Diagnostic accuracy of clinical diagnostic scoring systems for childhood tuberculosis: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction Diagnosis of childhood tuberculosis (TB) poses several challenges. Therefore, clinical signs and symptoms, radiological studies, laboratory examinations, point-based scoring systems or diagnostic algorithms have been developed to improve diagnostic yields in this population. However, there are limited data on the diagnostic test accuracy of paediatric TB scoring systems. Therefore, this systematic review and meta-analysis aims to synthesise the available evidence on the diagnostic accuracy of childhood TB diagnostic scoring systems.

Methods and analysis This protocol describes a systematic review, developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Diagnostic Test Accuracy. We will conduct a comprehensive literature search for relevant articles in the following databases: PubMed, CINAHL, Embase, Scopus and Cochrane Databases. The eligibility criteria for studies will be formulated based on the Participants (Population), Index Test, Comparator Test and Target Condition criteria for the review question. The index test will be defined as any attempt to diagnose childhood TB using either a scoring system or a diagnostic algorithm, whereas a composite reference standard will be used as a reference standard. This will include any attempt to confirm diagnosis of TB. Where bacteriological confirmation is not obtained and there are at least two of the following features: chest radiograph consistent with TB, immunological evidence of Mycobacterium tuberculosis infection and/or positive response to TB treatment will also be considered. The QUADAS-2 Tool will be used to assess the quality of the studies. The diagnostic accuracy measures (ie, sensitivity, specificity, negative predictive and positive predictive values) will be pooled with the random-effects or fixed-effects models, as appropriate. All statistical analyses will be performed using the Review Manager V.5.4.

Ethics and dissemination This research is exempt from ethics approval given that this is a protocol for a systematic review, which uses published data. The findings from this review will be disseminated through peer-reviewed publications and scientific conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study does follow the guidance offered by Preferred Reporting Items for Systematic Reviews and Meta-analyses of Diagnostic Test Accuracy.
⇒ The study did consider a composite reference standard, which tries to atone for lack of a gold reference standard.
⇒ Most of the included studies did use a different reference standard, this makes the results less generalisable.
⇒ Only original studies with enough data to construct a standard two-by-two diagnostic table were included.
⇒ We excluded editorials, letters to the editor, conference abstracts and presentations since they were deemed not to have enough data.

BACKGROUND

Tuberculosis (TB), caused by Mycobacterium tuberculosis complex, is an infectious disease of global public health significance causing major ill health and one of the leading causes of death worldwide (ref). In 2020, there was an estimated 10 million people who developed TB worldwide.1 Children and young adolescents aged under 15 years represented an estimated 11% of all these cases. This means 1.1 million children became ill with TB,3 however, in 2020, only 399 000 (36.27%) were notified.1 The rest were either undiagnosed, misdiagnosed or not reported. Approximately every one in five children (<15 years) who developed the TB lost their lives in 2020.1 A modelling study showed that 96% of TB deaths in children occur in children not receiving appropriate treatment for TB.3

The diagnosis of TB in children is missed due to several reasons. First, the symptoms of childhood TB are non-specific and tend to overlap with other common childhood illnesses such as pneumonia, HIV-associated lung diseases and malnutrition.4 Hence, on
clinical basis, most children with TB are not presumed. Moreover, even when presumed, there are difficulties in collecting suitable samples to confirm the isolation/identification of *M. tuberculosis*. If a sample is collected, the available diagnostic tests, when available, have a low diagnostic accuracy, because children have few bacilli to be detected by the currently available diagnostic tests.

The sensitivity of *M. tuberculosis* culture, the gold standard of diagnosis, rarely exceeds 30%–40%. Therefore, confirming childhood TB is the exception, not the norm. Because of the challenges in diagnosing childhood TB, individual clinical signs and symptoms, radiological studies, laboratory examinations, point-based scoring systems and/or diagnostic algorithms have been developed to aid in the diagnosis.

The first diagnostic scoring system for childhood TB was developed in 1969 and since then there have been several models with various iterations. Their major objective has been to provide a consistent and accurate way to diagnose childhood TB, especially in resource-limited settings. Although the diagnostic scoring systems for childhood TB having been used for over 53 years, their validity and reliability remain unclear. Different diagnostic scoring systems have been used in different locations, and may not have been validated. There is also limited literature on the validation of diagnostic scoring systems among malnourished or children coinfected with HIV and TB.

The last reviews of diagnostic scoring systems for childhood TB called for a consistent inclusion criterion and for the diagnostic systems to be validated in multiple geographical locations as well as patient populations. They also found very few studies that attempted to validate the diagnostic scoring systems. Since the last review was 10 years ago, we are setting out to systematically review the diagnostic accuracy of childhood TB diagnostic scoring systems.

**Objectives**

**Main objective**

To review the diagnostic accuracy of childhood TB diagnostic scoring system.

**Specific objectives**

1. To review evidence on the available childhood TB diagnostic scoring systems currently being used globally.
2. To review the sensitivity and specificity of the childhood TB diagnostic scoring systems.

