WHO consolidated guidelines on tuberculosis

Module 5: Management of tuberculosis in children and adolescents

Web Annex 4. Summaries of unpublished studies

World Health Organization

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WHO consolidated guidelines on tuberculosis

Module 5: Management of tuberculosis in children and adolescents

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Contents

PICO 2a: Integrated treatment decision algorithms for children with presumptive TB aged below 10 years

Performance of treatment-decision algorithms for children being evaluated for pulmonary tuberculosis: an individual participant data meta-analysis

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Introduction

Existing WHO guidance on the management of children with tuberculosis for whom bacteriologic evidence is unavailable is nonspecific.[1] There is no attempt to provide weight to specific evidence from the clinical evaluation or to offer specific decision points in the work-up of presumptive cases. Thus, healthcare workers are left with little guidance on how to put this evidence together to come up with a diagnosis; this results in heterogeneous practice depending on healthcare worker expertise and access to diagnostic tools. Integrated treatment-decision algorithms/scores aim to provide a solution that may standardize the evaluation of children with presumptive tuberculosis. Algorithms/scores provide practical guidance to make treatment decisions for children with presumptive tuberculosis and may empower healthcare workers, especially at peripheral health centers.[2]

We aimed to investigate the following PICO question: ***In children aged below 10 years with presumptive pulmonary TB attending healthcare facilities, should integrated treatment-decision algorithms be used?*** Given that there have been no published prospective evaluations of algorithm performance, we developed an individual participant data (IPD) meta-cohort consisting of diagnostic evaluations data from children aged <10 years to infer the sensitivity and specificity of treatment-decision algorithms/scores at identifying pulmonary tuberculosis.

Methods

This analysis used diagnostic evaluations IPD to infer the performance of several algorithms/scores at discriminating tuberculosis from non-tuberculosis using the U.S. National Institutes of Health (NIH) reference classification for intrathoracic tuberculosis.[3] Studies were eligible to share data for this analysis if they consecutively enrolled children <10 years old presenting passively to healthcare

facilities with symptoms suggestive of pulmonary tuberculosis. Given limited time to synthesize and analyze data for this analysis, it was not possible to do a systematic review; thus, we sourced IPD from a smaller number of studies carried out within a geographically diverse set of high tuberculosis-burden countries. We assessed risk of bias among each study using the QUADAS-2 tool.

We estimated study-level sensitivity and specificity of each algorithm/score, and produced estimates of their pooled sensitivity and specificity among the entire IPD meta-analysis cohort. We demonstrated algorithm/score sensitivity and specificity in classifying tuberculosis against the Union Desk Guide Algorithm, an attempt to operationalize the 2014 WHO guidance by outlining the steps a healthcare worker should take in evaluating a child with presumptive pulmonary tuberculosis.[4] In order to make full use of the data available to compare performance of these algorithms in different settings, we imputed for missing variables, collapsed heterogeneous definitions of variables, and made slight modifications to the algorithms/scores to use the variables available in the IPD meta-analysis cohort. We assessed the certainty of evidence as recommended using the GRADE approach in GRADE evidence tables.

Results

We identified 18 studies, of which four were excluded for not sufficiently meeting eligibility for analysis or for being unable to share IPD in the necessary timeframe. This resulted in 14 studies included with 5,494 IPD records, of which 4,811 IPD records had sufficient information to be included in this analysis. The entire meta-analysis cohort had a median age of 26 months IQR [13.4–58.3]; 38% of the children had tuberculosis, of which 30% was bacteriologically confirmed; 20% were living with HIV; and 14% were severely acutely malnourished. Most studies recruited inpatients from tertiary health centers, and only two studies recruited participants from only outpatient settings. Many studies were assessed as having a high risk of bias for the index test due to the need for imputation, and several studies were assessed as high or unclear risk of bias with respect to the reference standard as they did not use the updated NIH reference classification.

The Uganda National TB/Leprosy Control Program (NTLP) Algorithm had a 19% greater pooled sensitivity and a 25% reduced pooled specificity as compared to the Union Desk Guide Algorithm. The Stegen-Toledo Score (using a cutoff score of at least 5 as consistent with tuberculosis) had an 8% reduced pooled sensitivity and a 20% greater pooled specificity as compared to the Union Desk Guide Algorithm. Among the children living with HIV (excluding children from the study from which this algorithm was developed), the Marcy et al., 2019 Algorithm had a 7% reduced pooled sensitivity and a 21% greater pooled specificity as compared to the Union Desk Guide Algorithm. The Marais et al., 2006 Criteria had a 47% reduced pooled sensitivity and a 24% greater pooled specificity as compared to the Union Desk Guide Algorithm. The Keith Edward Score had a 28% greater pooled sensitivity and a 47% reduced pooled specificity as compared to the Union Desk Guide Algorithm. Among HIV-negative children (excluding children from the study from which this algorithm was developed), the Gunasekera et al., 2021 Algorithm had a 38% greater pooled sensitivity and a 67% reduced pooled specificity as compared to the Union Desk Guide Algorithm. The Brazilian Ministry of Health (MoH) Child PTB Scoring System (using a cutoff score of at least 30 as consistent with tuberculosis) had a 23% greater pooled sensitivity and a 24% reduced pooled specificity as compared to the Union Desk Guide. The certainty of evidence was graded as very low for all comparisons.

Discussion

We used prospectively collected, diagnostic evaluations IPD estimate the performance of widely cited algorithms/scores to support the evaluation of children <10 years presenting to healthcare with presumptive pulmonary tuberculosis. To our knowledge, this investigation into the performance of diagnostic algorithms/scores for childhood pulmonary tuberculosis is the largest to date. We observed study-level heterogeneity in algorithm/score performance, especially with respect to specificity.

Though we were unable to investigate this rigorously due to the limited number of studies included, differences in the healthcare level and geographic location from which individual participants were recruited may contribute to differences in algorithm performance.

Though these findings are limited by missing variables and heterogeneity in the reference classifications, this demonstrates that algorithms/scores may provide a useful tool to standardize the evaluation of and rapid treatment decision-making for children with presumptive pulmonary tuberculosis at peripheral health centers. Further work is necessary to investigate the acceptability and implementation of this tool that may empower healthcare workers to make treatment decisions for children being evaluated for childhood pulmonary tuberculosis, which may ultimately reduce the burden of childhood mortality.

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PICO 2b: Xpert MTB/RIF Ultra assay for pulmonary tuberculosis and rifampicin resistance in children: summary of the systematic review

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Background

We previously published a Cochrane Review assessing the diagnostic accuracy of Xpert MTB/RIF and Xpert Ultra for active tuberculosis in children (Kay 2020).[1] For pulmonary tuberculosis, for Xpert MTB/RIF we identified studies using sputum, gastric aspirate, nasopharyngeal aspirate, and stool; however, for Xpert Ultra we only identified studies using sputum and nasopharyngeal aspirate. For sputum specimens, Xpert Ultra pooled sensitivity and specificity verified by culture were 72.8% (95% confidence interval (CI) 64.7% to 79.6%) (3 studies, 136 participants; low-certainty evidence) and 97.5% (95% CI 95.8% to 98.5%) (3 studies, 551 participants; high-certainty evidence). For nasopharyngeal aspirate, Xpert Ultra sensitivity and specificity (95% CI) were 45.7% (95% CI 28.9% to 63.3%) and 97.5% (95% CI 93.7% to 99.3%) (1 study, 195 participants).

The current review update assessed the diagnostic accuracy of Xpert Ultra in gastric aspirate (lavage) and stool for the diagnosis of pulmonary tuberculosis and rifampicin resistance in children 0 to 9 years of age with signs and symptom of tuberculosis.

Methods

Methods are described in detail in Kay 2020.

[1] Kay AW, González Fernández L, Takwoingi Y, Eisenhut M, Detjen AK, Steingart KR, Mandalakas AM. Xpert MTB/RIF and Xpert MTB/RIF Ultra assays for active tuberculosis and rifampicin resistance in children. Cochrane Database of Systematic Reviews 2020, Issue 8. Art. No.: CD013359. DOI: 10.1002/14651858.CD013359.pub2

Selection criteria

We searched multiple databases to 27 January 2021 without language restriction. We included cross-sectional and cohort studies. For pulmonary tuberculosis, the reference standards comprised a microbiological reference standard (MRS, solid or liquid culture) and a CRS. The MRS for stool included Xpert MTB/RIF or Xpert Ultra results in a respiratory specimen in addition to culture. The CRS was defined as a positive test by culture or a clinical decision to initiate treatment for tuberculosis. For rifampicin resistance, the reference standards were culture-based phenotypic drug susceptibility testing and MTBDR*plus*.

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias and applicability using the Quality Assessment of Studies of Diagnostic Accuracy – Revised (QUADAS-2). We also requested data directly from the primary study authors. We used the bivariate model to estimate pooled sensitivity and specificity with 95% CIs. We stratified analyses by age group, type of specimen, and type of reference standard. We investigated potential sources of heterogeneity by nutrition and HIV status. We considered an Xpert Ultra trace result as positive (*Mycobacterium tuberculosis* detected) (WHO Xpert Ultra 2017; WHO Consolidated Guidelines (Module 3) 2020).

We assessed the certainty of evidence using the GRADE approach.

Results

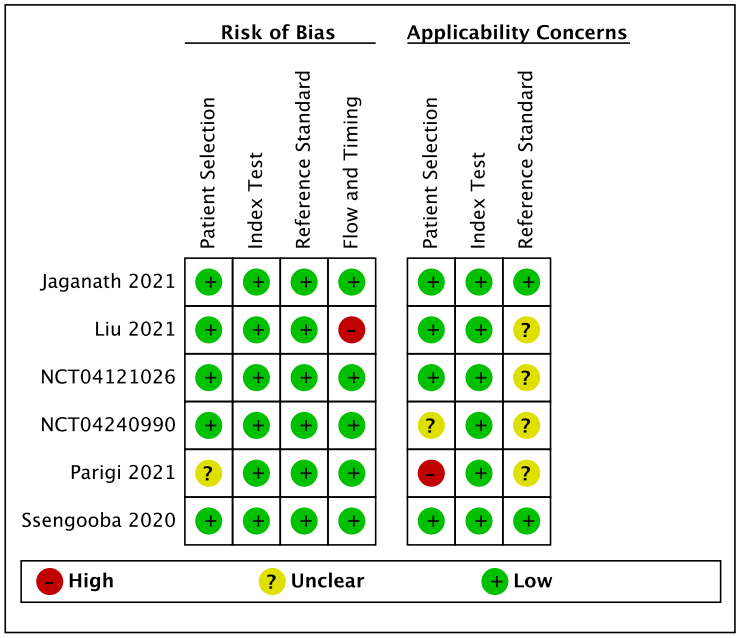
For pulmonary tuberculosis detection, we identified nine studies: gastric aspirate or lavage (3 studies); stool (3 studies); both gastric aspirate and stool (3 studies). Of the total nine studies, four studies (44%) took place in high tuberculosis burden and five (56%) in high TB/HIV burden countries. All nine studies verified pulmonary tuberculosis using MRS. Three studies evaluated gastric specimens and two studies evaluated stool specimens using CRS. Table 1 describes characteristics of the included studies. We did not identify any studies that evaluated Xpert Ultra for rifampicin resistance.

Methodological quality of included studies

Xpert Ultra in gastric aspirate specimens

We considered whether the findings of the included studies were at risk of bias and if there were concerns that the findings might not apply to the use of Xpert Ultra in standard practice. We judged most studies at low risk of bias in all four QUADAS-2 domains: patient selection, index test, reference standard, and flow and timing. Regarding applicability for patient selection, we judged low concern for most studies. Regarding applicability for the index test, we judged low concern for all studies (100%) owing to use of the standard method for processing Xpert Ultra in gastric specimens. Regarding applicability for the reference standard (assessed for studies with respect to culture), we judged low concern for two studies and unclear concern for four studies (67%) because in these studies, we could not tell whether isolates were confirmed as *Mycobacterium tuberculosis* complex.

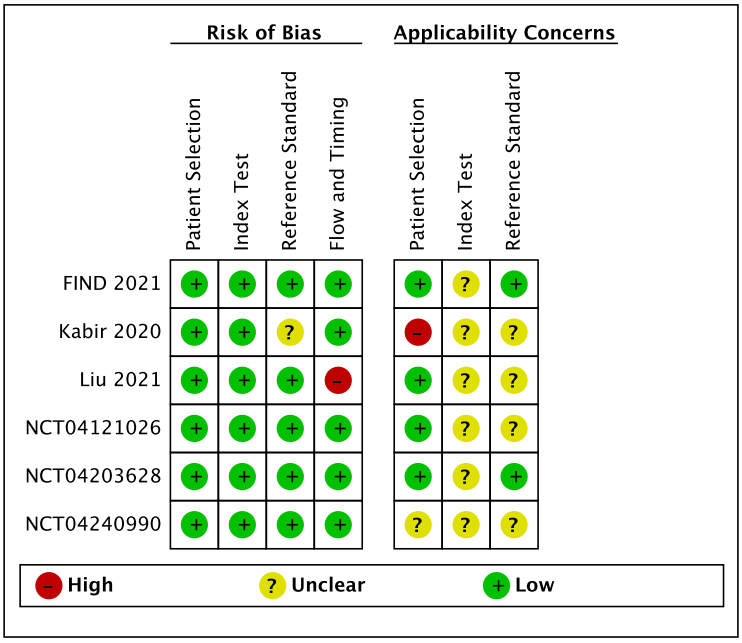
Figure 1. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study, gastric aspirate specimens



Xpert Ultra in stool specimens

We judged most studies at low risk of bias in all four QUADAS-2 domains. Regarding applicability for patient selection, we judged low concern for most studies. Regarding applicability for the index test, we judged unclear concern for all studies (100%) because there is no established technique for stool processing prior to performing Xpert Ultra. Regarding applicability for the reference standard (assessed for studies with respect to culture), we judged low concern for two studies and unclear concern for four studies (67%) because in these studies, we could not tell whether isolates were confirmed as *Mycobacterium tuberculosis* complex.

Figure 2. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study, stool specimens



Xpert Ultra trace results

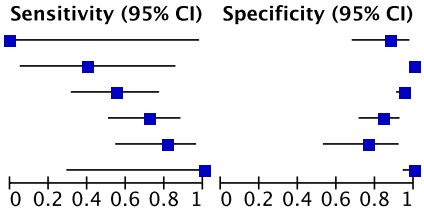
Of the total nine studies, eight (89%) reported the number of Xpert Ultra positive results that were trace results. In these eight studies, of the total Xpert Ultra positive results, the proportion (expressed as a percentage) of Ultra trace results ranged from 0% to 66% (median 52%) in studies evaluating gastric specimens and from 0% to 84% (median 52%) in studies evaluating stool specimens.

PICO question 2b pulmonary tuberculosis, children

Should Xpert Ultra in gastric aspirate be used to diagnose pulmonary tuberculosis in children aged below 10 years, against a MRS? Xpert Ultra pooled sensitivity and specificity (95% CI) were 63.6% (47.7 to 77.0) and 94.9% (CI 83.8 to 98.5), (6 studies, 659 participants; moderate-certainty evidence). *For a population of 1000 children where 100 have pulmonary tuberculosis on culture, 109 would be Xpert Ultra-positive: of these, 64 would have pulmonary tuberculosis (true-positives) and 45 would not have pulmonary tuberculosis (false-positives); 891 would be Xpert Ultra-negative: of these 855 would not have pulmonary tuberculosis (true-negatives) and 36 would have pulmonary tuberculosis (false-negatives).*

Figure 3. Forest plots of Xpert Ultra sensitivity and specificity for pulmonary tuberculosis in children aged below 10 years using gastric aspirates against a MRS. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. TP: true-positive; FP: false-positive; FN: false-negative; TN: true-negative

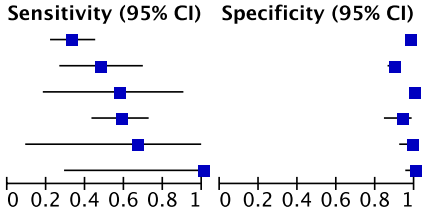
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Jaganath 2021	0	3	1	21	0.00 [0.00, 0.97]	0.88 [0.68, 0.97]
NCT04240990	2	1	3	215	0.40 [0.05, 0.85]	1.00 [0.97, 1.00]
Ssengooba 2020	11	12	9	203	0.55 [0.32, 0.77]	0.94 [0.90, 0.97]
Liu 2021	18	9	7	46	0.72 [0.51, 0.88]	0.84 [0.71, 0.92]
Parigi 2021	13	5	3	16	0.81 [0.54, 0.96]	0.76 [0.53, 0.92]
NCT04121026	3	0	0	58	1.00 [0.29, 1.00]	1.00 [0.94, 1.00]



Should Xpert Ultra in stool be used to diagnose pulmonary tuberculosis in children aged below 10 years, against a MRS? Xpert Ultra pooled sensitivity and specificity (95% CI) were 52.8% (35.0 to 69.9) and 98.0% (93.4 to 99.4), (6 studies, 1279 participants; moderate-certainty evidence). *For a population of 1000 children where 100 have pulmonary tuberculosis on culture,71 would be Xpert Ultra-positive: of these, 53 would have pulmonary tuberculosis (true-positives) and 18 would not have pulmonary tuberculosis (false-positives); 929 would be Xpert Ultra-negative: of these, 882 would not have pulmonary tuberculosis (true-negatives) and 47 would have pulmonary tuberculosis (false-negatives).*

Figure 4. Forest plots of Xpert Ultra sensitivity and specificity for pulmonary tuberculosis in children aged below 10 years using stool against a MRS. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. TP: true-positive; FP: false-positive; FN: false-negative; TN: true-negative

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
FIND 2021	23	8	47	313	0.33 [0.22, 0.45]	0.98 [0.95, 0.99]
Kabir 2020	11	40	12	339	0.48 [0.27, 0.69]	0.89 [0.86, 0.92]
NCT04240990	4	1	3	226	0.57 [0.18, 0.90]	1.00 [0.98, 1.00]
Liu 2021	28	4	20	57	0.58 [0.43, 0.72]	0.93 [0.84, 0.98]
NCT04121026	2	1	1	65	0.67 [0.09, 0.99]	0.98 [0.92, 1.00]
NCT 04203628	3	0	0	71	1.00 [0.29, 1.00]	1.00 [0.95, 1.00]



Children living with HIV and those with severe malnutrition or pneumonia

Gastric aspirate: children living with HIV: 4 studies, 99 participants (8 with tuberculosis); children with severe malnutrition: 4 studies, 259 participants (9 with tuberculosis).

