PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Paediatric Tuberculosis in Singapore - A Retrospective Review
AUTHORS	Loh, Sin Wee; Thoon, Koh Cheng; Tan, Natalie Woon Hui; Li, Jiahui; Chong, Chia Yin

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Stephen Owens Institution and Country: Department of Paediatric Immunology and Infectious Diseases, Great North Children's Hospital, Royal Victoria Infirmary, Newcastle-upon-Tyne, UNITED KINGDOM Competing interests: None.
REVIEW RETURNED	24-May-2018

GENERAL COMMENTS	Clearly-written manuscript, outlining a straightforward but informative analysis of paediatric tuberculosis in Singapore since 2007. This is timely as incidence of disease is increasing over the last decade in Singapore and epidemiology is changing with respect to HIV and demographic factors. The only substantive criticism I would make is that the prevalence of multi-drug resistance among the cohort is not mentioned at all - this would be of interest to those working in the region. Minor suggestions: I don't think "CXR" is defined anywhere in the manuscript. Might it be better (and more accurate) to write "chest radiography" instead? In the abstract page 2, lines 36-39 it would be better and more accurate to state that stand-alone T-spot had better positive and negative predictive values for culture-positive disease compared to TST or TST/T-spot combined testing. On page 4 line 47, consider replacing "positive" with "suggestive". On page 6 lines 45-49 please space the figures in parentheses correctly. On page 7, lines 35-49, an attempt is made to consider outcomes of CNS TB in comparison to PTB and seperately to EPTB. This is somewhat clumsily done. I wonder if it might be better to stick with a simple comparison of PTB and EPTB and close with a line highlighting the particularly poor event-free survival observed in CNS disease (a single measure of survival without sequelae), perhaps in comparison to both non-CNS EPTB and PTB. This would make it clear that CNS disease accounts for almost all mortality and sequelae in EPTB.

	On page 9, lines 41-46, the authors state in relation to BCG vaccination that "children who received BCG vaccination might have less chance of contracting EPTB. Clinical trials are needed to further ascertain the protectiveness of the vaccination towards EPTB." I think that the role of BCG in reducing the risk of disseminated TB disease is already well-established? Thanks for the opportunity to review this manuscript.

REVIEWER	Reviewer name: Stefano Finazzi Institution and Country: Mario Negri Institute for Pharmacological Research, Italy Competing interests: None
REVIEW RETURNED	15-Jun-2018

GENERAL COMMENTS	* Case definition is apparently incoherent. In the METHODS section, TB cases are defined as cases with at least one positive test among TB culture, PCR or TB smear, tuberculin skin test, IGRA plus clinical diagnosis. However in the results, sensitivity/specificity/PPV, and NPV of non-microbiological test is studied assuming TB culture as gold standard. I expect that if there is a gold standard, this standard should be used to define cases across the whole paper. Defining as "cases" all patients with at least one positive test may introduce serious selection biases, if not all the test are reliable (as indeed shown in Table 3). * The analysis of sensitivity/specificity/PPV, and NPV is not presented in the Method Section. * In the analysis of Table 3 it seems that only patients defined as "cases" in the Method Section were included. However, to properly perform this analysis, one must consider also patients for which all tests were negative, otherwise True Negatives are extremely underestimated (in the limit case in which one analyzed the performance of a single test versus a gold standard, the choice of including only patients for which either the test or the gold standard were positive would imply that the number of True Negatives is exactly 0). * For continuous variables, it is not clear which test was used (Student T or Mann-Whitney U). In the Methods section the adjectives "parametric" and "non-parametric" refer to "data" whereas they should be referred to a statistic. Since the Student T is used to test the difference between two means and no means are reported for continuous variables, I guess that the difference between distributions of continuous variables was always tested using Mann-Whitney U. For the sake of clarity, I think that the adopted test should be specified for each continuous variable in Table 2. Minor comments: * CNS is not defined in the abstract * In the introduction, values of age-standardized incidence rate was reported. According to which age distribution was this datum standardized? * Significant weight loss was defined for a variation of 1kg. I suppose that a difference of 1kg has a very different meaning in a 3 years-old and in a 15 years-old patient. Maybe a relative weight variation is more appropriate to spot weight loss. * Abnormal CXR is not present in Table 1.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Stephen Owens)

1. Prevalence of multi-drug resistance (MDR-TB) among the cohort.

• There were no cases of MDR-TB in our cohort (stated on page 9 line 7). Definition of MDR-TB was defined as resistance to both rifampicin and isoniazid (stated on page 6 line 19-20). Data from Ministry of Health, Singapore, Communicable diseases surveillance 2016 also showed low MDR-TB rate of 0.4%.

2. Definition of CXR

• Defined as Chest X-ray on Page 5 Line 19.

