Reviewer's report

Title: High prevalence of multi-drug resistant tuberculosis in African children in a setting of high HIV prevalence

Version: 2 Date: 1 November 2010

Reviewer: Scott Heysell

Reviewer's report:

Title:
Minor essential revision--
The title can be made more specific to identify accurately the location and scope of the study.
Suggest: “High prevalence of multidrug-resistant tuberculosis in an HIV prevalent setting in Johannesburg, South Africa: a cross sectional study”

Discretionary revision--
Note also the placement of the hyphen in multidrug-resistant (the more accepted convention).

Abstract:
Discretionary revisions - -
In Methods section, it would be helpful to clarify what culture and drug-susceptibility methodologies were used. It would be important to clarify if outcomes were reviewed for all subjects or only those with MDR-TB, as well as specifically defining what outcomes were measured. Age range of children (inclusion criteria) should also be defined here.

Major revision--
In Results section, please clarify if “episodes of childhood TB” corresponds to subjects with TB or specimens- this is also unclear in the body of the manuscript. One assumes that the total denominator is cases of TB, and that any one case may have had multiple specimens positive for TB, but it is necessary to clarify this in order to assure an accurate prevalence.

Discretionary revisions--
Also, was the total number of children treated for TB from the two hospitals during this time period? It would be helpful to clarify the background burden of TB: of those started on TB treatment, the vast majority will be TB suspects based on clinical criteria, a smaller percentage will have adequate specimen collection, and given paucibacillary nature of pediatric TB, an even smaller fraction will have a positive TB culture (5-30% given age, pulmonary TB, specimen collection method etc.)
In Conclusions section, the statement that drug-resistant TB was of high prevalence in a population with a high burden of HIV infection suggests that HIV infected patients were statistically more likely to have drug-resistant TB, which was not found here. HIV infection has been associated with primary drug-resistant TB in other locations but it is misleading in this context.

Background:
Discretionary revisions--
Punctuation for sentences should follow numbered references unless otherwise specified by editor.

In 2nd sentence of second paragraph, would state Mycobacterium tuberculosis (MTB) and then MTB abbreviation can be used thereafter.

In second paragraph, can eliminate 3rd sentence on survey data from 2003-2005 as next sentence compares the 2005-2007 study with same survey from a decade earlier. Would be helpful to answer the question of how this study/paper differs from the Cape Town survey? What additional perspective should the reader expect? Also, would be relevant to cite the recent paper on pediatric XDR-TB in HIV-infected children from rural South Africa (Thomas et al. Int J Tuber Lung Dis, 2010).

Methodology:
Discretionary revision--
Clarify editorial specifications for subheading and indent/italicize etc. as appropriate.

Minor essential revision--
In the specimens that did not have GenoType MTBDRplus (“Hain”) testing, how was M. tuberculosis confirmed on positive specimens (differentiated from non-tuberculous mycobacteria)? Niacin accumulation/nitrate reductase?

Discretionary revision--
If possible, please clarify the protocol for MDR-TB treatment as mentioned- what “additional resistance patterns” would dictate use of kanamycin for instance over amikacin (~100% cross-resistance, similar toxicity), or perhaps capreomycin was the intended medication?

Major revision--
Again, in statistical analysis section, the first sentence can be more clear with regard to denominator calculation. For instance, if this is an accurate statement then a similar approach can be used: The total number of subjects with one or more positive culture was used as the denominator.

Discretionary revision--
Drug resistance, does not need to be hyphenated, while drug-resistant TB (as used as an adjective) should be hyphenated.
Clearance number can be eliminated from Ethics section.

Results:

Major revision--

The first sentence of the results presents a limitation that needs further clarification. It is leap to assume all cultures exclusively from lymph nodes (15% of all culture confirmed cases) were disseminated BCG. While described, and more common in HIV infected children, BCG is unlikely to account for that degree of positive specimens. The age of the child (<6 months) and the location of the lymph node (axillary) might make BCG more likely. Scofula is a common form of childhood TB and often diagnosis is made only from the lymph node. XDR-TB has been documented from lymph node aspirates from rural South Africa (Heysell et al, Emerg Infect Dis, 2010). Assuming that these lymph node aspirates were all drug-susceptible (not MDR-TB) then the overall prevalence would decrease. Could these cases be reviewed?