Stool: children living with HIV children: 2 studies, 100 participants (3 with tuberculosis); children with severe malnutrition: 3 studies, 428 participants (19 with tuberculosis). The paucity of data meant we could not perform meta-analyses. No studies were identified that evaluated Xpert Ultra in gastric aspirate or stool in children with severe pneumonia.

Table 1. Characteristics of included studies

Study	Countries	High TB burden/ high TB/HIV burden	Clinical setting	Type of specimen	Study design	Patient selection	Number of cultures	Composite reference standard
FIND 2021	India, Uganda, South Africa	Yes/Yes	Inpatient and outpatient	Stool	Prospective cohort	Consecutive and referral	Multiple	No
Jaganath 2021	Uganda	No/Yes	Inpatient and outpatient	Gastric aspirate	Prospective cohort	Consecutive	Multiple	Yes
Kabir 2020	Bangladesh	Yes/No	Inpatient	Stool	Cross- sectional	Consecutive	Single	Yes
Liu 2020	China	Yes/Yes	Inpatient and outpatient	Gastric aspirate Stool	Prospective cohort	Consecutive	Multiple	Yes
NCT04121026 2021	Côte d'Ivoire, Mozambique, Uganda, Zambia	Yes/Yes	Inpatient and outpatient	Gastric aspirate Stool	Prospective cohort	Consecutive	Multiple	No
NCT04203628 2020	Uganda and Zambia	Yes/Yes	Inpatient and outpatient	Stool	Prospective cohort	Consecutive	Multiple	No
NCT04240990 2021	Uganda and Zambia	Yes/Yes	Inpatient	Gastric aspirate Stool	Prospective cohort	Consecutive	Multiple	No
Parigi 2021	Italy	No/No	Inpatient	Gastric aspirate	Prospective cohort	Unclear	Multiple	Yes
Ssengooba 2020	Uganda	No/Yes	Outpatient	Gastric aspirate and lavage	Prospective cohort	Consecutive	Multiple	Yes

Table 2. PICO 2b, diagnostic accuracy of Xpert Ultra for pulmonary tuberculosis in children under 10 years

Test, specimen, age group, reference standard	Studies	Total (cases)	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Positive predictive value (95% CI)	Negative predictive value (95% CI)
Xpert Ultra, gastric aspirate, 0 to 9 years, MRS	6	659 (70)	63.6 (47.7 to 77.0)	94.9 (83.8 to 98.5)	57.9 (31.0 to 80.9)	95.9 (94.1 to 97.2)
Xpert Ultra, gastric aspirate, 0 to 9 years, CRS	3	142 (101)	47.5 (38.0 to 57.2)	100 (91.4 to 100)*	100 (32.9 to 100)	94.5 (93.0 to 95.5)
Xpert Ultra, gastric aspirate, < 1 year, MRS	5	182 (26)	67.3 (43.5 to 84.6)	94.0 (84.7 to 97.8)	55.4 (31.5 to 77.1)	96.3 (93.1 to 98.0)
Xpert Ultra, gastric aspirate, 1 to 4 years, MRS	4	327 (30)	71.5 (40.0 to 90.4)	94.0 (73.8 to 98.9)	57.1 (25.1 to 84.1)	96.8 (92.5 to 98.6)
Xpert Ultra, stool, 0 to 9 years, MRS	6	1279 (154)	52.8 (35.0 to 69.9)	98.0 (93.4 to 99.4)	74.1 (55.2 to 96.6)	94.9 (92.7 to 96.6)
Xpert Ultra, stool, 0 to 9 years, CRS	2	511 (174)	47.1 (39.8 to 54.6)	99.7 (97.9 to 100)	94.6 (71.2 to 99.2)	94.4 (93.7 to 95.1)
Xpert Ultra, stool, < 1 year, MRS	4	295 (31)	65.2 (33.7 to 87.3)	96.2 (88.9 to 98.7)	65.3 (40.2 to 84.0)	96.2 (91.5 to 98.3)
Xpert Ultra, stool, 1 to 4 years, MRS	3	331 (30)	43.3 (27.1 to 61.2)	97.1 (74.8 to 99.7)	62.7 (13.2 to 94.9)	93.9 (91.8 to 95.5)
Xpert Ultra, stool, severe malnutrition, 0 to 9, MRS	3	428 (19)	63.2 (40.3 to 81.3)	98.5 (84.1 to 99.9)	82.3 (27.7 to 98.3)	96.1 (93.1 to 97.7)

Predictive values were determined at a pre-test probability of 10%. CI: confidence interval; CRS: composite reference standard; MRS: microbiological reference standard. * Meta-analysis using univariate fixed effect or random effects logistic regression models is not possible when all studies in a meta-analysis report 100% specificity. Therefore, the pooled specificity was calculated by dividing the total number of non-cases by the total number of true negatives.

Summary of main results

- For gastric aspirate, Xpert Ultra sensitivity was 64% in children 0 to 9 years, against MRS. Sensitivity was similar (67%) in children < 1 year and slightly higher (72%) in children 1 to 4 years. Specificity was 94% to 95% in these analyses.
- For stool, Xpert Ultra sensitivity was 53% in children 0 to 9 years, against MRS. Sensitivity was higher (65%) in children < 1 year and lower (43%) in children 1 to 4 years. Specificity was 96% to 98% in these analyses.
- Sensitivity estimates against a CRS were lower for both specimen types.
- The small number of children < 1 year and 1 to 4 years in the analyses limits our confidence in the precision of the estimates for these age groups.
- Xpert Ultra trace results were common in both gastric aspirate and stool specimens.
- There were no studies identified that evaluated the diagnostic accuracy of Xpert Ultra for detection of rifampicin resistance using gastric aspirate or stool specimens.

Authors' conclusions

Overall, Xpert Ultra sensitivity appeared to be higher in gastric aspirate than stool (no formal comparison). Xpert Ultra specificity in both specimens was > 94%. The small number of children < 1 year and 1 to 4 years included in the analyses limits our confidence in the precision of the estimates for these age groups.

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PICO 4: Drug-resistant TB Individual Patient Database

Summary Report for the World Health Organization Child and Adolescent Tuberculosis Working Group Guideline Development Group Meeting: Drug-resistant tuberculosis in children, PICO 4 and related questions

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Brief background

Rifampicin-resistant tuberculosis (RR-TB) in children is under-recognized, under-diagnosed and under-treated. Despite the fact that an estimated 32,000 children develop RR-TB each year and that historical studies have shown high mortality rates, little is known about optimal treatment regimens and disease outcomes. A systematic review and individual patient data (IPD) meta-analysis in 2014 sought to better characterize treatment outcomes in children treated for RR-TB, and informed the 2016 World Health Organization (WHO) MDR-TB treatment guidelines and leading to paediatric-specific treatment recommendations. Since 2014, the field has evolved substantially, and there have been important changes in the WHO guidance for paediatric RR-TB treatment. The most critical changes include the use of the novel drugs bedaquiline and delamanid, increasing use of the repurposed drugs linezolid and clofazimine, and reduction in the duration of RR-TB treatment for children with less severe RR-TB disease, declining use of injectable agents. Given the rapidly evolving landscape, there is a clear need to update the evidence-base for RR-TB treatment strategies for children. The Unitaid-funded BENEFIT Kids research consortium, led by the Desmond Tutu TB Centre (DTTC) at Stellenbosch University, with other key partners including the University of California San Francisco (UCSF) and the South African Medical Research Council (SAMRC), conducted a systematic review and individual patient data meta-analysis (SR/IPD-MA) of children and adolescents 0–19 years of age treated for any form of RR-TB. The dataset collated from this review was utilized to inform questions from the WHO GDG on RR-TB treatment in children and adolescents.

Methods

Aim: The aim of the SR/IPD-MA for the WHO GDG meeting was to evaluate the efficacy and safety of various RR-TB treatment regimens in children and adolescents treated for RR-TB through analyses

addressing both the focused PICO questions 4a/b, and the two additional questions raised by the WHO GDG.

a. In MDR/RR-TB patients aged below 6 years, should an all-oral treatment regimen containing bedaquiline versus other regimens conforming to WHO guidelines without bedaquiline be used?

b. In MDR/RR-TB patients aged below 3 years, should an all-oral treatment regimen containing delamanid versus other regimens conforming to WHO guidelines without delamanid be used?

In addition to PICO questions 4a and b, an analysis of individual patient-level data was requested to be conducted to provide evidence to the GDG on two additional questions. *Additional Question 1:* how to construct optimal treatment regimens in children with MDR/RR-TB who are not eligible for shorter, all oral regimens, considering age, resistance patterns in the child or the most likely source case, extent of TB disease and specific background settings. This analysis will consider optimal composition, based on current WHO recommended drug classification, as well as duration of the treatment regimens, to inform implementation considerations. *Additional Question 2:* an analysis of individual patient-level data will be conducted to provide evidence to the GDG on the outcomes of children aged 6–19 years treated with bedaquiline and children 3–19 years treated with delamanid.

Eligibility: In order to be included in this systematic review, studies were required to meet the following eligibility criteria:

Study design: Both controlled and non-controlled retrospective and prospective studies were eligible, including case series, cohort studies, non-randomized experimental studies, and randomized controlled trials (including case controls)

Published or unpublished studies: Unpublished existing data were included, as long as its collection was approved by the ethics board of its originating institution and could be shared with permission.

Included more than five children or adolescents meeting the following criteria:

- age 0–19 years at the time of RR-TB treatment initiation
- treated for clinically diagnosed or confirmed pulmonary or extrapulonary RR-TB within a defined paediatric or adult treatment cohort,
- report on RR-TB treatment outcomes
- report on regimen composition.

Primary authors agreed to collaborate and provided individual patient data in electronic format with the minimal essential information

Search, study selection, data extraction: A comprehensive electronic search for all relevant evidence, regardless of language or publication status, was utilized. The following databases were searched: PubMed, Scopus, and *The Cochrane Library* databases from 1 October 2014 through the initial search date (no later than April 2020). Individual studies conducted outside of the search time frame were also included if they consisted of unpublished data. We additionally searched all electronically available conference abstracts and trial registries. We reviewed the bibliographies of all retrieved articles for relevant studies and contacted experts in the field of paediatric TB. For all records, two authors independently screened potentially relevant studies by scanning the titles, abstracts, and descriptor terms of the references found by the search, applying the inclusion criteria as defined above. Any discrepancies were discussed to find resolution by the two reviewers, or an additional reviewer was consulted if needed. For records considered potentially eligible, full-text articles were sought and two authors independently applied the inclusion criteria to these. Where there was disagreement, a third party adjudicated. Where there were missing data, authors of relevant studies were contacted for clarification. For studies and cohorts that met required inclusion criteria, individual patient data were requested from study authors and persons responsible for individual cohorts. Eligible studies for which individual data was provided that met criteria, were included in the final dataset. Anonymized

individual patient data was uploaded by primary authors to a secure password-protected OneDrive folder at Stellenbosch University. After a series of data quality checks, key variables were extracted from each study's individual patient data into a combined final dataset.

Risk of bias assessment: Included studies were appraised independently by two reviewers using the Joanna Briggs critical appraisal tools. The results of the risk of bias assessment for each study design were considered in drafting the results and GRADE summary of findings for the review.

Assessment of overall certainty of evidence across studies: Where relevant, the GRADE approach was utilized and GRADEpro software (GRADEproGDT) was used to produce GRADE summary of findings tables, GRADE evidence profile tables for all outcomes of interest, and evidence to decision tables as needed. The overall quality of the evidence for each outcome was evaluated according to the GRADE approach. GRADE takes into account issues related to internal validity (risk of bias, inconsistency, imprecision, publication bias) and also external validity, such as directness of results.

Descriptive analysis: An overall summary of the data was provided after excluding those individuals with unknown study/cohort information, missing outcome, unknown treatment information and INH monoresistance and those older than 19 years of age. The number of studies, number of children included, key demographic and clinical characteristics for the included population, overall treatment outcomes and time to treatment outcome were summarized. Data on safety were not available at this time and thus are not included in this report.

Matched analysis on treatment effects: A matched analysis was undertaken to address PICO questions 4a/b. Patients with missing treatment duration, who were lost to follow up, and with missing age information were excluded from this analysis. Baseline patient characteristics of interest that were missing were imputed from other covariates or predictors using multivariate imputation via chained equations. To address PICO questions 4a and 4b, a combination of exact matching and propensity score matching was used. Patients who were in the intervention group (e.g. received bedaquiline [PICO 4a] or delamanid [PICO 4b] as part of an all-oral treatment regimen) were matched in a 1:3 ratio to patients who received WHO-conforming regimens without the intervention. Characteristics used for exact matching were basis of diagnosis (microbiologically confirmed TB), HIV status, AFB smear+, and previous TB treatment. Propensity score matching was used for age and sex using a caliper distance of 0.2 standard deviations of the logit of the propensity score. We summarized outcomes for the intervention and comparator groups, matching on key baseline and on-treatment characteristics as described. Logistic regression analysis was used to calculate adjusted odds ratios and their 95% confidence intervals for each outcome. Due to time constraints and the volume of data, results related to Additional question 1 (contructing optimal treatment regimens) were not presented to the GDG. This analysis is ongoing with the intent for results to contribute to the handbook, and will follow the analytical plan described below. For Additional question 2 regarding outcomes of children aged 6–12 years treated with bedaquiline and children 3–6 years treated with delamanid, a descriptive analysis of outcomes baseline, and on-treatment characteristics were summarized for children receiving bedaquiline- or delamanid-containing regimens compared to those not receiving the drug of interest. When supported by the data, a similar approach using a matched analysis as described above for PICO Questions 4a/b (2.2) was undertaken, using specific age stratification by 3–6 years (for delamanid), 6–12 years (for bedaquiline), depending on data availability.

Results

Results of search: Forty-four published and unpublished studies were included. Due to the large number of identified studies and individual patient records and required timeline, it was not feasible to include all studies into the analysis dataset for the WHO GDG. Large datasets and those containing patients treated with bedaquiline and delamanid were therefore prioritized for inclusion. Studies not included in the GDG analysis dataset represented only approximately 2% of the overall number of individual records, and their exclusion is highly unlikely to fundamentally alter the results of the analysis

or conclusions. The 44 included studies represented data from 52 countries with broad geographic and income level distribution; 19 of 30 WHO high-burden RR/MDR-TB countries were represented. All data were from observational studies or were routine programmatic data. The year of treatment ranged from 1998–2019, with 88% of data from 2011–2019. We appraised all published studies using the Joanna Briggs appraisal tool for case series studies.

Results of descriptive analysis: Overall, 24,231 children and adolescents treated for RR-TB were included in the descriptive analysis. All WHO regions are represented; South Africa and India jointly accounted for more than 90% of all included patients. Of included patients, 82.6% were 12 to 19 years of age and 14.6% were living with HIV. A high proportion (90.5%) had bacteriologically confirmed RR-TB. The mean year of treatment of patients was 2016, thus the data reflects a relatively contemporary group of patients. Overall, 72.1% of children had a favourable treatment outcome (treatment completed or cured), 12.3% died, 3.1% had treatment failure and 12.5% were lost-to-follow-up.

Results of bedaquiline analyses, PICO 4a: Overall 19, 919 children and adolescents were included in the matched analysis dataset. The main outcomes of successful (treatment completed or cured) versus unsuccessful outcome (failure or death) were assessed in the primary population of interest for bedaquiline, but there was insufficient data to perform pre-specified sub-analyses of interventions or to evaluate other pre-specified outcomes. In the matched analysis population, N=40 children <6 and N=68 children 6 to <12 years of age were treated with bedaquiline. Among the children <6 years of age, the bedaquiline-treated group appeared to have a higher proportion of children who were HIV-positive, had confirmed disease and were AFB smear positive, although no testing was done to assess statistical differences. In the primary comparison for PICO 4a (Table 1), bedaquiline treatment was not significantly associated with treatment outcome. Important limitations include the very small number of bedaquiline-treated patients, confounding by indication, and potential residual confounding that was unable to be accounted for in the matching, including the presence of fluoroquinolone-resistant TB. In secondary analyses, treatment with bedaquiline was significantly associated with a reduced duration of treatment among children 6 to <12 years of age (-3.60 months, 95% CI -5.2 to -1.9, p<0.001). Additionally, treatment with bedaquiline was significantly associated with a lower adjusted odds of receipt of an injectable drug among children <6 years of age (aOR 0.12, 95% CI 0.05 to 0.32, p<0.001) and 6 to <12 years of age (aOR 0.01, 95% CI 0.003 to 0.04, p<0.001).

Table 1. Results of matched logistic model regression evaluating the effect of bedaquiline vs. no bedaquiline treatment on successful (treatment completion and cure) vs. unsuccessful (death or treatment failure) outcome

	Bdq given (success/ total*)	Bdq NOT given (success/total*)	Matched logistic model regression	
			Adjusted OR (95%CI)	P-value
Primary Comparison				
Intervention: All-oral regimen with BDQ; *Comparator:* All-oral regimen without BDQ				
Bdq <6 years	24/27 (89%)	485/498 (97%)	0.94 (0.09, 10.3)	0.9
Bdq 6 to <12 years	50/55 (91%)	202/215 (94%)	0.31 (0.03, 2.96)	0.3
Secondary Comparisons				
Intervention: Any regimen with BDQ; *Comparator:* Any regimen without BDQ				
Bdq <6 years	30/33 (91%)	1486/1573 (94%)	0.87 (0.13, 5.96)	0.9
Bdq 6 to <12 years	53/58 (91%)	1523/1716 (89%)	1.17 (0.41, 3.32)	0.8

	Bdq given (success/ total*)	Bdq NOT given (success/total*)	Matched logistic model regression	
			Adjusted OR (95%CI)	P-value
Intervention: All-oral regimen with BDQ; *Comparator:* Any regimen without BDQ				
Bdq <6 years	24/27 (89%)	1486/1573 (94%)	0.7 (0.1, 4.6)	0.7
Bdq 6 to <12 years	50/55 (91%)	1523/1716 (89%)	1.01 (0.36, 2.9)	0.9

*Total = all children with successful and unsuccessful outcomes

Results of delamanid analyses, PICO 4b: As only N=7 children <3 years and N=14 children 3 to <6 years of age were treated with delamanid, there were too few to proceed with the planned matched analysis for PICO 4b and no GRADE evidence table was generated.

