u> REVISION comments	1. It would be recommended to use the term “diagnostic accuracy” in the title and/or abstract and as a key word, to make it easier to identify this study in electronic searches. Could use the term “diagnostic accuracy” instead of validity. (Refer to STARD recommendations) 2. The test methodologies are described in detail which is important. For non-microbiologists and for generalizability, please state whether these methods are in-line with the recommendations for doing these tests from WHO or CDC, and if not highlight where they differ? 3. Line 93 stating the number of children enrolled should be removed from the methods and included just in the results. 4. Please provide negative predictive values and positive predictive values for smears along with the sensitivity and specificities calculated. 5. Lines 221 and 231 refer to smear positive “rates”. A rate implies a unit of time should be included, and is the wrong epidemiologic term for the result here. The correct term should be used to describe these - proportions. 6. The background refers to a high burden of NTM in HIV-infected children. It is not clear whether NTM detected in cultures are pathogenic (disease causing) or are contaminants. It is likely that many are contaminants, and the background should clarify this.	Thanks. We’d retain “validity” in the title because validity connotes diagnostic test accuracy (sensitivity and specificity) and predictive values which were all assessed. Thanks for pointing out “rates”. Oversight! It’s been rectified.
<u>Optional/General</u> comments		