3. “In the abstract page 2, lines 36-39 it would be better and more accurate to state that stand-alone T-spot had better positive and negative predictive values for culture-positive disease compared to TST or TST/T-spot combined testing”

• Section on accuracy of tests was removed from the manuscript as suggested by editor in chief.

4. On page 4 line 47, consider replacing "positive" with "suggestive".

• Amended on Page 5 Line 19.

5. On page 6 lines 45-49 please space the figures in parentheses correctly

• Amended accordingly, now on page 8 line 19-22.

6. On page 7, lines 35-49, an attempt is made to consider outcomes of CNS TB in comparison to PTB and separately to EPTB.

• Amended on page 9 line 14-18. The section was changed to compare outcomes between PTB and EPTB showing that mortality and sequelae rate were higher in the EPTB group. I have also stated that CNS TB accounted for almost all mortality and sequelae in EPTB group.

7. On page 9, lines 41-46, the authors state in relation to BCG vaccination that "children who received BCG vaccination might have less chance of contracting EPTB. Clinical trials are needed to further ascertain the protectiveness of the vaccination towards EPTB." I think that the role of BCG in reducing the risk of disseminated TB disease is already well-established?

• Amended on page 10 line 11-16. This section highlights the role of BCG in reducing the risk of EPTB shown in our study, similar to a cohort study in China (Page 10 Line 11-16).

Reviewer 2 (Stefano Finazzi)

1. Case definition is apparently incoherent. In the METHODS section, TB cases are defined as cases with at least one positive test among TB culture, PCR or TB smear, tuberculin skin test, IGRA plus clinical diagnosis. However in the results, sensitivity/specificity/PPV, and NPV of non-microbiological test is studied assuming TB culture as gold standard. I expect that if there is a gold standard, this standard should be used to define cases across the whole paper. Defining as "cases" all patients with at least one positive test may introduce serious selection biases, if not all the test are reliable (as indeed shown in Table 3).

• Section on accuracy of tests was removed from the manuscript as suggested by editor in chief.

• It is known that only 60% of paediatric TB are culture positive (1). By limiting the diagnosis of paediatric TB to those who were culture positive, it will limit the number of cases in the whole paper. All our patients had signs and symptoms and/or contact history compatible with TB disease.

2. In the analysis of Table 3 it seems that only patients defined as "cases" in the Method Section were included. However, to properly perform this analysis, one must consider also patients for which all tests were negative, otherwise True Negatives are extremely underestimated (in the limit case in which one analyzed the performance of a single test versus a gold standard, the choice of including only patients for which either the test or the gold standard were positive would imply that the number of True Negatives is exactly 0).

3. Section on accuracy of tests was removed from the manuscript as suggested by editor in chief.

4. For continuous variables, it is not clear which test was used (Student T or Mann-Whitney U). In the Methods section the adjectives "parametric" and "non-parametric" refer to "data" whereas they should be referred to a statistic. Since the Student T is used to test the difference between two means and no means are reported for continuous variables, I guess that the difference between distributions of continuous variables was always tested using Mann-Whitney U.

• Amended on page 7 Line 1-6. In this study, all continuous data were expressed as median and interquartile ranges. Differences between continuous data were analysed by Mann-Whitney test.

5. CNS not defined in the abstract.

• Amended on page 3 Line 15. Further definition was added under “case definition” section (Page 5 Line 21 to Page 6 Line 1): CNS TB (subset of EPTB) defined as TB meningitis or meningoencephalitis.

6. In the introduction, values of age-standardized incidence rate was reported. According to which age distribution was this datum standardized?

• The crude incidence rate of TB was 41.2 per 100,000 population in 2016. To better reflect changes in incidence rate of TB, after accounting for changes in population demographics, age-standardised rates for the incidence of TB have been reported from 2012 and onwards, using 2010 as the reference year. The age-standardised incidence rate of TB was 28.7 per 100, 000 in 2016 (2).

• In order to avoid confusion, the word “age-standardised” was removed from the manuscript.

7. Significant weight loss was defined for a variation of 1kg. I suppose that a difference of 1kg has a very different meaning in a 3 years-old and in a 15 years-old patient. Maybe a relative weight variation is more appropriate to spot weight loss.

• To better reflect weight variation, weight loss was further expressed as percentage of body weight at diagnosis (Page 6 line 8-9). There was no significant difference of percentage weight loss between PTB and EPTB (Table 1).

8. Abnormal CXR is not present in Table 1

• Added to Table 1.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Stephen Owens Institution and Country: Newcastle University Competing interests: None
REVIEW RETURNED	25-Jul-2018

GENERAL COMMENTS	Better, tighter and more plainly descriptive manuscript which better reflect available data. page 9; line 20: miliary not military. p19; table 2: types of immunodeficiency, third row - "primary immune deficiency"

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1 (Stephen Owens)

1. page 9; line 20: miliary not military

- Amended on page 8 line 19 of marked copy.

2. p19; table 2: types of immunodeficiency, third row - "primary immune deficiency"

- Amended