Limitations: All of the data included were from observational studies, and much of which was routine programmatic data. The patients in the treatment groups of interest for PICO 4a (children <6 years of age treated with bedaquiline) and 4b (children <3 years of age treated with delamanid) were likely a highly selected group since there is no current recommendation for use of these drugs in these age groups and no clear dosing recommendation. Although it cannot be definitely demonstrated from the data, patients receiving these drugs were very likely to have had severe disease and/or limited other treatment options, so that the risk-benefit likely favoured the off-label use of bedaquiline or delamanid in these individuals. The sample sizes were small for the populations of interest for PICO 4a and 4b. The results of the primary matched analysis for PICO 4a (bedaquiline) should therefore be interpreted with caution; the planned analysis for 4b (delamanid) could not be undertaken due to the extremely small numbers. The matched analyses attempted to adjust for key clinical factors that would be expected to affect outcomes. However, there is still likely to be residual confounding, including confounding by indication. There was a lack of conclusive information on drug-susceptibility patterns, including to the fluoroquinolones, that could not be adjusted for.

Summary of results

4.1 Overall results: The overall systematic review included 24,231 children and adolescents routinely treated for RR-TB compared to the review in 2014 which included just over 1,000 children. The data is relatively contemporaneous, with 2016 being the average year of treatment, and includes data on children treated with newer drugs and shorter regimens. A high proportion (90.5%) of children had bacteriologically confirmed RR-TB, which likely reflects the older mean age (14.7 years) of the cohort, more severe forms of pulmonary TB as well as continuing hesitance among many clinicians to treat clinically diagnosed RR-TB. Overall, the outcomes were good, with 72.1% having a successful outcome, despite relatively severe disease with high proportion of bacteriological confirmation, indicative of a high bacillary burden.

4.2 Bedaquiline and delamanid: The evidence base for the use of delamanid and bedaquiline in the specified age groups considered by the GDG was limited. As expected, a relatively small number of children <12 years of age received bedaquiline in the dataset, with particularly few children <6 years of age for whom there was no recommendation for its use or a recommended dose. For bedaquiline (PICO 4a), although there were sufficient available data to proceed with the planned analysis, the number of patients was too small to draw robust conclusions. Children who received bedaquiline were however less likely to receive an injectable drug, and were likely to have been treated for a shorter overall duration, compared to children not receiving bedaquiline. Very few children received delamanid globally, particularly, but not limited to, those <3 years of age, for whom there was no recommendation for its use or a recommended dose. There was insufficient data to proceed with

the planned matched analysis, and so only a descriptive analysis was completed and presented to the GDG. The available evidence for the use of both bedaquiline and delamanid in the specified age groups remains of very low certainty due to small numbers and the observational nature of the data. Indirect evidence is available from the growing dataset for the use of these medicines in older children and in adults.

4.3 Other: Additional planned analyses are ongoing to address Additional Question 1 on how to optimally design an individually constructed RR-TB treatment regimen for children.

Conclusions

Although there was limited data to address the primary questions related to bedaquiline and delamanid use in young children, this large and diverse dataset has served as a useful resource and will continue to do in future analyses.

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PICO 5: Treatment of Pediatric TB Meningitis

Effectiveness of shorter regimens vs. a twelve-month regimen to treat drug-susceptible tuberculous meningitis in children and adolescents: a systematic review and aggregate-level data meta-analysis

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Rationale

The optimal chemotherapy regimen for rifampicin-susceptible tuberculous (TB) meningitis in children and adolescents is unknown. In 2010, the World Health Organization (WHO) recommended treatment of pediatric TB meningitis with a 12-month regimen consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide given daily for the first two months, followed by isoniazid and rifampicin given daily for ten additional months (2HRZE/10HR).[1] Shorter regimens are routinely used to treat pediatric TB meningitis in some settings. Of note, the "Cape Town regimen" consisting of daily isoniazid 20 mg/kg, rifampicin 20 mg/kg, pyrazinamide 40 mg/kg, and ethionamide 20 mg/kg for six months (6HRZEto) has been in use in South Africa for over 35 years.[2,3] In this regimen, duration is extended to nine months for HIV-infected children.[4] Shorter regimens may lead to higher treatment completion rates and reduce burden on patients and healthcare systems, but it is not known how outcomes compare to the WHO 12-month regimen.

Pico question

In children (<10 years old) and adolescents (10–19 years old) with microbiologically confirmed or clinically diagnosed rifampicin-susceptible TB meningitis, should a 6-month intensive regimen, compared to the current 12-month regimen that conforms to WHO guideline, be used?

Note: Although the primary intervention of interest was the Cape Town regimen, we also aimed to examine outcomes associated with other shorter regimens.

Methods

We updated our previous systematic review published in 2014,[5] searching PubMed, EMBASE Classic + EMBASE (Ovid), Web of Science, Cochrane Library, and LILACS through February 24, 2021. We also reviewed unpublished data known to the authors and/or the WHO Child and Adolescent TB Working Group and re-assessed the 19 studies included in our previous systematic review. Studies that described outcomes from the regimens of interest, included at least ten patients with TB meningitis, and were published in one of ten languages (English, Spanish, French, Italian, Portuguese, Romanian, German, Chinese, Russian, and Ukrainian) were eligible for inclusion. We excluded studies restricted to specific subsets of patients (e.g., drug-resistant TB cases, patients requiring shunt surgery). Additional data and clarifications were obtained from study authors whenever possible.

To assess the study risk of bias, we developed a tailored checklist to assess five domains pertaining to key potential sources of bias in the evaluation of pediatric TB meningitis outcomes: patient selection, diagnostic uncertainty, treatment allocation, outcome assessment and reporting, and confounding. Each domain consisted of several subdomains that were judged as having low, high, or uncertain risk of bias.

Two investigators independently conducted study screening, data extraction, and risk of bias assessment. Discrepancies were resolved by discussion or consultation with a third investigator.

The following five outcomes were assessed: 1) death by end of treatment (EOT); 2) loss to follow-up; 3) treatment success (i.e., alive at treatment completion); 4) neurological sequelae of any severity by EOT; 5) survival without sequelae. Proportions of all outcomes were estimated using the total number of patients starting treatment as the denominator, with one exception: for the neurological sequelae outcome, the denominator was the number of patients still alive at EOT. Using generalized linear mixed models with Gauss-Hermite quadrature, we estimated the pooled proportion of patients developing each outcome across studies and within regimens. We assessed between-study heterogeneity through visual inspection of forest plots. Because of the non-comparative nature of the studies, we did not compute relative or absolute measures of effect. Subgroup analyses were planned but could not be done due to insufficient data. All analyses were performed R version 3.6.3.[6]

Main findings

Seven studies (five published and two unpublished cohorts), none of which performed head-to-head comparisons of regimens, met our inclusion criteria.[2,3,7–11] **Table 1** summarizes the main study features.

Table 1. Characteristics of included studies

Reference	Study type and setting	Regimen	Patient characteristics	Major outcomes	Bias concerns
INTERVENTION					
van Toorn 2014	PC South Africa 2006–2009	6HRZEto + steroids	135 HIV-uninfected children. Median age: 2.9 years TBM stage: 16 stage 1; 68 stage 2; 51 stage 3.	Deaths: 6 (4.4%), all <8 days of treatment initiation. No relapses during 2-year post-treatment FUP. TS: 129 (95.6%). NS: 71/129 (55.0%).	Unknown adherence; confounding by age.
van Well 2009	RC South Africa 1985–2005	6HRZEto + steroids	554 children of whom 2013 with known HIV status and 8 HIV-infected. Median age: 5.5 years TBM stage: 14 stage 1; 318 stage 2; 222 stage 3.	Deaths: 53 (9.6%), mostly in stage 3 patients. TS: 435 (78.5%). NS: 294/435 (66.7%).	Confounding by indication; unknown adherence; >10% patients had missing outcome data; confounding by age.
Solomons (unpublished)	RC South Africa 2011–2014	6HRZEto + steroids (63% of patients)	35 children (3/35 HIV-infected). Median age: 2.5 years TBM stage: 6 stage 1; 15 stage 2; 14 stage 3.	Deaths: none. TS: 35 (100%). NS: 28/35 (80.0%).	Confounding by age.
Bang 2016	PC Vietnam 2009–2011	2HRZES/1HRZE/ 5HRE + steroids	100 children (4/96 HIV-infected). Median age: 2.7 years TBM stage: 59 stage 1; 23 stage 2; 18 stage 3.	Deaths: 15 (15.0%), 93.3% <45 days of diagnosis. TS: 81 (81.0%). NS: 27/81 (33.3%).	Confounding by indication; unknown adherence; potential inclusion of drug-resistant cases.

Reference	Study type and setting	Regimen	Patient characteristics	Major outcomes	Bias concerns
COMPARATOR					
Dhawan 2016	PC India 2010–2013	2HRZE/10HR + steroids	130 HIV-uninfected children (age unspecified). TBM stage: 26 stage 1; 56 stage 2; 48 stage 3.	Deaths: 39 (30.0%), mostly associated with stage 3 and occurring shortly after treatment initiation. TS: 91 (70.0%) NS: 29/91 (31.9%).	Patient sampling; confounding by indication; unknown adherence; confounding by age and stage.
Gupta 2017	PC India 2012–2014	2HRZE/10HR [adjunctive treatment unknown]	138 children aged <18 years.‡ TBM stage not reported.	Deaths: 29 (21.0%) – details not reported. TS: 109 (79.0%) NS: 42/109 (38.5%).	Patient sampling; confounding by indication; adherence and adjunctive treatment unknown; confounding by age and stage.
Thee (unpublished from ptbnet)	RC Europe (multiple countries) 2009–2016	2HRZE/10HR + steroids	14 HIV-uninfected children. Median age: 3.3 years. TBM stage: 2 stage 1; 11 stage 2; 1 stage 3.	Deaths: 1 (7.1%) in stage 3. TS: 12 (85.7%). NS: 6/12 (50.0%).	Patient sampling; confounding by indication; unknown adherence; non-standardized approach to assess NS.

FUP, follow-up; NS, neurological sequelae; PC, prospective cohort; RC, retrospective cohort; TBM, tuberculous meningitis; TS, treatment success.

‡ The study included both adults and children, and only a very small number of HIV-positive individuals was included in the entire cohort. Adult data were not included in this report.

Three of the four studies of intervention regimens reported on the Cape Town regimen;[2,3,10] as only one study reported on outcomes from an eight-month regimen in Vietnam,[7] it was excluded from meta-analysis. A total of 837 and 282 patients received intervention and comparator regimens, respectively. As most studies were restricted to HIV-negative children, HIV-positive children represented a small proportion of patients overall, and all belonged to intervention arm.

Patients who received the Cape Town or comparator regimens were staged at treatment initiation using the original or modified British Medical Research Council (MRC) staging system.[12,13] Of the 737 patients who received the Cape Town regimen, 38 (5.2%) presented in stage 1, 409 (55.5%) in stage 2, and 290 (39.3%) in stage 3. Of the 282 patients who received the comparator regimen, 28 (9.9%) presented in stage 1, 67 (23.8%) in stage 2, and 49 (17.4%) in stage 3; disease stage at presentation was not reported for the remaining 138 (48.9%). Patients in Vietnam who were five years and older were staged using the MRC classification; those who were younger than five years were staged using the Blantyre coma scale. Over half (59.0%) the patients in the study from Vietnam were diagnosed in stage 1.

The cumulative number of deaths was recorded at the end of treatment for each regimen (i.e. at six or eight months after treatment initiation in studies of intervention regimens; at 12 months after treatment initiation in studies of the comparator regimen). Amongst studies of the Cape Town regimen, 0.0 to 9.6% of patients died within six months; most deaths occurred early after hospital admission and primarily involved patients diagnosed in stage 3 at baseline. Among studies of the comparator regimen, 7.1 to 30.0% of patients died by the end of treatment; stage-disaggregated data were not available for two cohorts of comparator regimen, but stage 3 disease emerged as the strongest risk factor for death in one of them.

All but one study reported the number of patients who were lost to follow-up. The remaining study,[9] which reported on the comparator regimen, excluded children who were lost to follow-up.[9] In one of the studies from South Africa, 53/66 patients who were considered lost to follow-up likely were alive and had completed treatment;[3] however, because their outcomes were not recorded, these patients were considered lost to follow-up.

The percentage of patients with treatment success ranged from 78.5 to 100% amongst studies of the Cape Town regimen, and from 70 to 85.7% amongst studies of the comparator regimen.

Ascertainment and categorization of neurological sequelae varied widely across studies, which may have contributed to generate differences in outcomes between regimens. 50.0 to 66.7% of patients (mostly in stage 2 or 3) treated with 6HRZEto and 31.9 to 50.0% of those treated with 2HRZE/10HR had neurological sequelae. The percentage of patients who completed treatment and survived without sequelae was 20.0 to 43.0% among those who received the Cape Town regimen, versus 42.9 to 48.6% among those who received the comparator regimen.

Data on drug-related adverse events were available for only three cohorts,[2,7,8] and hepatotoxicity was the most commonly observed event. However, the limited and non-systematic reporting of this outcome hindered further analyses.

Pooled proportions of each outcome for the Cape Town regimen and the comparator regimen are summarized in **Table 2**.

Table 2. Pooled proportions and 95% confidence intervals (CIs) of each outcome, estimated through random-effects and fixed-effects meta-analysis models

Outcome	Intervention: 6HRZEto				Comparator: 2HRZE/10HR			
	No. studies	n/N	Pooled proportion (95% CI)		No. studies	n/N	Pooled proportion (95% CI)	
			Random-effects model	Fixed-effects model			Random-effects model	Fixed-effects model
Death	3	59/724	0.06 (0.02–0.13)	0.08 (0.06–0.10)	3	68/282	0.24 (0.18–0.32)	0.24 (0.20–0.30)
Loss to follow-up	3	66/724	0.0 (0.0–0.51)	0.09 (0.07–0.11)	2	1/144	0.01 (0.0–0.24)	0.01 (0.0–0.05)
Treatment success	3	599/724	0.95 (0.74–0.99)	0.83 (0.80–0.85)	3	212/282	0.75 (0.69–0.81)	0.75 (0.70–0.80)
Neurological sequelae	3	393/599	0.66 (0.55–0.75)	0.66 (0.62–0.69)	3	77/212	0.36 (0.30–0.43)	0..36 (0.30–0.43)
Survival without neurological sequelae	3	206/724	0.30 (0.20–0.41)	0.28 (0.25–0.32)	3	135/282	0.48 (0.42–0.54)	0.48 (0.42–0.54)

From the available evidence, we observed lower mortality but more frequent neurological sequelae among patients who received 6HRZEto compared to those who received 2HRZE/10HR. We also observed a higher proportion of survival without neurological sequelae among those who received 2HRZE/10HR. However, these findings should be interpreted with caution.

Because of the non-comparative nature of the studies, we did not estimate measures of effect but rather provided narrative descriptions, reporting pooled proportions within regimens along with their 95% confidence intervals. The certainty of evidence was deemed to be very low for all outcomes due to very serious risk of bias, serious or very serious inconsistency within regimens, and very serious indirectness. Imprecision could not be assessed due to the lack of comparative data.

All studies of the 6HRZEto were conducted in a single referral center in South Africa,[2,3,10] while most patients who received the WHO regimen were treated in India.[8,9] These distinct settings result in many additional sources of confounding, including time to diagnosis and treatment; the non-antimicrobial components of TB meningitis therapy, such as hydrocephalus management and cardiorespiratory support measures; and perhaps even genetic differences in anti-TB drug metabolism.

Further, the inconsistent reporting of patient characteristics and treatment outcomes across studies makes comparisons of different regimen even more challenging.

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PICO 6: Evidence review on decentralized, integrated, and family-centered care for children and adolescents affected by TB in high-burden settings

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Background

Tuberculosis (TB) remains a leading infectious cause of morbidity and mortality in children and adolescents worldwide. In 2019, 10 million people fell ill with TB, and an estimated 1.2 million of these were children < 15 years old.[1] However, approximately half of these children were diagnosed and treated, and only 27% of child contacts <5 years old eligible for TB preventive treatment in fact received it. Thus, major gaps persist in the detection and prevention of childhood TB. The effectiveness of TB detection and prevention programs for children and adolescents could be affected by the model of care delivery. As part of the process for updating the WHO guidelines on the management of child and adolescent TB, the WHO Guideline Development Group (GDG) requested a systematic review to evaluate the evidence for different models of care in high-TB burden settings. Specifically, we assessed the evidence whether or not decentralized, integrated, and family-centered care models should be recommended over traditional services to decrease the burden of TB in children and adolescents globally.

The terms of reference were:

- Conduct a systematic review on models of care for TB case detection and TB prevention in children and adolescents in high TB burden settings
- Draft a systematic review report for WHO and WHO GDG
- Create GRADE profiles in GradePro, based on the PICO question, incorporating the systematic review results as well as any non-published trial data, including a summary of accuracy data, quality assessment of the evidence, justification of the quality grading
- Powerpoint presentation for the session of the WHO GDG models of care
- Final systematic review report incorporating edits and revisions suggested by WHO and GDG members

All aspects of the terms of reference have been completed.

PICO question

The 4-part PICO question was focused on "models of care for TB case detection and TB prevention in high TB burden settings (prevalence of TB in the general population of 100 per 100,000 or more)" (Table 1).

Table 1. PICO question

Population	Intervention	Comparator	Outcome/s
Children and adolescents aged 0–19 years with signs and symptoms of TB in settings where the TB prevalence in the general population is 100 per 100,000 population or higher	Decentralization of TB diagnostic, treatment and/or care services to district hospital or primary healthcare or community level	Centralized paediatric TB diagnostic, treatment and care services (at referral or tertiary hospital level)	• TB case notifications • Time to diagnosis • Treatment outcomes (treatment success, treatment failure, death, loss to follow up) • Patient costs • Barriers to access • Access to schooling
Children and adolescents aged 0–19 years exposed to TB (i.e. TB contacts) in settings where the TB prevalence in the general population is 100 per 100,000 population or higher	Decentralization of TB prevention services to district hospital or primary healthcare or community level	Centralized paediatric TB prevention services (at referral or tertiary hospital level)	• Coverage of TB preventive treatment in eligible child and adolescent TB contacts • Time to TPT initiation • TPT completion rate
Children and adolescents aged 0–19 years with signs and symptoms of TB in settings where the TB prevalence in the general population is 100 per 100,000 population or higher	Family-centred, integrated services	Standard, non-family-centred, non-integrated services	• TB case notifications • Time to diagnosis • Treatment outcomes (treatment success, treatment failure, death, loss to follow up) • Patient costs • Barriers to access • Access to schooling
Children and adolescents aged 0–19 years exposed to TB (i.e. TB contacts) in settings where the TB prevalence in the general population is 100 per 100,000 population or higher	Family-centred, integrated services	Standard, non-family-centred, non-integrated services	• Coverage of TB preventive treatment in eligible child and adolescent TB contacts • Time to TPT initiation • TPT completion rate

Decentralized care was defined as "child and adolescent TB services at a lower level of the health system than the lowest level where this is currently routinely provided. In most settings, decentralization would apply to district hospital…and/or primary health care level and/or community level." Integrated care

was defined as "approaches to strengthen collaboration, coordination, integration and harmonization of child and adolescent TB services with other child health related programmes and services." Family-centered models of care "refer to interventions selected on the basis of the needs, values, and preferences of the child or adolescent and his or her family or caregiver."