**METHODS**

**Protocol and registration**

We shall develop, conduct and report this review following Preferred Reporting Items for Systematic Reviews and Meta-analyses of Diagnostic Test Accuracy. The protocol has been registered on PROSPERO (CRD42022367049)

**Eligibility criteria**

The eligibility criteria for studies have been formulated based on Participants (Population), Index Test, Comparator Test and Target Condition (PICT) for the review question. We will include studies that evaluated the diagnostic test accuracy of childhood TB scoring systems in terms of sensitivity and specificity, against a reference standard. Given that childhood TB has an imperfect reference standard, we shall use a composite reference standard (CRS), which will include microscopy, culture, chest radiography and tuberculin skin test. The participants will comprise children less than 15 years with presumptive TB who underwent a diagnostic TB scoring test or TB diagnostic algorithm. Only original studies in the English Language published until 30 September 2022, which describe their methods and report enough data for the construction of the standard two-by-two table will be included.

We shall include peer-reviewed prospective or retrospective cohort studies, cross-sectional studies, interventional and case–control studies that address the review question. Editorials, letters to the editors and conference abstracts will be excluded since they have insufficient information required for conducting the review.

**Index test**

The index test is any attempt to diagnose childhood TB using either a scoring system or a diagnostic algorithm. These often take into consideration the individual clinical signs and symptoms, radiological studies and laboratory examinations, which are used to construct a point-based scoring system or a diagnostic algorithm.

**Reference standard (comparator test)**

Any attempt to confirm a diagnosis of TB will be used as a reference standard. This will not be limited to Sputum Culture, GeneXpert MTB/RIF or Ultra and TB LAM given that TB does not have an ideal reference standard. We shall also consider unconfirmed TB as defined by Graham et al where bacteriological confirmation is not obtained but there are at least two of the following features: chest radiograph consistent with TB, immunological evidence of *M. tuberculosis* infection or positive response to anti-TB treatment. These tests will be used to calculate a CRS from patients with confirmed TB. While the target condition is intrathoracic childhood TB.

**Search strategy**

We will conduct a systematic search for relevant articles in the following databases: PubMed, CINAHL, Embase, Scopus and the Cochrane Database. The search strategy will include the following keywords: “pediatric tuberculosis”, OR “paediatric tuberculosis” OR “pediatric TB” OR “Paediatric TB” OR “childhood tuberculosis”, OR “childhood TB” AND “diagnostic accuracy” OR “sensitivity” OR “specificity” AND “algorithm” OR “score” OR “clinical score” OR “diagnostic score”, OR “diagnostic screen”. Furthermore, we shall also conduct a free-hand search for relevant articles in the references section.
of articles included in the review to avoid missing the eligible studies. We will include studies published up to 30 September 2022.

Data screening and extraction

The search results will be exported into Zotero. A research tool to collect, organise and manage research publication. Then transferred to Rayyan Artificial Intelligence Software for Systematic Reviews and Meta-analyses, which will be used to screen titles followed by abstracts. Our review team comprising of three members (FB, RO and MK) will independently review all the studies from the search and additional resources, which they will code as ‘include’, ‘exclude’ or ‘maybe’. The fourth reviewer JBB who was blinded to decisions of other reviewers. Will thoroughly review the disagreements between the other reviewers and make a final decision.

All the studies deemed eligible studies will be transferred back to Zotero. Where full-text articles of narrowed down abstracts will be assessed for inclusion using the PICT questions and inclusion criteria. Screened studies will be placed into appropriate subfolders created in Zotero based on decisions to include or exclude and the various subcategories.

Final data will be extracted from the included studies into an Excel spreadsheet. The following information will be extracted (if available): authors, year of publication, age distribution, study design, the diagnostic score, reference standard, country, sample size, setting and outcome measures recorded, that is, sensitivity and specificity. In case of any missing data, the authors of the study will be contacted for additional information. If they do not respond to the query, then those studies will be excluded.

MK and FB will independently extract the data, and RO and JBB will check the extracted data to ensure there is completeness and accuracy. On disagreements, all four reviewers will review the final extracted data, and disagreements will be resolved through discussion on inclusion and exclusion criteria via the majority’s decision.

Risk of bias

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 tool will be used to assess the methodological quality of all studies to be included in this systematic review. QUADAS-2 consists of four key domains: patient selection, index test, reference standard, and flow and timing. We shall assess all the domains for risk of bias potential using different signalling questions and the first three domains for applicability concerns. Based on this, the risk of bias will be judged as ‘low’, ‘high’ or ‘unclear’.

Summary of results of QUADAS-2 for all included studies will be presented in a tabular and graphical display generated via Review manager V.5.4. Two reviewers MK and FB will independently assess the risk of bias and the quality of the study. Disagreements between the authors will be resolved by further discussion and consensus with other researchers.

Statistical analysis and data synthesis

We shall extract data from studies to construct a standard two-by-two table used to calculate sensitivity and specificity. The analyses shall be conducted in R software V.4.0.2 using R package ‘mada’ V.0.5.8. While bivariate analysis will be done using the ‘reitsma’ command from R package ‘mada’ to obtain hierarchical summary receiver-operating characteristics (HSROC) parameters, which will then be used in Revman to obtain HSROC curve.

The studies will then be grouped based on (A) the diagnostic score, (B) setting, (C) HIV status and (D) risk of bias, that is, low or high. A random effects model will be used to calculate pooled sensitivity and specificity using Review Manager (Revman) V.5.4 if there is substantial heterogeneity. Otherwise, fixed effect models will be employed. Higgins’ I² will be used to measure heterogeneity (I²>50% indicating substantial heterogeneity).

Ethics and participant consent

This research is exempt from ethics approval given that this is a protocol for a systematic review, which uses published data.

The patient and public involvement statement

The is no patient involvement and there will be no patient involvement over conducting this study.

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