Reviewer’s report

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

Version: 3 Date: 20 Oct 2018

Reviewer: Simon Schaaf

Reviewer's report:

Review: A prospective study of socio-demography…Pakistan

The revised version is much improved but the reviewer still has some concerns especially regarding the discussion - it is very long and tries to address issues which cannot be substantiated by the findings of the study. There are also multiple grammatical corrections necessary, which the reviewer will try to point out and suggest corrections.

Major comments:
1. Results: Lines 169-171: The reviewer is surprised that not a single child diagnosed with tuberculosis during the study period had drug-resistant TB or co-morbid disease, which were exclusion criteria - is this actually correct?
2. Table 1 (p9): Did none of the children with EPTB have pulmonary TB? It may also be that some children had PTB with EPTB? It is rare to see no overlap at all? Also in table X-ray should be "CXR"
3. L257: I have no idea what this sentence means - I do not believe that, while the large majority initially had weights <5th percentile, now suddenly after treatment >95% of these children have weight for age >95 percentile - this is what this sentence says?
4. Discussion: Lines 274-282: This whole discussion should be deleted as the authors did not find a significant difference between male and female paediatric patients. This discussion is NOT based on results of this study but is purely speculative!
5. Discussion lines 285-287: The higher rates in young children has to do with increased risk of developing disease after infection compared to older children, a high risk of being infected at a young age in a population with a high TB incidence and a broad base of young children in developing countries such as Pakistan. These arguments need to be added. Household members only transmit infection if they themselves have TB, so that is not the primary argument.
6. Discussion L289 and also several other places: Is it acceptable to refer to a study only by the reference? This looks very odd to the reviewer. Usually a study is referred to by the first author and then the reference is added?
7. Discussion L300-301: what do the authors men by "mirroring the distractedness to the child"? Are they implying that poor education means parents don't care about their children? This would be grossly unfair?
8. **Discussion L316-325:** This study was not done to show effectiveness of BCG. This whole discussion should be deleted as it has nothing to do with the study or study results other than that a few children did not have a BCG scar (which does not even mean that they did not receive BCG).

9. **Discussion: L367-371:** Delete these sentences as results showed this NOT to be significant on multivariate analysis - purely speculative.

10. **Table 3:** The reviewer does not see the reason for the statistical comparison between these groups. What do these "significantly different" p-values tell us? What did the authors try to show with these comparisons? Please explain.

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**Minor comments/suggested corrections:**

**Abstract:**
- P2, L43: "...and those who had known contact with TB…
- P2, L46: delete "the" (already in previous line)
- P2, L47-48: "adverse drug reactions and household contact with…” (lower case, delete abbreviation, delete "s" from contacts)

**Background:**
- L56: "The World…” and delete "the" before directly observed therapy, short-course (DOTS) (see style)
- L58: add "a" before "National"
- L64: add "the" before NTP
- L70-71: Change as follows: …presumptive TB cases go unrecognized, the diagnosed and treated cases are not reported to the NTP, or the…
- L77: risk factors of what - poor outcome? Then state as such
- L81: Can only describe a "trend" if you have previous values or have done the study over several time periods. Suggest "to describe the proportion of child TB cases of the total number of TB cases"
- L82: is the age group less than or equal to 14 years or less than 14 years? (it differs between lines 82 and 85)

**Methods:**
- L86: …in the following public sector… (add "the following")
- L112-113: The socio-demographic variables included: (corrected version)
- L116: Rewrite as follows: …of acid-fast bacilli (AFB) and Xpert MTB/RIF (Cepheid, NJ, USA)
- L118: relapse, lost to follow-up or failure (correct version)
- L119: delete "clinical" from laboratory results
- L122-123: antituberculosis treatment (ATT). Also delete "using" (repeated twice)
- L125 and 126: delete "s" in both "percentiles"

**Diagnosis:**
- L135-136: …history of TB contact, tuberculin skin test (TST), scoring…
- L137: on chest X-ray
- L139: drug-resistant… Children presenting…
- L141: extra-pulmonary
- L142: change "is" to "was"
Results:
- From 1st June...
- TB cases (not burden)
- Maximum number of were registered at LUMHS-CHH (145; 28.5%) compared to SGH-QH (15; 3%), SBGH-LH (22; 4.3%) and SBS-THM (52; 10.2%).
- Patients had pulmonary TB. Of EPTB cases, most cases (38.4%) had peripheral...
- MTB = M. tuberculosis (in italics). Also the sentence from line 185-187 is not clear: were all cases in whom a sputum smear was performed also sent for Xpert for documenting M. tuberculosis complex and screening for rifampicin resistance?
- replace "whereas" with "while"
- Seventy two (14.2%) had no BCG scar. HIV test was done in all children; none were HIV-positive.
- Caregivers of 37% of the patients complained of decreased physical activity.
- higher than what? Use "high" or "increased"
- higher compared to?
- were lost to follow-up
- "Of the retreatment patients 18 of 21 (86%) completed 8 months of treatment, while 2 died. Of the new cases 465/481 (96.7%) completed their 6 months treatment regimen, while 4 died.
- "Of the 6...
- patients with known TB contact (COR...) - same in line 251
- The doses of the drugs were adjusted…
- The majority…
- fr the 80% please give also number/denominator
- …end of the continuation phase.

Discussion:
- is one of few studies…the patient profiles and..
- study site (spelling) during the study period. (delete "time"). Delete "Beside this"
- the difference was not significant.
- What is the value of Pakistan rupees in US dollar for comparison?
- change has to have
- …cohort may have an association with their…
- This statement is very much debatable - where is the reference? Studies have both shown associations and no association with haematology therefore one could argue either way. Would the authors base a diagnosis of TB on haematological evidence?
- were lost to follow-up. …were lost to follow-up during…
- delete "psychological"
- If it is not significant then it is not significant! Delete "whereas females…lost to follow-up rates."
- Delete: "three (50%)…3-5 months." - already in results where this belongs
- replace calculates with determines
- L353: replace unformed with immature
- L355-356: TB, such as …meningitis is associated…mortality and is more frequent…
- L371-372: …is an important risk factor for TB in children.
- L377: Seven of the source cases had multidrug-resistant TB… (corrected style/spelling). Were the children in contact with these cases treated as having drug susceptible TB?

Limitations:
- L382: delete "ought to…the study"
- L387: …were not collected and thus…

Conclusions:
- L393-395: …indicates a high rate of TB transmission… The next sentence should be deleted as it does not make sense. Would change third sentence to read: This high transmission of TB in children needs urgent attention, as it means that TB in adults with infectious TB is not properly controlled. Lines 402-405 is also speculative and not findings of this study?

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

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:

Not suitable for publication unless extensively edited

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