Review methods

Study selection

To develop our search strategy, we first defined key features of decentralized, integrated, and family-centered care in consultation with the World Health Organization and stakeholders with experience working in TB programs of middle-income countries. We developed search terms based on the results of these discussions. We also consulted existing systematic reviews on these care models and added search terms used in these reviews. We executed the abstract search in PubMed, Embase, Web of Science, the WHO regional databases of the Global Index Medicus, Global Health, and Cochrane Central. We reviewed a sample of 400 abstracts and 45 full text articles to better define the care models, and we consulted stakeholders to resolve ambiguity. Based on our refined definitions, we supplemented our database search with manual searches of the references from 17 additional systematic and non-systematic reviews to identify articles that might have been incompletely captured by our database search.[2–18] Additionally, WHO GDG members reached out to investigators with unpublished data related to the care models of interest and requested the sharing of preliminary findings.

Our database search terms included four blocks of terms (Table 2). The first block specified TB, the second block specified children and adolescents, the third block specified terms related to the care models, and the fourth block, which was used for the Pubmed, Embase, Web of Science, and Global Health searches, specified the countries of interest. To limit the review to countries with high TB burdens, we created a list of 74 countries of interest comprising those that either had an estimated TB incidence of ≥100 per 100,000 in the 2020 WHO Global TB Report (N=64) or appeared on the WHO's list of TB priority countries in 2020 based on overall TB, drug-resistant TB, or TB/HIV burden (N=48).[1]

Table 2. Summary of search terms and database searches

Search term block	Concepts	Number of search terms*	Example search terms
1	Tuberculosis	3	• Tuberculosis (MeSH or Emtree) • Tuberculosis (text) • TB (text)
2	Children and adolescents	17	• Child (MeSH or Emtree) • Pediatrics (MeSH or Emtree) • Adolescent (MeSH or Emtree) • Child* (text) • Adolescen* (text)

Search term block	Concepts	Number of search terms*	Example search terms
3	Decentralized care	26	• Primary health care (MeSH or Emtree) • Community health services (MeSH) • Community health (Emtree) • Decentral* (text) • Nonspecialized (text) • Primary level (text) • Home based (text)
	Integrated care	10	• Delivery of health care, integrated [MeSH} • Integrated health care system (Emtree) • Integrat* (text) • Coordinat* (text) • Colocat* (text)
	Family-centered care	15	• Patient-centered care (MeSH) • Family-centered care (Emtree) • Patient-centered (text) • Family-centered (text) • Person-centered (text) • Individualiz* (text) • Holistic (text)
4	Countries of interest	88	Text terms for names of each country (including variants), plus MeSH and Emtree terms for Africa region

Search	Database	Search date	Number of results
1–4/ AND	Pubmed	5 February, 2021	1761
1–4/ AND	Embase	5 February, 2021	1429
1–4/ AND	Web of Science	9 February, 2021	623
1–4/ AND	Global Health	15 February, 2021	606
1–3/ AND	Cochrane Central Register of Controlled Trials	15 February, 2021	67
1–3/ AND	Global Index Medicus	15 February, 2021	451

* Numbers of search terms are given for the Pubmed search. This number differed slightly across databases because of difference in indexing search terms; all search terms in a block were linked by "OR" logic

Abstracts and full-text articles were double-reviewed with disagreements arbitrated by a third reviewer. We included articles in any language that reported a program or intervention with a decentralized, integrated, or family-centered care model, and from which we could extract outcome data as counts or notification rates for an age group ≤19 years old.

Analysis

We used the Cochrane Risk of Bias 2 tool for cluster-randomized trials to assess risk of bias for randomized studies and an adapted Newcastle-Ottawa scale to assess risk of bias in non-randomized studies. For cohort studies, effect estimates were calculated as risk ratios (RR) and risk differences based on extracted count data. For studies where the outcome was case notifications, we estimated annual incidence rate ratios (IRR) based on the number of events and the duration of the intervention and pre-intervention periods, assuming the size of the underlying population to remain constant between the pre-intervention and intervention periods. Where possible, we calculated IRRs adjusted for changes in case notification rate over time in a control area (i.e. the ratio of IRRs between the intervention and control area). A large normal approximation was used to estimate 95% confidence intervals for unadjusted IRRs.

Results

We identified 26 studies that met our inclusion criteria (Figure 1). However, four studies[19–22] included only treatment completion outcomes and assessed community-based directly observed therapy (DOT) or DOT-like interventions. Given an existing WHO recommendation for community-based DOT, the WHO GDG decided to exclude these studies from the current evidence synthesis. The remaining 22 studies are summarized in Table 3. The interventions in the identified studies were heterogeneous and often comprised multifaceted approaches. Due to the heterogeneity of interventions, we did not perform a meta-analysis to create pooled estimates.

Figure 1. PRISMA flow diagram for study selection

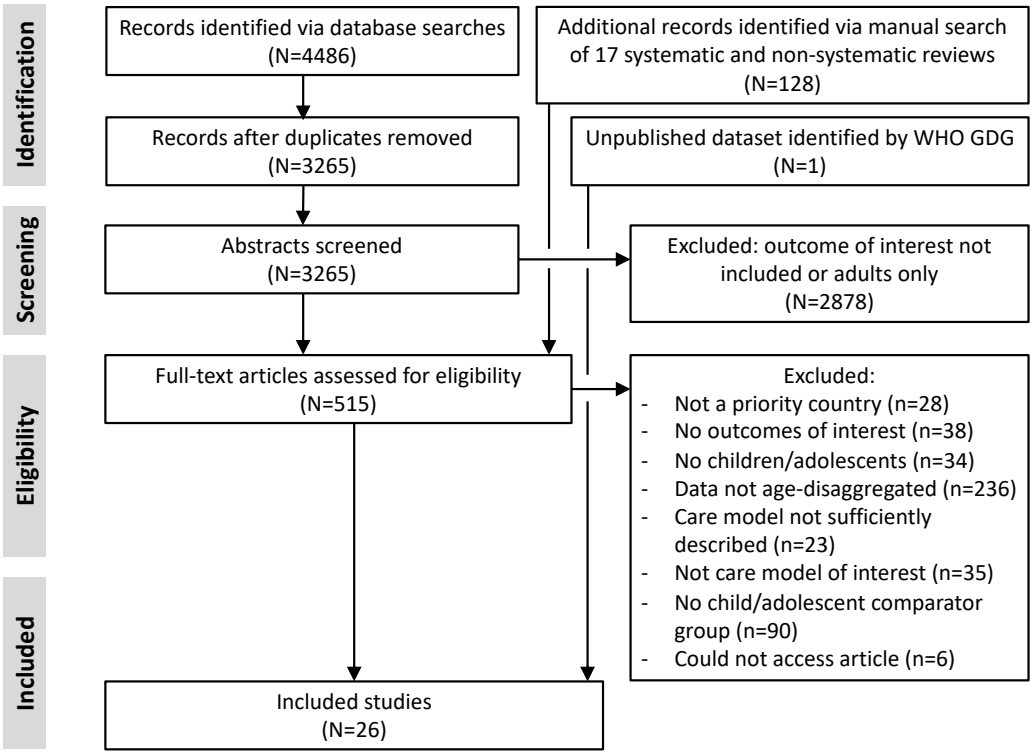

Table 3. Included studies

Authors	Year	Study design	Country	Primary care model	Key intervention components	Outcome(s) reported
Talukder et al[23]	2012	Cluster-randomized trial	Bangladesh	Decentralized	Primary-level provider training, supplies given to diagnostic centers, community awareness activities	TB diagnoses
Khan et al[24]	2012	Pre-post	Pakistan	Decentralized	Screeners in primary care (private sector), community awareness activities	TB notifications
Malik et al[25]	2018	Pre-post	Pakistan	Decentralized	Screeners in primary care, primary-level provider training, transport enablers for contacts, community awareness activities	TB notifications
Zawedde-Muyanja et al[26]	2018	Pre-post	Uganda	Decentralized	Primary-level provider training, home visits for contact screening and referral, procurement support	TB notifications
Maha et al[27]	2019	Pre-post	Papua New Guinea	Decentralized	Primary-level provider training, community awareness activities	TB treatment initiations
Islam et al[28]	2017	Pre-post	Bangladesh	Decentralized	Primary-level provider training, community awareness activities, procurement support	TB diagnoses
CaP-TB study unpublished data[29]	N/A	Pre-post	Cameroon, Cote D'Ivoire, DR Congo, Kenya, Lesotho, Malawi, Tanzania, Uganda, Zimbabwe, India	Decentralized	Primary-level provider training, screeners in primary care settings, screeners in integrated settings (HIV, MCH, nutrition clinics), home visits for contact screening and referral, supplies for sputum collection provided	TB treatment initiations, TPT initiations
Oshi et al[30]	2016	Pre-post	Nigeria	Decentralized	Primary-level provider training, screeners in primary care settings, screeners in ART clinics, home visits for contact screening, community awareness activities, purified protein derivative provided	TB notifications

Authors	Year	Study design	Country	Primary care model	Key intervention components	Outcome(s) reported
Joshi et al[31]	2015	Pre-post	Nepal	Decentralized	Screeners in communities, schools, MCH clinics; home visits for contact screening with sputum collection or referral; private sector engagement;	TB notifications
Hanrahan et al[32]	2019	Cluster-randomized trial	South Africa	Decentralized	Home visits for contact screening with sputum collection	TB treatment initiations
Moyo et al[33]	2012	Randomized trial	South Africa	Decentralized	Home visits for screening and referral	TB diagnoses
Davis et al[34]	2019	Cluster-randomized trial	Uganda	Decentralized	Home visits for contact screening with sputum collection	TB diagnoses
Fatima et al[35]	2016	Pre-post	Pakistan	Decentralized	Home visits for screening and referral	TB notifications
Reddy et al[36]	2015	Pre-post	India	Decentralized	Home visits for screening with sputum collection or referral	TB notifications (smear positive)
Bayona et al[37]	2013	Prospective cohort	Peru	Decentralized	Home visits for contact screening and referral	TB diagnoses
Sachdeva et al[38]	2015	Pre-post	India	Decentralized	Xpert MTB/RIF introduced into decentralized microscopy centers	TB diagnoses
Yassin et al[39]	2013	Pre-post	Ethiopia	Decentralized	Field supervisors screened household contacts and initiated TPT	TPT initiations
Zachariah et al[40]	2003	Pre-post	Malawi	Decentralized	Home visits for contact screening and referral	TPT initiations
Ketema et al[41]	2020	Stepped-wedge trial	Ethiopia	Integrated	Screening in IMNCI clinics	TB diagnoses

Authors	Year	Study design	Country	Primary care model	Key intervention components	Outcome(s) reported
Miyano et al[42]	2013	Pre-post	Zambia	Integrated	Co-location of ART services in health facilities that already had TB services	TB treatment initiations
Wingfield et al[43]	2017	Cluster-randomized trial	Peru	Family-centered	Social support, conditional cash transfers to defray hidden costs of treatment	TPT initiations
Rocha et al[44]	2011	Pre-post	Peru	Family-centered	Psychosocial support, poverty reduction activities including food and cash transfers	TPT initiations, TPT completion

Abbreviations: MCH = maternal and child health, ART = antiretroviral therapy, IMNCI = Integrated maternal, neonatal, and child illnesses

Studies where the primary intervention was decentralization mostly assessed diagnosis or case notification outcomes (n=16), with fewer assessing TPT outcomes (n=3). In general, interventions that included both strengthening diagnostic capacity in primary care settings as well as strengthening linkages between communities and facilities consistently showed increases in case notifications, while interventions that involved only home-based screening did not. Across nine studies[23–31] of interventions that both strengthened diagnostic capacity in primary care settings and strengthened linkages between communities and facilities, notifications among individuals 0–14 years old increased by 1.14 to 7.32-fold, with varying degrees of precision. In contrast, four of the six interventions that involved home-based screening alone failed to increase overall notifications in the 0–14 age group or diagnoses among contacts.[32,34,36,37] The only study in this group that showed a substantial impact of the intervention was a randomized trial showing that home screening visits every 3 months increased TB diagnoses among a cohort of children 0–26 months old (IRR 2.6, 95% CI 1.8–4.0).[33] Notably, in this study, children with TB signs/symptoms were evaluated by a study team that performed X-ray and culture for all children evaluated, while all other studies relied on the routine health services to make TB diagnoses.

Three studies assessed interventions to increase the number of young child contacts initiating TPT through decentralized care. Two studies of multifaceted interventions that included strengthening TPT services in primary-level health facilities as well as household visits for contact management observed substantial increases in the numbers of child contacts initiating TPT.[29,39] The third study found that household visits did not significantly increase the proportion of child contacts initiating TPT because existing barriers to accessing x-ray prevented children from completing the evaluation required to prescribe TPT.[40]

We identified two studies of service integration, which showed limited impact on case notifications. A stepped-wedge trial found that integrating TB screening into 30 Integrated Maternal, Neonatal and Childhood Illnesses (IMNCI) clinics significantly increased the number of children 0–4 years old diagnosed with TB among IMNCI clinic attendants, although the absolute effect size was small (0.5 additional diagnosis per facility per each 4 months of intervention).[41] A non-randomized study assessed the effect of introducing ART services into rural health centers that were already providing TB treatment.[42] While there was an increase in notifications (IRR 2.67, 95% 1.05–6.76), the confidence intervals were wide due to small numbers of diagnoses in the 0–14 age group.

We did not identify any studies specifically evaluating the effect of family-centered care on diagnostic or treatment outcomes. However, four studies included an integrated or family-centered component in a multifaceted intervention that also involved decentralization.[25,29–31] Because the primary intervention was decentralization, we included them among the decentralized studies. We identified two studies of family-centered care, showing that provision of socioeconomic support packages to families affected by TB was associated with increased TPT initiation and completion. In a randomized trial, provision of a package including empowerment meetings and conditional cash transfers to defray expenses incurred by seeking care was associated with an absolute increase of an additional 18% (95% CI 4–33%) of contacts initiating TPT.[43] The non-randomized study, which included a wider range of socioeconomic and psychosocial support interventions, observed an additional 48% (95% CI 45–52%) of contacts initiating TPT and an additional 59% (95% CI 56–64%) completing TPT.[44]

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Background question 1: The socioeconomic impact of tuberculosis on children, adolescents and families: A scoping review

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Executive summary

Introduction

Tuberculosis (TB) is a disease of poverty which most affects those of lower socioeconomic status. TB can exacerbate poverty and social deprivation, through catastrophic health costs and reduced household income (1). In total, 1.04 million children and adolescents under 15 were treated for TB in 2018–2019 (2). There is little child or adolescent-specific data available for TB, an issue that is likely to improve with disaggregated reporting requirements by the WHO (2).

Most children develop TB as a consequence of contact with adult family member(s) with active pulmonary TB, and high numbers of child TB cases indicate an ongoing adult epidemic (3). However, TB in the family unit does not only result in transmission to children, but a threat to household income and financial security. Some examples of TB's impact on children include children being more likely to 'drop-out' of school following parental bereavement from TB, and children resorting to working to maintain household income where families have difficulty in affording food or basic educational tools (4). Further, another study suggests that TB in childhood or adolescence impacts on disrupting or delaying schooling, and 'wasting' due to malnutrition with impaired growth (5).

There is little known about the long-term socioeconomic consequences of TB. Disruptions in schooling, cognitive or behavioural effects of anti-TB medicines, and household poverty can impact on children's development, educational attainment, and their working life in the long term. At worst, a TB event in the household can spiral a family into a cycle of poverty which is perpetuated over generations.

To date, existing evidence has focused on the socioeconomic impact of TB on adults with large emphasis on income loss (1). To complement this information, this study was conducted to understand the pathways and mechanisms through which TB impacts on children and adolescents, and secondarily to develop a conceptual framework representing these pathways. We conducted a scoping review to summarise available evidence on the socioeconomic impact of TB on children, adolescents and families, focusing on both the direct and indirect effects of TB for affected children and adolescents.

Methods

We developed an initial framework via existing epidemiological theory from related conditions. We searched known long-term diseases affecting children (e.g. HIV) and incorporated known impacts from these to develop an understanding of the pathways through which TB affects children and adolescents. **We then conducted a scoping review of studies including TB's effect on children, adolescents and families.** Studies published in peer-reviewed journals in any language from January 1st, 1990 through April 6th, 2021 were identified using the databases PubMed, CINAHL ProQuest and Scopus. Additional grey literature was identified searching Open Grey and Google Scholar, where the first 20 first pages were reviewed. To complement the search, additional literature was gathered through personal correspondence with key informants. Lastly, the bibliographies of the included articles were scanned, and hand searched for additional references. Quantitative data were analysed descriptively, and qualitative data were analysed using thematic analysis.

Results

We screened 13621 titles and identified 42 studies from different WHO regions for the review, including Africa(n=18) South-East Asia (n=8), the Americas (n=5), Western Pacific (n=5) and one paper from the Eastern Mediterranean. We also included six reviews, one indicating their area as low-and middle-income countries, while five did not specify a review area. All but two papers ((6) – Spanish, (7)-Portuguese) were in English. Studies utilized mainly qualitative methods (n=29). Five were quantitative and two mixed methods studies. Six included studies were reviews, including systematic reviews.

The papers reported varying sample sizes (range 3–1146 participants). Overall, the included papers reported on 52 focus group discussions in addition to individual data on 3397 individuals. In total, 19 of the papers had children as a main focus while 26 had a marginal focus on children. In terms of the age ranges of the children included, 15 studies did not specify the age of children or adolescents discussed or included in the studies. Six papers included some adolescents or children in a larger sample. Using our definitions with children being 9 years old or below, and adolescents between 10 and 19 years of age, five papers focused on children 9 or below, nine included adolescents, and 13 included both children and adolescents in the study.

Conceptual framework

We developed an initial conceptual framework encompassing the pathways and mechanisms that most plausibly explain the socioeconomic impact of TB on children and adolescents based on a review of studies among children in other chronic conditions (e.g. HIV).

