Reviewer’s report

Title: A prospective study of socio-demographic, clinical characteristics and treatment outcomes of children with Tuberculosis in Sindh, Pakistan

Version: 2 Date: 30 Aug 2018

Reviewer: Simon Schaaf

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Review: A prospective study of socio-demographic, clinical characteristics and treatment outcomes of children with Tuberculosis in Sindh, Pakistan

The authors have done a lot of work to collect data on many children with TB and follow them up until the end of treatment. Although this study was a prospective study, data or special investigations remain incomplete, which unfortunately hampers the study (e.g. only 16% of children had respiratory specimens sent for bacteriology). It still is a worthwhile study, but the reviewer has a number of comments:

Major comments:

1. Background:
   - lines 52-55: delete sentence "An effective…of infection." It does not read well, repeats what is said in first sentence and does not add much
   - lines 63-70: These sentences need grammatical correction to make the message clear.

2. Methods:
   - Lines 83 and 93 has repetition: Suggest change to: (line 83) "This prospective observational study of TB in children less than 14 years of age was conducted over a period of 18 months. The study was conducted in public sector hospitals…Pakistan. (Add how hospitals were selected and then provide names of these hospitals)
   Children diagnosed with TB from 1 June 2016 through 30 November 2016 were consecutively enrolled and followed up monthly until the end of treatment. Children with drug-resistant TB and comorbidities were excluded. Verbal consent…"
   - The paragraph on statistics (lines 97-102) should follow after the paragraphs on data collection

3. Data collection:
   - line 109: As it is written here, Xpert MTB/RIF was repeated on follow-up visits, but this is not a test that is of value in follow-up once TB is confirmed. Was Xpert repeated on follow-up?
4. Diagnosis:
- lines 108-109; 122; 129-131: From the results it is clear that a very small proportion (16%) had bacteriological studies done (on sputum). It is not clear how these cases were selected and why it was not done in all patients (as it seems that these children all came to large hospitals). The problem is that this creates severe selection bias in the interpretation of these results (e.g. risk factors for unsuccessful treatment)

5. Results:
- The total number of children in the study is 508. It is not mentioned how many children were diagnosed with TB but excluded according to the exclusion criteria of drug-resistant TB (such as direct contacts of adult source cases with drug-resistant TB or only those few identified by drug susceptibility testing?) and TB with comorbidities (also not specified what this means). This needs clarification
- Could the numbers diagnosed at each hospital not be included in table 1 and deleted from the text - not well written and percentages should be added

6. Sociodemographic…
- Lines 157-170: There is a lot of repetition of numbers and percentages which is already in the table which should be deleted from the text - only a few main points should remain.
- lines 158-159: The median age with interquartile range would be a much better way of expressing the age than median and standard deviation - the latter is pushed upwards by a few older children while the median age is <5 years (from the table).
- lines 160-161: This percentage of underweight for age children makes me think that the CDC (US) Weight-for-Age charts may not be the most appropriate for the population. Why was the CDC charts chosen?
- lines 161-162: How was PTB and EPTB defined - did the one (PTB) override EPTB if both were present? In my experience it is very hard to believe that there were no children who had both PTB and EPTB. This could affect the number of cases with different forms of EPTB
- lines 163-167: It is very difficult to interpret the bacteriological results. The authors mention that "Among 508 patients, 5.7% were identified as smear-positive…" However, this is not correct, as looking at table 1, only 81 children had bacteriology done on sputum. No mention is made of any other respiratory specimens, such as gastric aspirates, and no mention is made of bacteriologically confirmed EPTB. This needs careful rethinking and should also be mentioned as a limitation to the study
- Line 170: How many children were tested for HIV? This is very important to include

7. Baseline symptoms…:
- Please add exact numbers and denominators (in how many cases were these symptoms evaluated). "Nearly half" and "Around" are not very scientific terms in results. What do the authors mean with "lethargic" - same definition as integrated management of childhood illness in which it is defined as awake but not responding to stimuli?

8. Laboratory values…& Table 2.
- If the numbers and percentages are presented in table 2, it should not be repeated in the text and in the view of the reviewer "nearly 95.7%" and "Approximately 23.2% and 36.8%" are unacceptable in scientific data presentation. What are the "higher" lymphocytes and ESR values compared to (higher means compared to)?
- In Table 2, Row of Haemoglobin: If the mean +/- SD of Hb is 13.95+/-.9, how is it possible that 95.7% of the children have anaemia or are the values of the anaemic group not provided? Are the authors really convinced that the haematological values which are so variable in this patient group are of any value in making a diagnosis of TB?
9. Association of socio-demographic…:
- The treatment for the different groups should actually be in the methods section - also add what percentage of the treatment should have been taken to classify patients as treatment completion (we all know that many patients miss doses and often >80% of doses over the treatment period is seen as "completion" - what was the norm in this study?). What should be presented in the results is how many (number plus percentage) completed 6 months or 8 months of treatment? Was treatment adapted for MDR-TB contacts?

