Reviewer’s report

Title: Prevalence and Risk Factors for Multidrug/Rifampicin Resistant Tuberculosis in Botswana

Version: 0 Date: 26 Aug 2018

Reviewer: Sanghyuk Shin

Reviewer’s report:

Overall, this is a well-written manuscript of prevalence and correlates of RR and MDR-TB in Botswana. However, there are a number of major limitations that should be addressed, including the inadequate description of DST testing practices during the study period and the eligibility criteria used for inclusion in the study. These need to be clarified to better interpret the DR-TB prevalence results.

Title

* Title should include that this is a study of TB patients suspected of having drug-resistant TB, which would affect prevalence estimates compared to study done among all TB patients.

Abstract

* In results and conclusions, the statement that more males than females had MDR-TB is technically correct, but misleading, as the proportions were similar to all TB patients included in the study. I suggest removing this text.

* In results and also throughout the manuscript, the word "development" is used to describe the prevalence of MDR-TB. "Development" implies that there are longitudinal data showing a susceptible TB case develop DR-TB over time. I suggest replacing the word "development" with prevalence or some other wording that is consistent with the study design.

Introduction

* Line 17. "Emergency" should be change to "emergence".

* Line 29. Define "RR-TB"

* Line 56. These mortality estimates are very high. It might reflect pre-ART estimates. Please add reference for these estimates. If it is an old reference, please update with more recent estimates (e.g. from the recent WHO Global TB Report).
Lines 33-49. I don't think listing this very long list of risk factors from the literature is helpful. I suggest organizing these into meaningful categories, such as individual risk factors for developing MDR-TB, risk factors for MDR-TB transmission, social risk factors, etc. Also, treatment failure and positive smear during treatment are not risk factors, but likely, consequences of inadequate treatment for undetected DR-TB. Focusing on baseline, pre-treatment factors associated with MDR-TB would be useful.

Methods

Study design and patient population. There are a number of details that are missing that are critical for interpreting DR-TB prevalence. 1) What was the practice of DR-TB testing at primary health facilities during the study period? For example, the interpretation of findings would be very different if there was universal testing for RR/MDR vs. if there was an algorithm (e.g. HIV-infected patients and previous hx of treatment) that determines who gets tested and who doesn't. 2) related to #1, "suspected drug resistant TB patients" were included in this study, but the definition of what constitutes "suspected" is not described. 3) Also related, there is no description of the eligibility criteria.

Describe the "census" in greater detail. How was it done? Did it include data from all public health facilities in Botswana? How many were there? I assume this was done by extracting data from the electronic TB register. Please describe this process.

The primary outcome variable, RR/MDR-TB, needs to be described in greater detail. For example, why were some patients tested with Xpert and others with LJ-DST? What was the standard of care that led to this difference? Justify why RR-TB and MDR-TB are combined. Are you including all DST results or just the baseline (pre-treatment) results? How did you handle discordance between Xpert and LJ-DST and between multiple time points (if multiple time points were included)?

Data analysis: p<=0.05 should be changed to p<0.05, which is the standard.

Multivariate logistic regression analysis: please describe how you selected variables for inclusion in the final model.

Age categorized at age 14 makes sense, but why was there no examination of multiple age categories?

Ethical consideration. Given that this was a medical records study, the data were not anonymized at the time of data collection. This term should be removed.

Results
If available, please indicate how many total TB cases were identified during the study period and, of these, what proportion was determined to be "suspected DR-TB".

Table 1. There appears to very high missing values for nearly all variables. Please add "missing" as a category. I am surprised that over 10% are missing age and 30% are missing HIV status. Botswana has a "opt-out" HIV testing policy so I would expect the missingness to be much lower. I suggest doing an analysis of reasons for missingness (e.g. certain health clinics did not collect the information) and explaining how this might have affected the results.

Figure 1. Please also included the % resistance figure separately by Xpert RR-TB results and LJ-DST results.

Table 2. Are these based on multivariable logistic regression analysis? If so, that should be described in the title. Also, all acronyms should be spelled out as a footnote. Please also include the effective N for this analysis, as missing results are typically excluded from statistical programs. The OR or p-value appears to be wrong for urban vs. rural. The 95% CI indicate significant overlap with 1 while the p-value is 0.008. Please correct this discrepancy. Also, P-value '0.000' should be changed to P-value <0.001. Lastly, please add the actual prevalence estimate in each category in this table or a separate table.

Discussion

Page 11. Lines 10-13. This may be too strong of a conclusion as the DR-TB survey of 2008 tested all baseline specimens while it is unclear how the testing practice and inclusion criteria may have impacted the prevalence estimates for this study.

Page 11. Lines 22-23. This is highly unlikely as GeneXpert was not widely implemented in Botswana at the time of the study, and population-level reduction in MDR-TB prevalence is not likely to occur very fast after Xpert implementation. In addition, I am not aware of any study that documents reduction of MDR-TB prevalence after Xpert implementation. If there are such studies, the authors should cite them.

Page 12. Lines 17-25. This finding is highly dependent on the testing practices at the time of the study. For example, if HIV-infected patients were more likely to get Xpert testing but more high risk HIV-uninfected patients were tested, we would likely observe an artificially higher DR-TB prevalence among HIV-uninfected persons. At present, it is not possible to adequately interpret this finding.

Page 13. Lines 11-19. This is not really "one possible explanation", but an established mechanism by which drug resistant TB develops in the context of inadequate treatment, etc. mentioned in the text preceding this sentence. I suggest removing this sentence or rewording it accordingly.
* Page 13. Line 27. Please check the OR of 1.16 which is not consistent with what is reported in Table 2.

* Page 13. Lines 42-50. In the methods, it is indicated that the residence of the patients were extracted. However, this section indicates that the rural/urban variable may reflect the location of the referral health center. Please clarify this discrepancy.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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