In this conceptual framework the impact of TB was defined as either i. *direct*: affecting children/adolescents in the household or ii. *indirect*: affecting other household members, and/or main caregivers. Combining both direct and indirect effects of TB on children and adolescents, we adopted a broad definition of socioeconomic impact, examining consequences of material impacts (e.g. impoverishment – Pathway 1), educational impacts (e.g. school withdrawal – Pathway 2), and psychosocial impacts (e.g. neglect, orphanhood – Pathway 3).

In the material pathway (Pathway 1), across both direct and indirect impacts, we anticipated that the socioeconomic impact of TB occurs via reduced income, food insecurity and loss of household income (if an economically active member of the household is affected by TB). These factors may, in the most extreme conditions, result in displacement of the child or adolescent to another household and/or child labour and/or withdrawal from school. When a child or adolescent is directly affected by TB this may also result in income loss for the household, as economically active household members may be required to provide care. Children and adolescents may also be malnourished, with potential for stunting or wasting, due to TB itself or the secondary effects of reduced household income. In turn, these factors may contribute to reduced school attendance or eventual withdrawal from school.

In the educational pathway (Pathway 2), we postulated TB (either directly or indirectly) affected children/adolescents' school attendance and/or learning and cognitive skills (which in turn may impact a child materially or psychosocially).

In the psychosocial pathway (Pathway 3), we hypothesised that children and adolescents affected by TB may experience (self-)stigmatisation and discrimination, with potential for isolation and violence. If their main caregiver is affected by TB, there may also be the potential for neglect and other forms of abuse. Attachment may also be compromised, and there is potential for separation during prolonged hospital admissions, or even through bereavement and orphanhood. These experiences are likely traumatic, and risk onward impacts on mental health and wellbeing. The general impact and stress associated with a (relatively) chronic disease i may also contribute to mental ill health for children and adolescents with TB.

All three pathways can result in child impoverishment, missed educational opportunities, reduced physical, intellectual, and emotional growth, and poor mental health. If ignored, these disparities may persist and threaten onward trajectories to health and financial security in adulthood (Figure 1). The life-course perspective (8), a multidisciplinary approach to help understand the physical, mental, and social health of people incorporating life span and life stage concepts, is overlooked in the existing evidence base. However, given the severity and relative chronicity of the disease, often alongside inadequate mitigation measures, we deemed this life-course perspective lens as necessary to defining the complete socioeconomic impact of TB in childhood and adolescence.

Scoping review findings

Quantitative findings: In total six studies provided quantitative data findings. With the exception of two studies (9, 10), all papers were from sub-Saharan African countries. Three studies out of six reported evidence from TB cases directly involving children and adolescents (11–13); even in these examples, relevant data parameters (ie, sample size and age of children/adolescents included in the study population) were largely unavailable.

Overall, all types of socioeconomic impact (i.e. financial, educational, and psychosocial) were documented both where TB's impact was direct and indirect. The limited number of studies, focussed on child and adolescent TB, did not allow detection of any difference in the three pathways involved (including both indirect and direct effects). The socioeconomic impact of TB was consistently negative across all studies. Whilst a comparison group was often unavailable, impact appeared to be in some cases quantitatively large: for example – 80% of children experienced cognitive impairment, 43% experienced poor scholastic progress, and 40% experienced emotional disturbance, as reported in a study on TB meningitis (12). We did not find any papers discussing physical impairment due to TB. Of particular concern are also longer-term sequelae, both in terms of cognitive and behavioural aspects, as reported for children affected by TB meningitis (12, 13). Two studies reported school drop out respectively as 2.6% and 11% for children/adolescents (4, 10) while studying a larger sample of adults. In one Indian study (10), 8% of children had to start working to support the family during a TB episode in the household as anticipated by the indirect educational pathway.

Qualitative findings: Overall, the qualitative results suggest that experiencing TB during childhood/adolescence (whether directly or indirectly) appears to impact negatively. Effects were seen in the papers on financial impact of TB: where work relating to caring and treatment requirements by parents impacted on family spending, nutrition and education, and overall reduced household income was associated with reduced family wellbeing. TB impacted on children's education, particularly when the affected family member was male and the primary source of household income. Hospitalisation and other challenging aspects of TB treatment, including directly observed treatment, also impacted on school attendance. Stigma was broadly reported in the studies (n = 15). Stigma was both perceived and enacted. Even where TB did not result in enacted stigma or explicit discrimination, perceived stigma persisted. Perceived stigma may be defined as individuals thinking or believing that others will discriminate or persecute against them, based on societal stigma or the belief systems of others, contributing to heightened anxiety, fear, and barriers to access, noted in two studies from South Africa (14, 15). Stigma was noted in the studies to have practical implications for TB diagnosis, clinic attendance and treatment. The experience of stigma also related to gender and sex. Papers reported a stronger TB-related stigma for women than for men, which also applied to girls as opposed to boys, particularly at the age of marriage. Reports from Vietnam (16), India (17) and Ghana (18) suggested that TB and its associated stigma could impact particularly a young woman's perceived eligibility and marriage potential.

TB also had other psychosocial impacts beyond stigma – with some positive findings of support groups extending into broader social networks (19). However, TB in the family was reported to contribute to the breakdown of parental relationships (14, 20). One possible cause for this was increased household stress, and indeed, parental stress due to the social and economic implications of TB (15, 21, 22). Parental guilt was also described, given the possibility of TB transmission from a parent, or another family member, to their child (15, 21, 22), or fear of onward TB transmission (14). Fear of TB transmission resulted in voluntary separation of children from their parents (16, 20, 22–25). TB in the family influenced how and by whom children were cared for in Ghana, China, and Nepal (18, 26–28).

We included six reviews in the study. The reviews mainly corroborated the evidence from primary studies.

Gaps in evidence: Comparing the conceptual framework with located evidence

Overall, most pathways (except for violence, which we had expected might be reported) seem to be supported by the evidence identified. However, the articles considered in this review were generally too few to distinguish between multiple theoretical pathways, whether quantitative or qualitative.

There were no overt differences identified between the pathways involved in the direct and indirect effects of TB: most pathways were documented in both domains. There was an imbalance in the evidence identified – stigma is an area that has been researched extensively, and we could find more evidence for its effects, than that of, for example, education. There were also gaps in the way in which the financial impact of TB was represented. While we know that the financial impact of TB can result in catastrophic costs for households (e.g. (1)), data presented by several studies was not specific to children and adolescents, suggesting a need for disaggregation to understand the financial impact in this group.

There were no unanticipated impacts that we discovered in our detailed search of the literature, suggesting that the framework captured relevant types of impacts adequately. However, more, and more robust research is needed on each of the components of the framework, and on understanding how they impact on children's and adolescents' wellbeing.

Discussion

To our knowledge, this is the first attempt to systematically appraise the socioeconomic impact of TB specifically on children and adolescents. Our review indicates that TB impacts negatively on the social, economic and psychological wellbeing of children, adolescents and families. Most studies identified, however, were cross-sectional, examining these issues in the short-term. Little is known of the longer-term consequences of TB on the family unit, including of the separation of children from parents during critical stages of development.

The financial impact of TB on the family unit was more pronounced in studies that explicitly studied the economic effects of TB on individuals and households (e.g. (4)). It was evident that parents, frequently mothers, had to give up work in order to care for their children with TB (29). Maintaining household income was made more difficult by clinic opening times that often conflicted with working hours (30). The challenges in prioritizing TB treatment and care for families and individuals are well established (31). One study emphasised the role of 'home care' as opposed to facility based care, which was more flexible, took less time, and allowed parents to combine caring for their children with employment (32). In combination with the hidden costs of visiting children in hospital, home care with adequate medical and social support may be a potential strategy to reduce financial strain to households and reduce parental stress and anxiety. However, as highlighted by our consultation interview, such transfers of care from healthcare facilities to the community for e.g. monitoring their medication intake should only be done with adequate support for the parents responsible for the care of an unwell child.

The gathered evidence suggests that TB among children or adolescents, or in the family, could impact on children or adolescents' education, either through children being excluded from school or being too ill to attend it; or having to take up work or give up school due to financial struggles. TB can impact children and adolescents at a critical period, during preparation for 'final' or 'exit' exams that may contribute to their perceived educational attainment and onward career choice (21, 27). Examples of altered behaviour and/or cognition following TB meningitis (14) are of equal concern. Policies to support children and adolescents should include supporting them to continue in education while they are being treated for TB. Sadly, TB may be stigmatising, or misunderstood, by teachers and schools, with examples of children not permitted to return to school while on TB treatment (14, 27).

Stigma was examined in several included studies. Stigma among people with TB is extensively studied, and is thought to contribute to diagnostic delay, treatment non-adherence and adverse TB treatment outcomes (33). Stigma was identified in our review even for those requiring isoniazid preventive therapy in childhood, in an HIV endemic area (e.g. (34). Addressing stigma through community level interventions is relevant, including increased education among communities about the ways in which TB may be transmitted. Stigma may also be internalised by people with TB, which can contribute to anxiety and increased barriers to accessing care. Initial reports suggest that interventions such as TB 'clubs' and more patient centred care can be useful to reduce internalized stigma (35)

The findings of this review also emphasise the interconnected nature of family units. Even when only one person is affected by TB in the household, if that person provides the primary source of household income, the negative impact can be worse on children in their household (10). If the person affected is the mother, this impacts on household dynamics and care giving arrangements (e.g. (36)). In addition, evidence from this review suggested that TB may contribute to the breakdown of parental relationships, and consequently the family unit. These factors may all have profound effects on children or adolescents in the long term. The loss of a parent may predispose a child to poverty (independent of pre-existing wealth) and lower educational attainment (37). Single parent households are also predisposed to poverty, even in high income settings (38). We also found that families often separated children from their caregivers to prevent TB transmission, which may impact on child and adolescent wellbeing.

While we found no evidence of child abuse and neglect in the studies included, it is not uncommon for high levels of stress and extreme poverty to increase the risk of domestic violence. The consequences of violence for children include developmental delay, mental ill health and poor school performance, amongst others (39). We also found no evidence of alcohol or other substance use within affected households, though our consultation interview suggested that this is an important factor to consider.

Strengths and limitations

The strengths of this study include that the review evaluated several databases alongside grey literature, was authored by a large multidisciplinary team with independent selection of studies included. The search period was broad – from 1990 onward – which allowed for including important insights on TB meningitis (29), and caregiver perceptions of TB treatment for children (15). However, this scoping review is subject to limitations. First, as expected, there are few studies that focus on the socioeconomic impact of TB in children and adolescents (either directly or indirectly), and even less so using a quantitative methodology. We initially included, but then excluded four quantitative studies that had included children in their sample but failed to disaggregate findings for age groups (9, 40, 41). This emphasises the need to disaggregate data according to standardised age groups, to allow for comparison across different settings, as suggested by the WHO (2). Studies that did not disaggregate their findings could potentially have included valuable data for this review.

Expert recommendations

As a review team, based on the findings of our scoping review we recommend the following steps to better understand the socioeconomic impact of TB on adolescents and children:

1. Standardisation of age groups to allow for comparison of samples globally, alongside the disaggregation of all studies in terms of age groups affected to allow for responsive and/or focused mitigation strategies;
2. Consideration of alternative treatment adherence strategies, which may prioritise 'home treatment', to minimize the risks of exacerbating poverty during anti-TB therapy, while carefully weighing their potential burden to households; and

3. Further experimental and quasi-experimental studies evaluating social protection, including child grants, and other mitigation strategies suitable for addressing the burden of TB for children and adolescents.
4. Further large-scale ecological and big data of pooled dataset studies to evaluate the broader socioeconomic impacts of TB on children, adolescents and family units across different settings and comparison of effects according to different age groups in the short- and long-term;
5. Further prospective studies to investigate strategies to implement to best mitigate the long-term consequences of TB;
6. Consideration of the impact on the entire family unit and/or household when designing strategies and policies to mitigate the direct and indirect effects on TB on children and adolescents.

Conclusion

Our review found 42 studies across the world on the socioeconomic impact of TB among children and adolescents. Though most papers had a marginal focus on these age groups, the findings suggest that TB impacts on the wellbeing of children, adolescents, and families. The life course impact of TB on children and adolescents is highly plausible: the type of impact that was reported (either financial, psychosocial and educational) can potentially change the developmental trajectory of these individuals. The studies included in this scoping review could not fully demonstrate these impacts due to the lack of longitudinal and follow up data. We found the impact of TB to be mostly negative, with respect to the financial, educational, and psychosocial wellbeing of children, adolescents, and their families. More high quality, longitudinal research is needed to understand the long-term impact of TB on the life-course of children and adolescents.

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Background question 2: Teens with TB: Current Evidence and Expert Consensus Recommendations to Address Adolescent Needs in Tuberculosis Care

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The World Health Organization (WHO) defines adolescents as individuals between 10–19 years of age.[1,2] Adolescents are distinct from younger children and adults; they undergo dynamic physical, psychological, emotional, cognitive, and social development – all of which have implications for their health and well-being. Despite the specific characteristics of this age group, adolescent health data, including on tuberculosis (TB), are frequently grouped together with those of younger children or adults, resulting in the obfuscation of their specific needs, challenges, and outcomes.[3,4]

Impacts of TB disease and treatment on adolescent well-being

While further research is needed to inform each of these areas, TB and its treatment have clear, negative impacts across the following domains of adolescent well-being.[9]

Physical and mental health: Adolescents are at risk for TB infection, progression to TB disease, and loss to follow-up from TB care. Adolescents with multidrug-resistant TB (MDR-TB) and/or with TB-HIV co-infection are at particular risk for poor treatment outcomes, including death. Adverse effects of TB treatment, particularly second-line medications, have impacts on adherence, stigma, mental health, and quality of life. The risks of post-TB lung disease and other sequelae in adolescents have not yet been defined. Substance or alcohol use may impact treatment toxicity and care outcomes, but the prevalence of this problem among adolescents with TB is unknown, and strategies for recognizing and managing this comorbidity have not been defined. Further, there is a lack of data on TB risk and outcomes for pregnant adolescents.

Meanwhile, specific factors related to adolescent development and vulnerabilities impact engagement in TB prevention and treatment. Adolescents are not prioritized for provision of TB preventive therapy

(TPT). TPT uptake and completion rates for adolescents are seldom reported, though lower adherence to TPT has been associated with stigma, costs or challenges associated with clinic visits, and presence of risk behaviors.[10,11]

While data is limited, existing studies highlight treatment challenges for adolescents with TB. Some research suggests that adolescents with TB experience delayed or missed diagnosis.[12–14] Studies across diverse settings have found that adolescents have increased risk for poor adherence to TB treatment, including loss to follow-up.[5,15–19] Risk factors for poor adherence include HIV co-infection, age 15–19 years, prior TB treatment, and extrapulmonary TB.

A range of qualitative factors across socioecological levels impede adolescent engagement with TB treatment: family challenges, poverty, stigma, attending work or school, and migration. Further, treatment fatigue and adverse effects impact treatment adherence, particularly among adolescents with MDR-TB and/or TB-HIV-co-infection. Disengagement often occurs during the continuation phase of treatment when adolescents' symptoms improve and treatment frequency decreases. Facility-based directly observed therapy (DOT) presents particular barriers to adolescent engagement. Anticipated stigma, concerns about confidentiality, travel costs, and needs to attend school or work can make facility-based DOT inaccessible or unacceptable to adolescents.[20] Supportive relationships with family members, caregivers and healthcare providers promote treatment adherence.

Connectedness and positive contribution to society: Prolonged isolation and hospitalization have substantial psychosocial and emotional impacts on adolescents, for whom peer and family relationships are critical from a developmental standpoint. Further, TB-related stigma impacts adolescent well-being and engagement with TB services. Family and peer relationships may, in turn, be disrupted or strained by isolation, separation, or by the effects of stigma.

Safety and a supportive environment: Adolescents with TB may experience threats to their human rights, including rights to safety, basic needs, access to healthcare without discrimination, protection against unnecessary hospitalization, and a right to benefit from scientific progress. Adolescents and their families may incur devastating financial impacts, loss of income, and food insecurity from TB and its treatment. Social and economic vulnerabilities place adolescents at risk for poorer treatment outcomes, including loss to follow-up, treatment failure, and death. Further, adolescents with TB are denied rights to benefit from scientific progress when they are excluded from research studies. Gender-based inequalities may be reflected in adolescent females' increased risk of HIV infection and, subsequently, TB disease.

Learning, competence, education, skills, and employability: Adolescents experience marked disruptions to their education due to TB and its treatment. The time-intensive demands of facility-based DOT interfere with ongoing education; conversely, needs for education may disrupt engagement with TB services. Prolonged isolation or hospitalization further exacerbates educational disruptions or setbacks. As a result, impacts may be significant on adolescents' future livelihoods.

Agency and resilience: Effects of stigma and of hierarchical models of care, e.g., facility-based DOT, may undermine adolescent agency. Further, threats to social networks and rise in mental health challenges may impact adolescent resilience. At the same time, some adolescents with TB demonstrate resilience by forming strong relationships with peers who also are on treatment and/or finding a sense of purpose or meaning from their illness experience.

Expert consensus recommendations for adolescent TB care engagement

Investments in adolescent-friendly TB services are urgently needed to ameliorate negative consequences of TB and its treatment on adolescent health, well-being, and future livelihoods. To support the well-being of adolescents with TB and to optimize their engagement in care, an international group of

experts in TB and adolescent health, including clinicians, researchers, advocates, and former patients propose: (A) the urgent reform of current practices that are harmful to adolescents with TB, and (B) the development of an adolescent-specific plan within each National TB Program (NTP) to provide high-quality adolescent-centered TB services.