Discretionary revision--

Would make introductory statement of results discuss total number of cases treated for TB at both hospitals during the time period (if available) and if possible, determination of how many had specimens submitted for culture, and of those submitted, how many were positive for M. tuberculosis.

Minor essential revisions--

The method of specimen collection and yield from each method is interesting. For instance, is the statement that blood was positive in 16 cases (7.8%) suggest that in those subjects blood was the only fluid that was positive? If so, did those subjects also have sputum or gastric aspirate collected? This clarification should be made for the reader to understand the impact of this finding and assess the accuracy of the proposed prevalence of MDR-TB. Also, the yield of drug-resistant TB stratified by specimen source could be performed.

The reason for absence of drug susceptibility on some specimens should be stated.

Discretionary revisions--

When presenting median results (as done for CD4 count for instance), an interquartile range is more appropriate to describe when data is not normally distributed.

Continual comparison with CHBH and RMMCH is distracting unless there was specific hypothesis to be tested. Would suggest eliminating this comparison unless otherwise necessary.

Long paragraph of description of two cases of presumed acquired MDR-TB (following prior drug exposure) can be eliminated.

The final two paragraphs of the Results section can be condensed. It would be reasonable to report the deaths prior to the 12 month follow-up and then report...
the outcomes at 12 months only. To report the 6 and 12 month outcomes is redundant and not additionally informative. Table 4, can similarly be reported as baseline and 12 month follow-up outcomes.

Discussion:

Minor essential revisions--

The discussion within the first paragraph about the lack of MDR-TB contacts in household members is important and could be enriched. Is there any other evidence as to where this transmission was taking place? Were the MDR-TB children previously hospitalized? Could nosocomial transmission be playing a role (see Thomas et al, IJTLID 2010). If this information is not known, it would be important to clarify with a statement such as: lack of MDR-TB household contacts suggests transmission outside the home, but further epidemiologic patterns could not be ascertained.

The second paragraph is also an important discussion point, however, were those subjects with HIV more likely to be INH-(mono)resistant? Only MDR-TB compared to drug-susceptible TB, and may be worth comparing any INH resistance by HIV status in order to better inform the comment that IPT does not improve TB-free survival in HIV infected children. Similarly, it would be helpful to know in those with Hain testing and INH resistance, was this related to inhA and katG or both- in order to determine the prevalence of low-level or high-level of INH resistance (and consequent ability to overcome with high-dose INH therapy).

The third paragraph is also important point and could be better clarified—many in the field believe that susceptibility testing should be performed for all TB isolated in areas of high drug-resistant prevalence regardless of smear status or comorbidity, although much is resource dependent. Why then were susceptibility tests performed here, contrary to South African guidelines as suggested? This is critical for the reader to understand whether this was a guided study or whether or not a physician had to indicate an order for susceptibility testing where one would not have usually been performed. In other words, could those with susceptibility testing performed be biased toward patients at higher risk of drug-resistant TB?

Discretionary revisions--

Clarify the statement or cite, “future plans are to enhance the capacity for routine testing of all smear positive adult and paediatric specimens…” Whose future plans? DHLS? In Johannesburg or elsewhere?

With regard to the attributable mortality from MDR-TB, did the children that die have a longer time to culture diagnosis? Were those that died diagnosed only by culture and not the Hain test for instance?

In the third to last paragraph, regarding possible BCG lymphadenitis, a simple clarification would be to describe the pattern of resistance for those isolates. Previous comments regarding the exclusion of those isolates from analysis should be heeded.
Second to last paragraph- statements of primacy are not relevant. Also, p-value for lack of association with HIV infection can be inserted in results section.

Table 1. Again, not sure of value of comparing hospitals unless underlying epidemiological hypothesis. Would start with Table 2.

Table 2. Usually HIV infected, uninfected and unknown would be analyzed as categorical variable with HIV uninfected as referent. Also gender should be included as standard demographic variable.

Table 4. Condense to baseline and 12 month follow-up only.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.