10. Follow-up results:
- line 232: This is really an "unfair" comparison of before and after treatment, as children were in their rapidly growing period and weights before and after treatment were 6-8 (or more) months apart. I suppose you could mention this, but what would be more realistic is to indicate how many crossed percentiles upwards and that there was a reduction of children with weights <5th percentile after treatment

11. Discussion:
- The discussion should start with the main important findings of the study - such as the high percentage of children with TB of the total TB burden, the very young age of children with TB (recent transmission in the community) and the high rate of underweight for age in this cohort of children with TB. Despite this the outcomes were good (although need to acknowledge the possibility of overdiagnosis of TB in these children with such a high number of normal CXRs even in so-called PTB cases)
- Lines 239-241: This statement, even if possibly correct, should come much later after the case for this is made
- Lines 241-251: The reviewer is not at all convinced that female children are significantly more affected than male children - there was no statistics to demonstrate this nor was population data of how many female and male children there are in this setting presented. If female children in the population outnumber the male children by the same percentage in the population or more, then the difference is definitely not significant. Before all of this is addressed the discussion in these lines is purely speculation
- Lines 252-260: The young age is important - recent transmission. It is true that young children <2 years develop more disease after infection. The question could be asked how many of these children had known source cases, and if they had, was preventive therapy provided (should be discussed). What was the BCG coverage especially in these young children, as BCG stock-outs was a problem in many countries from about 2014.
- The reviewer has reservations about the value of haematology in TB diagnosis - abnormal white cell values also occur in pneumonia and so does ESR abnormalities
- Lines 353-354: Co-morbidities were supposed to be an exclusion criteria although the reviewer does not really know why this should be?
- Grammatical corrections needed in the discussion also

12. Tables 3 & 4
- The reviewer really does not understand the comparisons made in these two tables and what it is supposed to indicate - what is compared to what and what is the meaning thereof?
Minor comments:

1. Abstract:
   - line 25: delete "particular"
   - line 26: delete "so as" and "the"
   - line 28: delete "therefore"
   - line 29: add at end of sentence "with TB."
   - line 31: delete "in the present study"
   - line 40: add denominator "268/508 (52.8%)"; add "the" before majority
   - line 43: "and those who had contact with TB source cases"
   - line 45-46: …demonstrates the continuation of TB transmission in the study setting."

2. Background:
   - line 55: Write out "WHO" at first use in text; DOTS = "directly observed therapy, short-course"
   - line 56: I think the 85% has been increased in 2016 or 2017?
   - line 57: In UK English "programme" (check throughout manuscript)
   - line 59: add "treatment" before "cure"
   - line 61: Add percentage after 51000; delete "cases of"
   - line 62: Add "a" before "total"
   - line 78: Delete "so as"
   - line 79: Add "possible" before "risks"

3. Data collection:
   - line 104: A standardised…
   - line 107: …, level of education, …
   - line 107: household contact (if referring to contacts, then it is those in contact with the source cases)
   - line 108: …sputum smear microscopy for acid-fast bacilli (AFB)…
   - line 109: Add data to Xpert MTB/RIF (company of manufacture, city, country)
   - line 115: Body weight and age was used to determine weight for age using…. 
   - line 116: replace "by" with "of"
   - lines 116-117: <5th percentile; >95th percentile weight for age

4. Diagnosis:
   - line 121: write out TST at first use
   - line 123: Children who presented…were examined for TB (note additions). What about those with extrapulmonary TB?
   - line 126: TST was done using 5 tuberculin units (5 TU in 0.1ml?) - also add which company made this as well as city and country of manufacture
   - line 127: 10mm induration (?) add "induration" if this is what was measured
   - line 136: does "definitive diagnosis" refer to culture?
   - line 142 (and all other places in manuscript where defaulted/defaulters is used). Defaulter or default has been replaced by "lost to follow-up" and default has become an unacceptable term in TB
   - line 144: PTB patient who became smear-negative

5. Results:
   - line 169: If 72 had no BCG scar then it cannot be "around" 72?

6. Table 1:
   - Title: should include the province and country of study
- The EPTB percentages do not have a denominator of 508 but of 112 - not clear in table
- Retreatment usually referred to as previously treated cases (treated >1 month with any antituberculosis treatment)
- CXRs: How do the authors explain the large number of normal CXRs - most likely many of the EPTB cases were included in those that did not have a CXR done? How many of the CXRs that were "abnormal" were typical of TB? Who read the CXRs and how were these evaluated (methods)?

7. Risk factors…:
- lines 219-222: In the statistics section (methods) OR is described, what is COR?
- line 222: either "TB contact" or "TB source cases"
- lines 224-226: What is AOR and how does it differ from COR?
- The comparison of the smear-positives - are only those children who had sputum smear microscopy done compared or sputum-positives to the whole of the remaining group with PTB? Should mention as limitation the very small number of children who had sputum smear microscopy done - factor for serious bias

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

Yes

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

Unable to assess

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

No

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I recommend additional statistical review

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