A. Current practices that are detrimental to adolescent well-being should be urgently reformed.

1. Because adolescents aged 10–19 years old and young adults aged 20–24 years old have unique TB-related risks and healthcare needs with respect to care engagement and their dynamic trajectories in growth and development, NTPs should report age-disaggregated data for 10–14, 15–19, and 20–24 year-olds.
2. Because adolescents have particular epidemiological risks for TB exposure and increased biological risk for developing TB disease after infection, they should be included as a priority group for active TB case-finding, contact tracing, treatment of TB infection, and TB education.
3. Daily *facility-based* DOT harms adolescents by disrupting social relationships, education, and vocational training. Moreover, daily facility-based DOT acts as a barrier to adherence because it is inconvenient and because individuals fear being seen receiving TB care. Family-oriented, community-based models of care *should replace* daily facility-based DOT for adolescents. Within developmentally-appropriate treatment models, DOT may be delivered in a context-specific manner by a community health worker, a peer supporter, and/or by digital adherence technologies, such as video DOT. Alternatively, medication administration by a family member or caregiver who is trained and supported by health providers may be considered for selected adolescents.
4. Because adolescents treated for TB in diverse settings report loss of interpersonal relationships, significant interruptions to education, and depression that are greatly exacerbated by prolonged isolation and/or hospitalization for TB treatment, country-specific approaches should minimize isolation and hospitalization for TB. Isolation policies should be implemented only on the basis of evidence for infectiousness. Adolescents should be allowed back to school, higher education, vocational training, or work as soon as they are no longer infectious and appropriate support and treatment adherence structures are in place.
5. Adolescents younger than 18 years of age often are excluded from TB research; as a result, they are unable to benefit from new advances in TB therapeutics. Adolescents – especially those under the age of 18 years – should be prioritized in clinical trials and observational studies of treatments for infection and disease caused by drug-susceptible and drug-resistant TB, as well as research on TB diagnostics.
6. Because adolescents have greater challenges around adherence to treatment, including loss to follow-up from TB care, and because TB treatment often interferes with their education and other developmental tasks, adolescents should receive the shortest effective TB treatment regimens.
7. Adverse treatment events, including consideration of the acceptability to adolescents of a drug's potential adverse effects, should be discussed with adolescents and their caregivers prior to starting treatment. For instance, clofazimine is increasingly used as part of drug-resistant TB regimens, but the reversible skin discoloration associated with clofazimine can lead to discrimination and negative impacts on social relationships. This known adverse effect causes significant distress for adolescents and their families, who often do not know that skin discoloration reverses soon after clofazimine is discontinued.
8. Because rifamycins render hormone-based contraception less effective, TB providers should counsel or help adolescents access alternative contraception methods.
9. Adolescents should not receive injectable agents, unless as a last resort. Due to their youth, hearing loss associated with injectable agents is particularly devastating for adolescents: they not only are in school or entering the workforce, but also ideally have decades of healthy life ahead

of them. Moreover, facility-administered daily administration of injectable agents is time-intensive and interrupts schooling, vocational training, higher education, and work.

B. NTPs should develop and implement policies to provide high-quality adolescent-centered TB services that promote adolescent engagement in TB care and successful treatment outcomes, without compromising other aspects of their health, development, and well-being.

The WHO established standards for quality adolescent health services, which are equitable, accessible, acceptable, appropriate, and effective.[21,22] There is an urgent need to adopt these standards within TB programs to provide quality care and achieve successful TB outcomes for adolescents.

Each NTP should immediately begin to develop a plan to provide high-quality adolescent-friendly services. Plans should be developed through processes overseen by expert committees in TB care and adolescent health, adolescents and young adults who have been treated for TB and their families, and youth advocates. Committees should assess current gaps and barriers to delivering quality adolescent healthcare within TB programs. Plans should be informed by age-disaggregated TB data and indicators, as well as by existing adolescent-friendly models of care for HIV, sexual and reproductive health, and other health conditions. The implementation of adolescent-oriented plans should be monitored and disclosed as part of national reporting.

NTP plans to improve adolescent TB services should be setting-specific, and should include the following components:

1. Optimally, adolescents should be managed by providers who are knowledgeable and skilled in caring for this age group. Training should be regularly provided to TB clinicians, nurses, and/or multidisciplinary staff about adolescent health, with the goal of better understanding and responding to the needs, values, and preferences of adolescents, and providing confidential, nonjudgmental, and destigmatizing care.
2. Training should be provided to general and specialist healthcare providers to increase their awareness of adolescent-specific risks with respect to TB, and the appropriate use of TB screening, diagnostics, and/or referral.
3. Increase adolescents' access to TB services, such as by offering after-school and weekend clinic hours; minimizing clinic wait times for adolescents; providing community-based or decentralized TB care for adolescents; and facilitating easy transfer between TB care sites when adolescents need to relocate, such as for school, work, or changing living situations.
4. TB services should actively identify wider healthcare needs of adolescents with TB by integrating TB care with other health services, such as within comprehensive adolescent health clinics. In the absence of co-located services, TB services need to develop clear referral pathways for common health concerns such as reproductive healthcare, prenatal care, HIV care, treatment of substance use disorders, immunization, and mental healthcare.
5. Provide education and youth-friendly information that is accessible to adolescents, their caregivers, and the general public, with the goal of reducing TB-related stigma and increasing public awareness about adolescents' susceptibility to TB, TB symptoms, and ways to access TB testing.
6. Address the psychosocial and mental health needs of adolescents with TB, including risks for depression and substance use. Interventions to prevent common mental disorders (e.g., depression and anxiety) should promote social connectedness. Consider routine screening for mental health disorders, provision of counseling and other forms of psychological support, employment of trained peer counselors, and formation of peer support groups.

7. Empower caregivers to effectively support adolescents' TB treatment. Empowering caregivers may include education, counseling, and identifying and addressing family or caregiver needs, such as financial hardship.
8. Collaborate with the education sector to develop policies that promote school engagement and retention of students with TB, facilitate TB screening and contact tracing, and provide adherence support for TB treatment if needed for students at school. Actively engage with local schools to build student understanding of TB and support the ability of schools to practically and positively respond to students with TB.
9. Work with other sectors to address basic needs for adolescents with TB and their families. These may relate to catastrophic financial impacts (both direct and indirect) of TB and its treatment on basic needs including food security and needs for adolescents to continue education.

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Cost-effectiveness of integrated and family-centred models of care

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The CaP TB project included 9 sub-Saharan Africa countries and sought to: 1) improve detection of children (0–14 years) through facility-based intensified case-finding (ICF); 2) improve provision of tuberculosis preventive therapy (TPT) among a) household contacts 0–4 years, and b) children living with HIV attending HIV clinics. The ICF intervention included implementation of systematic TB screening in different child -health entry points (OPD, IPD, HIV, MCH, and nutrition clinic), building frontline HCWs capacity to clinically diagnose pediatric TB, introduction of sample collection procedures and support for Xpert testing as initial diagnostic test, support for access to CXR. The TB screening was performed using a child-adapted TB screening tool including signs and symptoms of pediatric TB. In health services with high volumes of attending patients, the TB screening was performed by community health care workers (CHWs) in waiting areas and/or triaging areas. The contact investigation and TPT interventions used community-based household contact screening where possible, and included referral to facilities for symptomatic children aged 0–14 years for TB evaluation, as well as asymptomatic 0–4 years for TPT initiation. Enhanced pediatric TB training, site-support and supervision was provided to support pediatric TB management and project interventions. The comparator was standard of care (SoC) in each country.

The project also included a programme evaluation ('TIPPI') that recorded before/after intervention data at a site-level. We analysed TIPPI before/after site-level data on anti-TB treatment (ATT) and TPT rates for Côte d'Ivoire, Democratic Republic of the Congo, Malawi, and Zimbabwe: the 5 of 9 countries with regulatory approval so far granted for data analysis. The intervention data included in the analysis covers the period between December 2018 and December 2020.

For ATT, 77% of sites had higher rates during the intervention (mean site rate 0.99 treatment initiations per month) compared to during SOC (mean site rate 0.42 treatment initiations per month), and country ATT success rates all increased (median 81% to 89%). One country experienced drops in ATT rates due to challenges on the ground that were unrelated to the intervention implementation. A hierarchical model provided a meta-analytic summary rate ratio across all countries of 1.38 (95%CrI: 0.41 – 4.26), corresponding to a 38% increment in children aged 0–14 years treated.

For TPT, 93% of sites had higher rates during the intervention (mean site rate 4.62 TPT initiations per month) compared to before intervention (mean site rate 1.05 TPT initiations per month) and country TPT completion rates all increased (median 74% to 91%). A hierarchical model gave a summary rate ratio estimate of 4.52 (95%CrI: 1.99 – 9.53), corresponding to a 350% increment in children aged 0–14 years starting TPT.

We analysed project financial and cascade data to estimate the cost of the intervention relative to baseline rates, capturing changes in resources used and additional investments in training and M&E. We modelled changes in mortality and discounted expected life-years lost (3% discount rate) to

estimate the interventions' impact on health and the incremental cost-effectiveness ratios (ICERs) in terms of US$ per DALY averted.

It is important to note that very preliminary data was available for sharing with the WHO GDG (June 10, 2021). The preliminary data has since gone through additional review and analyses which has identified several cost classifications that require revision to ensure costs inclusion accuracy. These revisions are still ongoing and are essential before considering the results presented, and subsequent conclusions drawn, to be final. The original preliminary data shared with the GDG is included below; however, these data are expected to change and should not be considered final.

For the ICF intervention, country central estimates of deaths averted per 100 children starting ATT under SoC varied between 11 & 46 (excluding the country that experienced drops). Country ICERs ranged between 238 & 646 US$/DALY (excluding the country that experienced drops). These positive ICERs were less than GDP and comparable or less than 0.5 x GDP, except in one country.

For the TPT interventions (including household case-finding), country central estimates of deaths averted per 100 children starting TPT under SOC varied between 3 & 21. Country ICERs ranged between 301 & 1529 US$/DALY. ICERs were less than GDP and comparable or less than 0.5 x GDP in one country, and over GDP in the other countries. The costs associated with TPT are higher than expected and the underlying allocation of costs is under review, which is likely to change these results.

Analysing both ICF and TPT intervention components as a single intervention gave ICERs similar to those of the ICF component, which accounted for most of the incremental costs and health benefits of the combined package. Interventions were more cost-effective among children aged 0–4 years than among children 5–14 years. Limitations of our analyses include confounding with before/after comparisons (eg the country that experienced drops in ATT rates), omission of patient costs, difficulty in isolating project costs that may exceed analogs under implementation (eg wage rates), and modelled rather than measured health outcomes. Most limitations are on the side of biasing ICERs upwards (ie towards being less cost-effective).

As mentioned, those data have to be considered preliminary and will be updated in a number of respects. In particular, regulatory approval to use before/after site-level will allow inclusion of the remaining 4 TIPPI countries in sub-Saharan Africa. Additional costing work is ongoing to better separate out the costs of facility-based vs household screening and preventive therapy, and to revise unit costs in some countries where ongoing ramp-up during data collection may introduce bias.

Feasibility and acceptability of decentralizing paediatric TB microbiological diagnostic approaches

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Background

Childhood tuberculosis (TB) remains largely underdiagnosed. The vast majority of childhood TB deaths are as a result of lack of access to treatment mainly due to under-diagnosis, especially among young children. Most of this limited access to TB services is structural: in most resource-limited countries, childhood TB services are centralised at secondary and tertiary care levels: primary health care centres (PHC)s are not routinely involved in TB care and are supposed to refer cases with clinical suspicion of TB. However, in many PHCs staff are not trained to identify potential TB cases and referral is poor. In

some countries, proper paediatric TB services are not even available at secondary level of healthcare, i.e. at district hospital. In some countries, childhood TB services are also poorly accessible at district hospital (DH).

There is limited evidence on the feasibility of decentralisation of TB services in children and the best decentralization model for diagnosis of childhood TB. However, some studies reporting decentralising adult TB services have shown improved patient access and quality of care.

Design/Methods

1. Feasibility (Uptake) and yield of deploying systematic screening and an innovative TB diagnostic package, and of decentralizing NPA and stool testing with Xpert MTB-RIF Ultra at district hospitals and primary health clinics levels – Preliminary data

TB-Speed Decentralization is an operational research study using a before and after cross-sectional design to assess the impact of decentralizing an innovative childhood TB diagnostic approach on case detection. The intervention is at two levels: at patient care level where an innovative childhood TB diagnostic approach is implemented, including systematic TB screening, clinical evaluation, nasopharyngeal aspirate (NPA) and stool or sputum testing using Xpert MTB/RIF Ultra (Ultra), and optimised chest X-ray (CXR) reading (digitalization, training and quality assurance); and at health systems level where two distinct decentralization strategies are implemented, the DH-focused and the PHC-focused strategies. Two districts with one DH and 4 PHCs per participating countries have been randomly assigned to implement the DH or PHC-focused strategies. We assessed the feasibility (uptake) and yield of deploying systematic screening and an innovative TB diagnostic package, and of decentralizing NPA and stool testing with Xpert MTB-RIF Ultra, at DH and PHC levels. Data of OPD attendance/screened children and presumptive TB are from aggregated data collected during the study. Data of enrolment and TB diagnosis are from individual data collected during the study.

2. Knowledge on childhood TB and feasibility and acceptability of decentralizing TB diagnosis including NPA and Stool collection for Ultra testing at district hospital and primary health level clinics – HCW perspective – Preliminary data

We aimed to assess the knowledge, attitudes and practices (KAP) of health care workers (HCW)s from the study DH and PHCs on childhood TB, and assess their experience, and perceptions regarding the childhood TB diagnosis approach implemented in their facility. We conducted a repeated cross-sectional survey among 400 to 500 HCWs, before the intervention period and in the last 3 months of the intervention period, based on a self-administered KAP questionnaire.

3. Feasibility and acceptability of decentralizing NPA and Stool collection for Ultra testing at District hospital and primary health clinics – Health Systems Perspective – Preliminary data

We aimed to describe the early successes and challenges of implementing the childhood TB diagnostic approach at DH and PHC level. We reviewed the findings from support supervision and clinical mentoring visits, which included observations, document review and open-ended interviews

Results

1. Feasibility (Uptake) and yield of deploying systematic screening and an innovative TB diagnostic package, and of decentralizing NPA and stool testing with Xpert MTB-RIF Ultra at district hospitals and primary health clinics levels – Preliminary data

By 31st March 2021, a total of 35140 sick children had attended OPD at DH and 76804 at PHC.

	DH	PHC
	N % of upper level *(% of OPD attendance)*	N % of upper level *(% of OPD attendance)*
OPD attendance	35140	76804
Screened	22978 65.4%	64400 83.8%
Presumptive TB	1926 8.4% *(5.6%)*	1303 2.0% *(1.7%)*
Enrolled in the study	1099 57.1% *(3.1%)*	647 49.7% *(0.8%)*
TB diagnosed	201 18.3% *(0.6%)*	36 5.6% *(<0.1%)*

Of 1746 children with presumptive TB enrolled, 1228 (70%) had a valid Ultra result obtained from stools (71.5% at DH and 77.9% at PHC), and 1582 (91%) had a valid Ultra result obtained from NPA sample (89% at DH and 95.2% at PHC). Thirty-nine children (2.2%) had a positive Ultra on either stools or NPA. Additionally, 198 (11.3%) children with negative/missing Ultra initiated TB treatment or were diagnosed with TB.

2. Knowledge on childhood TB and feasibility and acceptability of decentralizing TB diagnosis including NPA and Stool collection for Ultra testing at district hospital and primary health level clinics – HCW perspective – Preliminary data

In the 497 HCWs surveyed, knowledge of childhood TB (global score) was 10.2 in median (maximum 18) during the pre-intervention survey, and increase moderately to 11.0 during the post-intervention survey of 404 HCWs. Knowledge scores were comparable at DH and PHC levels.

Systematic screening was perceived as not so easy in 37% of HCW at DH and 23% at PHC-level, however all reported positive attitudes regarding the role of screening in childhood TB diagnosis. From 10% HCWs at DH and 16% at PHC reported not always being able to collect stool from children on the spot. Between 45% of HCWs at DH and 65% at PHC reported always needing help to restrain the child during the NPA procedure. Among HCWs involved in TB diagnosis, 11% of HCWs at DH and 12% at PHC reported facing challenges in accessing CXR on time for TB diagnosis and more than 25% of them reported always basing their decision on clinical diagnosis only.

3. Feasibility and acceptability of decentralizing NPA and Stool collection for Ultra testing at District hospital and primary health clinics – Health Systems Perspective – Preliminary data

Overall, 138 support supervision visits were conducted across the 59 study sites/health facilities in 6 countries. Among the main lessons learned from **early stages of implementing** the diagnosis approach at DH and PHC-levels are:

- TB-Speed screening questions were complex to understand (for HCWs and parents) => required to be phrased in 2 steps (presence of symptoms and then duration of symptoms)
- Stigma associated with TB screening in waiting area
- Quality of NPA procedure is correct but sample volume is low
- Difficulties to collect stool during the child's presence at health facility; challenges for parents to travel back with stool container (no transport, no money)
- Power instability (PHC as well as DH) in most countries impacting on sample testing

- Long turnaround time for stool testing at DH (up to 8 days) mostly due to attitudes of staff (extra work, reluctance, demand for extra incentives)
- Poor transport conditions (long distance, bad terrain and heavy rains; sample transported without maintaining temperature)
- Unavailability of radiographers for CXR: leave, training
- Referral to DH often sub-optimal: distance, time, money, and reluctance from parents, but also poor communication means and follow up mechanisms between PHC/DH
- Lack of trained staff onsite due to rotation/transfer to other facilities

Clinical mentoring was conducted concurrently with support supervision in all sites except the PHC in the DH focused strategies.

Observation of clinical examination practices was rarely done as there were no eligible participants on the day of mentoring. Mentors observed that most clinicians were getting more confident over time with making a TB diagnosis decision. Some remain hesitant to make a TB diagnosis decision if Ultra results and CXR findings were negative.

Conclusion

Preliminary findings from the TB-Speed Decentralization study show the overall good feasibility of decentralizing childhood TB diagnosis at low level of healthcare including primary healthcare level. They also highlight structural and organizational challenges in the early implementation of the childhood TB diagnostic approach at decentralized levels of care, but no major differences between DH and PHC. There is a high uptake of NPA and stool sample collection methods at both DH and PHC level but the overall Ultra detection yield is low. Ongoing support supervision has been addressing many of the operational challenges; and clinical mentoring is key to help clinicians getting better confidence in clinical and CXR reading skills for diagnosis. Childhood TB diagnosis decentralized at DH and PH seems highly acceptable to HCWs (positive attitudes shared within the post-intervention KAP survey). Preliminary findings underline the important contribution and role of clinical diagnosis of TB at decentralized levels of care.

Trial registration: TB-Speed Decentralisation: ClinicalTrials.gov, NCT04038632; https://clinicaltrials.gov/ct2/show/NCT04038632

Keywords: children, decentralisation, tuberculosis, nasopharyngeal aspirate, stool, Xpert MTB/RIF Ultra

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Background

Nasopharyngeal aspirate (NPA) and stool sample have been recently endorsed by WHO for diagnosis of paediatric tuberculosis using Xpert MTB/RIF. Additional data using Ultra will be available soon but feasibility and acceptability data of using these samples is still lacking from high burden and resource limited countries. In addition, there are almost no safety data so far published using NPA in children for diagnosis of TB. Both stool and NPA are specimen collected and tested with Ultra for diagnosis of TB in children in ongoing TB-Speed studies.

Design/Methods

1. Feasibility (uptake) and yield of Ultra testing on stool samples in children <15 years with presumptive TB at district level

TB-Speed Decentralization is an operational research study using a before and after cross-sectional design to assess the impact of decentralizing an innovative childhood TB diagnostic approach. The intervention is at two levels: at patient care level where an innovative childhood TB diagnostic approach is implemented, including systematic TB screening, clinical evaluation, NPA and stool or sputum testing using Xpert MTB/RIF Ultra (Ultra), and optimised CXR reading; and at health systems level where two distinct decentralization strategies are implemented: the district hospital (DH)-focused and the PHC-focused strategies. Two districts with one DH and 4 PHCs per participating countries have been randomly assigned to implement the DH or PHC-focused strategies. We assessed the feasibility (uptake) and yield of Ultra on stool samples in children with presumptive TB enrolled in the study.

2. Feasibility (uptake) and yield of Ultra testing on stool samples in children <5 years hospitalized with severe pneumonia

TB-Speed Pneumonia is a stepped-wedge cluster-randomized trial enrolling children aged <5 years with WHO-defined severe pneumonia in 15 hospitals from 6 high and very TB incidence rate countries (Cambodia, Cameroon, Côte d'Ivoire, Mozambique, Uganda, and Zambia) to evaluate the impact on mortality of a systematic TB detection. The intervention consisted of systematic Ultra testing on 1 NPA and 1 stool sample at hospital admission. Children were followed-up for 12 weeks. We assessed the feasibility (uptake) and yield of Ultra on stool samples in children with severe pneumonia.

3. Feasibility and acceptability of stool samples in children with severe pneumonia, HCW and parents' perspectives

Social sciences research assistants conducted semi-structured individual interviews with selected parents of children enrolled in the TB-Speed Pneumonia study (n=59), and with all study nurses (n=63) from the 15 hospitals. We assessed their experience and perceptions of stool sample collection.

4. Feasibility (uptake), safety, tolerability, acceptability of Ultra testing on NPA in stool samples in children with presumptive TB at district level and in children <5 years hospitalized with severe pneumonia

We assessed feasibility of Ultra testing on NPA using similar methods to stool feasibility assessment. Study nurses reported adverse events occurring during NPA collection on standardized forms. We assessed tolerability of NPA by assessing discomfort/distress/pain experienced by the child before and during NPA collection using 3 validated pain scales, the Wong Baker Face scale (WBFS; assessment by the child if aged >3 years), the Visual Analog Scale (VAS; assessment by the parent/guardian), and the Face Legs Activity Cry Consolability Behavioral scale (FLACC; assessed by study nurse themselves).

We used the same qualitative methods as report the assessment of stool acceptability to assess parents' and HCW's perspective on NPA collection (and Ultra testing).

Results:

1. Feasibility (uptake) and yield of Ultra testing on stool samples in children <15 years with presumptive TB at district level

Data are presented for 1746 children with presumptive TB; 818 (46.9%) were female, with a median age of 3 [1, 7] years; 69 (4%) presented with severe acute malnutrition.

Of those 1746 children, 1390 (79.6%) children had stools collected, 1333 (76.3%) stools tested with Ultra, 1228 (70.3%) with a valid Ultra result, and 16 (0.9%) testing positive.

There were 39 children with microbiologically diagnosed TB and 230 (13.2%) clinically diagnosed with TB. Yield of ultra in children with TB diagnosis was 16/269 (5.9%) for stool samples, 30/269 (11.2%) for NPA, and 39/269 (14.5%) for both samples.

2. Feasibility (uptake) and yield of Ultra testing on stool samples in children <5 years hospitalized with severe pneumonia

We enrolled 1170 children in the intervention arm; 492 (42.1%) were female, with a median age of 11 [6, 20] months. 60 (5.1%) were HIV-infected, and 289 (24.7%) presented with severe acute malnutrition. The median peripheral oxygen saturation at admission was 94% [IQR: 88, 97].

944 (80.7%) children had a stool sample collected, including 921 (78.7%) with stool tested with Ultra, 905 (77.4%) with a valid Ultra result, and 16 (1.4%) testing positive. Overall, 24 (2.1%) children had a positive Ultra on either NPA or stools.

Additionally, 58 (5.0%) children were clinically diagnosed. Yield of Ultra in children diagnosed with TB was 16/82 (19.5%) for stool samples, 21/82 (25.6%) for NPA, and 24/82 (29.3%) for both samples.

3. Feasibility and acceptability of stool samples in children with severe pneumonia, HCW and parents' perspectives

We report on preliminary findings from 50 interviews (32 parents and 18 nurses). Most respondents were female. Nurse's experience in TB-Speed Pneumonia study ranged from 1 month to 2 years.

The large majority of **parents** of all the 6 countries found that stool collection was an easy, straightforward and **normal** way of collecting a sample. Some parents however felt stool sample collection was **not that rapid and easy**, as sometimes children cannot pass stool immediately, and thus doctor/nurse are unable to do the test. Parents reported having **lacked information** about the purpose of and procedure (quantity) for stool sample collection and **did not always clearly understand** the role of stool sample collection for TB diagnosis.

Nurses appreciated that stool collection was effortless and painless (compared to NPA) and a sample collection method **adapted to all children** as long as they can produce stool. They reported challenges with **delays** in obtaining the samples, need to rely on parental collaboration and fear of **contaminated samples** when stool is collected by parents and if not done appropriately. Some nurses were taught for the first time that stool could be tested for TB diagnosis and appreciated that stool could be an alternative diagnostic tool for children.

4. Feasibility (uptake), safety, tolerability, acceptability of Ultra testing on NPA in stool samples in children with presumptive TB at district level and children <5 years hospitalized with severe pneumonia

Of 1746 children enrolled in the study at district level, 1648 (94.4%) had a NPA attempted, including 1653 (94.7%) with a successful NPA collection, 1634 (93.6%) with a NPA tested with Ultra, 1582 (90.6%) with a valid Ultra result, and 30 (1.7%) testing positive.

Of 1170 children with severe pneumonia, 1148 (98%) children had a NPA attempted, including 1141 (97.5%) with a successful NPA collection, 1131 (96.7%) with a NPA tested with Ultra, 1120 (95.7%)

with a valid Ultra result, and 21 (1.8%) testing positive. The overall median turnaround time (TAT), i.e. from sample collection to Ultra result communicated to the clinician, was 2.45 [1.78 – 3.85] hours for NPA, and 4.48 [2.67 – 19.0] hours for stools. No severe adverse events related to NPA were reported.

In terms of tolerability, the median increase in the discomfort/distress/pain score between before and during NPA procedure was +4 (IQR: 2, 4) as assessed by the child (WBFS, n=46), +2 (IQR: 0, 4) as assessed by the parents (VAS; n=543); +3 as assessed by the study nurses (FLACC, n=543).

Most parents across all countries felt that NPA was a painful and fearful procedure for their child with severe pneumonia, some parents were **not able to stay** in the same room with their child during this procedure. Despite this, all participants reported **positive attitudes** towards NPA: this procedure aims to improve child health so it is worth it. They **trusted** nurses' skills, the fact that nurses were precise during the procedure, and didactic about it. Parents did not always clearly **understand** the diagnostic role of NPA sample collection for TB diagnosis. Some parents perceived NPA as a procedure which **helped** to facilitate their child's breathing.

Nurses, as parents, perceived NPA as an **unpleasant/painful procedure** for children, which often required repeated aspiration. Almost all the nurses reported that NPA is not possible by a HCW alone, it **requires additional support** from another colleague or parents to restrain the child, to reassure the child. Overall, however, nurses were **positive** about NPA as it contributes to improve child health and probably, in fine, contributes to reduce mortality. Most of the nurses believed that, being less invasive and quicker to perform, NPA sample collection could replace other diagnostic tools like Gastric Aspirate.

Conclusion:

Overall stool samples could be collected in 4 out of 5 children (80%). However, the uptake not reaching levels obtained with NPA (95%).

Combined NPA and stool samples was highly feasible in children with presumptive at district level, and contributed to microbiological confirmation in 14.4% (39/269) of TB diagnosed cases.

Combined NPA and stool samples was safe, highly feasible in this vulnerable population, and contributed to microbiological confirmation in 30% (24/82) of TB diagnosed cases.

Parents and nurses having experienced stool sample collection (together with NPA sample collection) reported positive attitudes, in spite of delays in obtaining samples. Main factors contributing to acceptability of this procedure were valuing child health benefits, being informed and supported, and obtaining quicker results.

Trial registration:

TB-Speed Decentralisation: ClinicalTrials.gov, NCT04038632; https://clinicaltrials.gov/ct2/show/NCT04038632

TB-Speed Pneumonia: ClinicalTrials.gov, NCT03831906; https://clinicaltrials.gov/ct2/show/NCT03831906

Performance of Xpert MTB/RIF Ultra on stool samples among children with presumptive TB: A head-to-head comparison of three stool processing methods – Preliminary analysis summary

Sponsors

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FIND (SPK co-developer)

TB-Speed (OSF developer)

KNCV Tuberculosis Foundation (SOS developer)

University of California San Francisco (Site partner, Mulago Hospital, Uganda)

Heidelberg University (Economic assessment)

Rutgers University (SPK co-developer)

University of Cape Town (SPK co-developer)

Johns Hopkins University (Site partner, KEM Hospital, India)

Background

Among all cases of tuberculosis (TB) in 2019, children accounted for 12% of them with about 1.2 million cases[2]. However, diagnosing TB in young children is difficult, as the disease is often paucibacillary and it

[2] Global tuberculosis report 2020. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO

can be challenging to obtain adequate specimens, therefore these figures are likely an underestimation of the real TB burden in children.

Young children are unable to expectorate sputum, and so more invasive approaches, such as gastric aspiration, sputum induction or bronchoalveolar lavage, need to be used to collect specimens for diagnostic evaluation. Since such collection methods are not available in most settings in resource-limited countries, there is a critical need for a test using non-invasive specimens that can rapidly and accurately detect TB in children and simultaneously test for drug resistance.

Stool has shown promise as a specimen for the diagnosis of paediatric TB. *Mycobacterium tuberculosis* (MTB) bacilli are found in a sick child's stool, which can be sampled simply and non-invasively[3]. FIND and the TB-Speed Consortium (TB-Speed) are conducting two prospective, multicentre, diagnostic accuracy studies to assess the performance of stool processing solutions prior to Ultra testing for the diagnosis of pulmonary TB in children in Asia and sub-Saharan Africa. As part of these studies, three centrifuge-free stool processing methods are being compared head-to-head (H2H) using Xpert MTB/RIF Ultra (Ultra), namely: Optimized Sucrose Flotation (OSF), Simple One-Step (SOS) stool and Stool Processing Kit (SPK).

We present here a summary of pooled data from the two studies using similar protocols (referred to as "study" or "H2H study" for simplicity from here onward). These data were presented to the WHO Guideline Development Group (GDG) in June 2021 with the aim of supporting the evidence required to update the guidelines on the implementation of Ultra using stool samples for the diagnosis of pulmonary TB. Moreover, data from FIND and TB-Speed was also included in a systematic review commissioned by WHO in preparation to the GDG meeting. A cost-effectiveness analysis has also been conducted to support decision-making on the potential uptake of these methods, and the results are available in a separate report.

Methods

We performed pooled data analysis from two prospective multicentre diagnostic accuracy studies conducted by FIND and the TB-Speed at six sites in Uganda, South Africa, India and Zambia. Recruitment was done at a combination of sites from peripheral health centres to reference hospitals. Stool processing and Ultra was performed at the reference laboratory in each site.

The study objectives were:

- To determine the diagnostic accuracy of three stool processing methods in combination with Ultra for TB detection using microbiological confirmation on respiratory specimens as reference standard.
- To determine the acceptability and feasibility of three stool processing methods using standardized questionnaires applied to laboratory technicians responsible for stool testing.

[3] Walters E, Demers AM, van der Zalm MM, et al. Stool Culture for Diagnosis of Pulmonary Tuberculosis in Children. J Clin Microbiol. 2017; 55:3355–3365

Table 1. Overview of the main technical aspects of the three centrifuge-free stool processing solutions

	Stool SOS/Ultra	Stool SPK/Ultra	Stool OSF/Ultra
Developer	KNCV Tuberculosis Foundation	Alland Lab. (Rutgers), Nicol Lab. (UCT) & FIND	TB-Speed Consortium
Development stage	Completed	Design transfer (prototype)	Design validation
Additional supplies	Stool transfer supplies	Kit (including: filter device, stool transfer supplies, SPB/buffer)	Stool transfer supplies, scale, sample prep tubes, Sheather's solution*
Steps	• Estimate stool vol. visually • Mix with SR • Let sediment • Transfer supernatant into Ultra	– Measure stool – Mix with SPB & SR – Filter into Ultra cartridge	• Weigh stool • Mix with Sheather's solution • Let sediment • Transfer supernatant, mix with SR • Transfer into Ultra cartridge
Preparation time (median, range)**	23′ (20′–30′)	38′ (33′–55′)	56′ (45–87)***

SOS=Simple One-Step; SPK=Stool Processing Kit; OSF=Optimized Sucrose Flotation; SPB=Stool Processing Buffer; SR=Sample Reagent

*56% sucrose solution, to be prepared before use

**Data provided by M. Gaeddert et al. *An economic evaluation of three novel stool processing methods for diagnosis of tuberculosis in children five and under – Preliminary Analysis*, June 2021

***Excluding sucrose preparation time

After enrolment, children 0–14 years old with clinical suspicion of active pulmonary tuberculosis were asked to provide two sputa (or induced sputum, gastric aspirate or nasopharyngeal aspirate samples for very young children) and up to two stool samples. Three separate "aliquots" were obtained from each stool sample and were processed with each of the processing methods following the order given by a pre-defined Stool Sampling Randomization List, before Ultra testing.

Laboratory technicians/operators responsible for stool testing were trained on SPK, SOS and OSF by FIND, KNCV and TB-Speed respectively (or through a train-the-trainer approach), either onsite or remotely via videoconference. Standardized training material was provided to the laboratory. After the initial training, operators underwent a proficiency test individually. A moderator observed without intervening or correcting mistakes.

Primary diagnostic accuracy analysis was done using the microbiological reference standard (MRS) on respiratory samples using Mycobacteria Growth Indicator Tube (MGIT) 960 culture and Ultra. MRS-positive cases were defined as MTB culture positive or Ultra MTB detected (including trace). MRS-negative cases were those with MTB culture negative and Ultra not positive (i.e. MTB not detected, or invalid/error/no result in cases where MTB culture was negative).

For acceptability and feasibility assessment, the laboratory technicians were asked to independently fill a standard questionnaire based on their perception of ease of use, quality of the instructional material, and perceived feasibility at each step at two different time points.

Results

Of the 471 eligible children for the current analysis, 64.3% were younger than 5 years old, 47.6% were female, 24.5% were HIV-positive and 14.9% had a positive culture or Ultra result on respiratory samples. After exclusion of non-determinate Ultra results, the sensitivity and specificity of Ultra in stool were calculated with a 95% confidence interval (CI) (see Table 2).

Table 2. Performance stool processing methods against MRS

	N	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ultra/SOS	332	25	7	23	277	52.1 (38.3–65.5)	97.5 (94.9–98.9)
Ultra/SPK	368	28	9	30	301	48.3 (35.9–60.8)	97.1 (94.5–98.5)
Ultra/OSF	319	22	6	25	266	46.8 (33.4–60.8)	97.8 (95.1–99.1)

N=total number; TP=true positive; FP=false positive; FN=false negative; TN=true negative; CI=confidence interval

Children with results for all stool processing methods on the same sample and MRS results were included in a sub-matched-data analysis. Considering only the 27 MRS-positive samples with stool positive samples by at least 1 method, 17/27 (63%) stool samples were positive by all methods and 24/27 (89%) were positive by at least 2 methods. Among the 11 MRS-negative samples but stool positive by least 1 method, 6/11 (55%) stool samples were positive by at least 2 methods. Of the 5/11 (45%) stool samples that were positive by a single method, 4 were Ultra trace and for 1 the semi-quantitative result was not available. The Fleiss' Kappa coefficient for agreement between the three methods (positive and negative Ultra/stool) was 0.85 (95% CI 0.78–0.92).

Based on the initial Ultra runs, the proportion of non-determinate results were 8.7% (35/401) for SOS, 11.8% (53/451) for SPK, and 10.3% (40/388) for OSF.

Seventeen laboratory technicians answered the questionnaire. The three methods were reported as not difficult to perform by most of the participants, but 65% of respondents reported that the OSF method is time consuming as compared to only 12% for the SOS and 29% for the SPK methods. We asked participants to indicate any difficult step for each method and they reported the estimation of stool volume, depending on the type of stool, for SOS; filter block for SPK; and precise weighing and pipetting for OSF. Overall, there was no major biosafety risk identified for the three methods compared to Ultra sputum processing. The most cited barrier for implementation of SPK and OSF in routine settings was the need for additional supplies/reagents compared to Ultra sputum testing. Also, hands-on time for preparation and processing was commonly reported as a barrier for OSF. Overall respondents considered the three methods similarly easy to perform by laboratory staff. When asked about feasibility of processing by non-laboratory staff, 30% found that the SOS procedure could not be performed by non-laboratory staff, 47% thought the same for SPK and 59% for OSF. In terms of infrastructure, most participants found that all methods could be implemented in a peripheral health centre (PHC) equipped with a microscopy laboratory but 22% considered that the SOS method could not be implemented at a PHC without a laboratory (even if a GeneXpert were available), 41% thought that for SPK and 65% for OSF. The SOS method was the preferred method by 10 out of the 17 participants (59%), followed by SPK (7/17, 41%) and then OSF (1/17, 6%).

Discussion

Results to date show a similar performance of Ultra in combination with the three stool processing methods in terms of sensitivity and specificity. The limited number of children with a positive MRS in this dataset, results in rather wide confidence intervals for the estimation of sensitivity. Regarding the frequency of Ultra non-determinate results, this appears to be less frequent for SOS compared to the other two methods. Further analysis will be done to look at the error codes and interpret these in line with the type of specimens used.

In terms of user acceptability and feasibility, and given the study design, we conducted the assessment at reference laboratories with operators who are highly experienced and familiar with the biosafety requirements for TB testing. Nevertheless, these preliminary results show good acceptability of stool as a sample for TB diagnosis in children. All methods were found to be easy to process by laboratory staff at reference level and had a median high ease-of-use score. However, most users considered that these methods cannot be performed by non-laboratory staff, such as nurses or health care workers, in primary-health care settings without access to a laboratory. Therefore, assessment at this level of the health system would be needed. Overall, SOS appeared to be the preferred method as it does not require additional equipment and is comparable to Ultra sputum processing. Regarding OSF, users were less positive mostly due to the Sheather's solution preparation, weighing of stool with an electronic balance and the overall processing time, which was longer when compared to the other two methods. It should be mentioned, however, that OSF is still at a clinical validation stage. Development of a kit to simplify the implementation of the method is expected.

Our study and report have several limitations. First, given that this constitutes a preliminary analysis of an ongoing study, our analyses to assess diagnostic accuracy were limited by the small number of TB-confirmed cases. Therefore, the sensitivity estimates have wide confidence intervals. At the time of analysis, there was insufficient sample size to perform sub-group analyses and the results of the composite reference standard are still pending for most participants. Second, all three processing methods are currently at different development stages, which may add some complexity for a direct comparison.

Nevertheless, and despite these limitations, this is the first study comparing H2H the performance of three stool processing methods that avoids all selection and methodological biases highlighted by a recent meta-analysis (MacLean E et. al). The studies are still ongoing and final data will provide additional insights regarding the performance of the three methods.

Community views on active case finding for tuberculosis in low- and middle-income countries: a qualitative evidence synthesis focusing on children

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The work here builds on a Cochrane qualitative evidence synthesis in progress (16). The Cochrane review considered evidence for views of community-based screening programmes, from the perspective of community members with and without tuberculosis and community-based health workers. Community-based tuberculosis screening programmes included screening of whole populations (i.e., in the workplace or in schools) and screening of individuals, via active case finding and contact tracing efforts in the community. This report tailors the findings to children and adolescents.

Review question: In areas of the world where tuberculosis is common, what views do communities and high-risk populations hold about tuberculosis active case finding programmes?

Summary of methods: Our Cochrane qualitative evidence synthesis sought community views of active case finding and contact tracing for tuberculosis. After systematic searching and screening (search date March 2021; search strategies are published in protocol), data were extracted from studies reporting 'thick' or detailed findings (see protocol). We also extracted data from select studies assessed as having less detailed findings to inform our understanding of specific aspects of tuberculosis care not fully addressed in the thick studies. From these included studies (N=29), two review authors separately extracted data and created codes. The authors then discussed the data for each 'thick' paper and agreed to the codes, before one author entered this information into Atlas.ti.[4] For papers with less detailed data, one author extracted and coded the data before entering this information into Atlas.ti. A second author then checked the codes to confirm their accuracy. The full author team discussed the codes in weekly meetings to iteratively develop themes and an overarching framework. We assessed the quality of each included study and evaluated each finding with CERQual methods. We specifically tailored our findings to address PICO 6 of the guideline, Models of care for TB case detection and TB prevention. We conducted keyword searches of our study database to identify all evidence related to adolescents and children.

[4] ATLAS.ti 2020 [Computer programme]. Atlas.ti Version 9 for Mac. Berlin: Scientific Software Development GmbH, 2020. Available at www.atlasti.com. Accessed 17 May 2021.

Description of studies: The original review included 29 studies. Four of these studies focused specifically on tuberculosis in children (4, 9, 20, 25). Fifteen studies offered evidence about care of children and adolescents (2, 4, 6, 7, 9, 10, 13, 15, 20, 21, 22, 23, 25, 27, 28).

Quality assessment: We assessed the quality of included studies in terms of rigour in the sampling, data collection and analysis, whether the study grounded in/ supported by the data, and the study's breadth and depth.[5] Overall, all included studies were of good quality.

CERQual assessment: We evaluated our confidence in each finding by applying CERQual methods[6], to consider:

- **Methodological limitations** – concerns about the design or conduct of primary studies
- **Coherence** – how clear, well-supported and compelling is the fit between study data and finding
- **Adequacy of data** – the degree of detail and quantity of data supporting a finding
- **Relevance** – whether data supporting a finding is applicable to the review context

We assessed all findings to be of high confidence, or "'It is highly likely that the review finding is a reasonable representation of the phenomenon of interest."

Brief Findings:

Part 1. Introduction: Children were part of the population sought by Tuberculosis active case finding (ACF) and contact tracing programmes. Their contact with TB and ACF programmes depended largely on adults, many of whom responded to tuberculosis outreach according to their own priorities. Both sick and well adults prioritised employment over tuberculosis health services, which had direct implications for children.

Finding 1.1: Community-based tuberculosis active case finding and contact tracing improved access for those missed with previous case finding strategies (2, 3, 9, 11, 13, 17, 24, 26, 27).

Finding 1.2: Children were put at risk by contact with parents and teachers who, if they felt well, avoided tuberculosis screening. Some people with symptoms waited until their illness became severe, in part to avoid the social consequences of disease (4, 5, 8, 13, 17, 19, 20, 21, 23, 28).

Finding 1.3: Parents and others prioritised retaining their employment over tuberculosis services (4, 5, 7, 8, 10, 13, 15, 21, 23, 24, 28).

Part 2 – Communities on the edge: Tuberculosis active case finding and contact tracing improved access to health services for those with worse health and fewer resources. ACF found this population exposed to deprived living conditions, but without being sensitive to additional dimensions of their plight, such as their marginalisation or their information needs. Lack of information impacted community members and health workers alike and sometimes led to harm.

Finding 2.1: Many children in communities targeted for tuberculosis outreach suffered from material deprivation (4, 9, 11, 12, 13, 15, 17, 19, 27, 29).

Finding 2.2: Some respondents viewed tuberculosis as a dimension of material deprivation, like hunger. Where tuberculosis was strongly associated with material deprivation, people viewed secure socioeconomic status as protective against disease (4, 6, 8, 12, 19, 21, 24, 28).

Finding 2.3: Migrant and unstable populations, difficult geography and environmental pollution further compromised some marginalised communities (3, 4, 10, 11, 13, 17, 19, 22, 29).

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[5] Lester S, Lorenc T, Sutcliff K, Khatwa M, Stansfield C, Sowden A, et al. *What helps to support people affected by Adverse Childhood Experiences? A Review of Evidence*. London (UK): EPPI-Centre, Social Science Research Unit, UCL Institute of Education, University College London, 2019.

[6] Lewin S, Bohren M, Rashidian A, Munthe-Kaas H, Glenton C, Colvin CJ, et al. Applying GRADE-CERQual to qualitative evidence synthesis findings-paper 2: how to make an overall CERQual assessment of confidence and create a Summary of Qualitative Findings table. *Implementation Science* 2018;13(Suppl 1):10.

Finding 2.4: Community education improved awareness of tuberculosis in some settings, but lack of full information impacted community members, parents, and health workers, and sometimes led to harm for children (3, 4, 5, 8, 9, 12, 13, 14, 15, 17, 18, 19, 20, 21, 23, 24, 25, 27).

Part 3 – Being ill had practical consequences: Children relied on adults, who had to navigate practical consequences of illness: out-of-pocket costs for travel, diagnostic tests and treatment, and adequate food to enable tolerance of drugs and speed recovery.

Finding 3.1 Some people sought care from local pharmacies or traditional health providers, especially if they did not recognise their illness as tuberculosis. Traditional healers sometimes referred individuals to formal tuberculosis care (5, 6, 8, 19, 20, 28).

Finding 3.2 Out of pocket costs for travel, treatment and nutrition persisted even in the context of community tuberculosis programmes. Care initiated in the community could not always be completed in clinics (2, 3, 4, 5, 8, 9, 10, 13, 15, 22, 23, 24, 26, 27).

Finding 3.3: Tuberculosis screening programmes created expectations about follow-up healthcare amongst those who were ill. People experienced frustration and disappointment when these expectations were not met (2, 3, 4, 9, 10, 11, 13, 15, 22, 25, 28).

Part 4 – Being ill had frightening consequences: Many community members expressed fears related to tuberculosis active case finding and contact tracing. People were afraid infecting others in their family or workplace, of painful side effects of treatment for themselves or for their children, and of dying from tuberculosis. People were also afraid of being labelled with tuberculosis or with HIV.

Finding 4.1: Respondents across several settings were afraid of dying from tuberculosis (5, 6, 15, 18, 22, 27).

Finding 4.2: Individuals feared side-effects of treatment for themselves and for their children. People avoided tuberculosis screening to avoid medicines; parents sometimes concealed their children from contact tracing to avoid medication (5, 13, 23, 25, 27).

Finding 4.3: Individuals with tuberculosis feared infecting others around them. Community health workers feared infection because aspects of their work exposed them and their families to disease (2, 3, 10, 15, 21, 22, 26, 29).

Finding 4.4: Community members expressed fear of being labelled with tuberculosis. Fear of the TB label was closely aligned with the fear of being labelled HIV+ (2, 3, 7, 8, 11, 14, 15, 17, 20, 21, 22).

Part 5 – Tuberculosis stigma and discrimination: Tuberculosis stigma set people apart, whether they were targeted for screening or received diagnosis and treatment. This setting apart exposed people to discrimination along distinct pathways: isolation from their wider community, lost employment, fraught social interaction with health care workers both in the clinic and on the doorstep, and discord and divisiveness within families. HIV stigma compounded tuberculosis stigma and heightened vulnerability to discrimination along these same pathways.

Finding 5.1: Schools offered a location for TB screening that was preferred by some people. Others preferred the clinic, the home, or workplaces, but all respondents were concerned with discretion, privacy and confidentiality whatever the location (2, 3, 7, 11, 17, 22, 24).

Finding 5.2: People valued privacy and discretion for screening and for all subsequent tuberculosis care to avoid or to mitigate tuberculosis and HIV stigma and consequent discrimination (2, 3, 4, 7, 11, 17, 19, 21, 22, 28, 30).

Finding 5.3: Discrimination isolated people from their wider community (2, 4, 8, 14, 21, 27, 28).

Finding 5.4: Discrimination introduced discord and divisiveness within families (2, 3, 4, 7, 8, 15, 21, 27).

Finding 5.5: Discrimination sometimes involved being shunned at work or lost employment (7, 8, 21, 26, 28).

Finding 5.6: Tuberculosis stigma framed the way community members and healthcare workers responded to one another and at times enabled discrimination (2, 3, 4, 6, 7, 10, 11, 15, 22, 24, 29).

Finding 5.7: HIV stigma compounded tuberculosis stigma and enabled discrimination within the community and workplace, in healthcare settings and within families (2, 3, 5, 11, 15, 17, 19, 20, 22, 26, 29).

Part 6 – The local economy of tuberculosis: In many settings, lack of resources restricted what services were available for TB, and this had implications for the care of children. Programme health workers and community members described a skeleton service in competition for resources, infrastructure, and staff. In this context of low investment, tuberculosis health services sometimes reinforced, rather than alleviated, deprivation and discrimination. Parents and children faced repeated tests and clinic visits, wasted time and fraught social interaction with health providers.

Finding 6.1: Lack of investment has resulted in a weak and sparse tuberculosis infrastructure in competition with other disease campaigns (3, 4, 7, 10, 15, 17, 23, 24, 28).

Finding 6.2: Lack of investment made follow up care difficult. Parents and children faced repeated tests and visits, wasted time, and had fractious interactions with health providers (2, 3, 4, 5, 8, 9, 10, 13, 15, 17, 19, 21, 22, 23).

Included studies

1. Armstrong-Hough M, Ggita J, Ayakaka I, Dowdy D, Cattamanchi A, Haberer JE, et al. Brief Report: "Give Me Some Time": Facilitators of and Barriers to Uptake of Home-Based HIV Testing During Household Contact Investigation for Tuberculosis in Kampala, Uganda. J Acquir Immune Defic Syndr. 2018;77(4):400–4.
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An economic evaluation of three novel stool processing methods for diagnosis of tuberculosis in children five and under

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Background

The pediatric TB diagnostic gap is substantial, leading to untreated disease and preventable morbidity and mortality in children. Stool has been considered as a non-invasive alternative sample for TB diagnosis in children. Three novel stool pre-processing methods (SPMs) have been developed to remove inhibitors before use with Xpert Ultra MTB/RIF (Cepheid, USA). These new methods are: Stool Processing Kit (SPK), Simple One Step (SOS), and Optimized Sucrose Flotation (OSF), developed by FIND, KNCV, and TB-Speed respectively. Each of these methods involves different levels of complexity, numbers of steps, and materials. The accuracy and feasibility of these methods for the diagnosis of pediatric TB were evaluated in a multi-center clinical diagnostic accuracy study and are presented in a separate report.

This analysis aimed to provide an economic assessment to inform decision-making on the implementation of the new SPMs/Ultra. The analysis was performed for Uganda only; the additional analysis planned for India was not possible due to the COVID-19 pandemic.

The specific objectives of this report were to:

Part 1: Estimate the incremental costs of each SPM/Ultra at the study site of a referral level hospital.

Part 2: Estimate the potential cost-effectiveness of implementing SPM/Ultra testing at peripheral level outpatient clinics in Uganda

Since most children from about 6 years old can provide sputum samples without the need for invasive procedures, the most meaningful application for stool testing is in younger children. Therefore, the analysis focused on children ≤5 being evaluated for pulmonary TB. We adopted health system perspective and all costs were assessed in 2020 United States Dollars (USD).

Part 1 Methods & Results – Referral hospital

The analysis used the setting of a referral hospital (Mulago National Referral Hospital in Kampala, Uganda) where the clinical study enrollment and all laboratory procedures were conducted. Full details of the SPMs are given in the corresponding report from FIND and TB Speed. Briefly, all methods follow generally the same procedures with different reagents, quantities, and incubation times: an amount of stool is mixed with a buffer solution, incubated until the stool is liquified, and then dispensed into the Ultra cartridge. The SPK included materials in a pre-assembled kit with its own buffer solution. The OSF required a sucrose buffer solution which had to be made in batches monthly; the time required to prepare the solution was included in the costing. The SOS used the buffer included with the Ultra cartridge.

We used a bottom-up micro-costing approach following three sequential steps: identification of resources based on the laboratory processes, measurement of resource consumption, and valuation of resource consumption. Given that the three SPMs require similar infrastructure (buildings and electricity) and equipment, we included only recurrent costs (staff time, reagents, and consumables) related to conducting SPM/Ultra in the research laboratory. Because laboratory staff time represented a major cost, we recorded the exact time that technicians spent processing the stool for each method. The time for Ultra testing was not included, as it was the same for all SPMs.

In the event of an invalid or error result on SPM/Ultra, the stool processing and Ultra test was repeated, requiring additional time and materials. The cost of invalid-repeat testing was calculated as a function of the invalid rate and cost per repeat SPM and Ultra testing (assumed to involve same testing procedure).

Of the three sample processing methods, the SOS/Ultra has the lowest average cost at $13.90 per test, followed by OSF/Ultra at $19.89 and SPK/Ultra at $20.27 (Table 1). One of the main differences in cost per processing method was the cost of consumables. This was the lowest for SOS/Ultra, as very few additional materials are used besides those provided with the Ultra cartridge. Another difference was in the length of time required to conduct the procedures, and corresponding cost of staff time. OSF processing took at least 20 minutes longer than the other methods on average, including two incubation steps and time to prepare the sucrose solution. Also, the rate of invalid Ultra results was lowest for SOS, requiring less repeat testing and proportionately lower costs.

From the clinical accuracy study, SOS/Ultra had the highest point-estimate of sensitivity (52%), compared to SPK/Ultra (48%) and OSF/Ultra (47%). Therefore, SOS/Ultra has the lowest cost and highest effectiveness, and was used for modelling of implementation in Part 2.

Part 2 Methods & Results – Implementation at level 1

For the second part, the setting was expanded to model national implementation of SPM/Ultra testing at level 1 facilities. In Uganda, GeneXpert machines are placed in district hospitals (level 2 facilities) with a 'hub and spoke' system to transport specimens from peripheral clinics (level 1 facilities) for testing. We assumed that stool samples would be collected at level 1 facilities and transported via the existing system, so no new infrastructure for sample transport was necessary.

We built a decision tree model to relate costs to the health outcome measured as life years (LY) saved over a time horizon of one year. The model began at level 1 clinics with children £5 who were screened and reported at least one of the following symptoms: cough or fever for 2 weeks or more, poor weight gain in the last month, or contact with a TB case. According to Ugandan guidelines, these children should be characterized as 'presumptive TB' and have a clinical examination and relevant testing (1).

The model followed the clinical pathway from initial evaluation to a final outcome of survival or death, with separate arms comparing stool testing to the status quo based on clinical examination only. In practice not all children provide a stool sample, so the model included a pathway of no stool testing. If the stool test was positive, the child would be initiated on TB treatment. If the stool test was negative, or no stool sample was provided, the decision to initiate TB treatment would be based on clinical evaluation. If the child was not diagnosed during these steps, they would remain sick with TB and be referred to level 2 for further evaluation, including Chest X-ray and gastric aspirate for Ultra testing. The comparator arm was the same pathway beginning with clinical evaluation at level 1 and possible referral to level 2, with no stool testing. We assumed there was no pre-diagnostic loss to follow-up (LTFU). If a patient was lost during TB treatment, outcomes included self-cure, death from TB disease with partial treatment, or death from other causes.

Estimates for the clinical parameters (Table 2) were taken from the literature and supplemented with expert opinion due to the limited data available for pediatric TB. The cost parameters were adjusted to include sample collection at level 1, sample transport, and Ultra testing at a level 2 laboratory.

The incremental cost-effectiveness ratio (ICER) per LY saved was calculated. When diagnosed with TB and initiated on treatment, children are assumed to live their full life expectancy, and death from TB would be averted. The calculation of LYs saved used the life expectancy for children 1–5 years old in Uganda, and LYs were discounted at 3% per year in the main analysis.

The ICER per LYs saved of SOS/Ultra compared to clinical diagnosis was estimated to be $611 (Table 3). Testing with SOS/Ultra had a higher cost and greater effectiveness than the status quo of clinical diagnosis.

To place the results in the context of health system resource constraints, a country-specific cost-effectiveness threshold (CET) was used. For Uganda, the CET ranged from $11 to $288 USD (2) based on 2019 Gross Domestic Product (3). When compared with the CET, SOS/Ultra would not be considered cost-effective if implemented under the conditions in this model.

Also, one-way sensitivity analyses were conducted to evaluate the range of uncertainty in the model parameters. The prevalence of TB disease, sensitivity of clinical diagnosis, and cost of SOS/Ultra were the main drivers (Figure 1). A higher prevalence of TB disease, lower sensitivity of clinical diagnosis, and lower SOS cost reduced the ICER. While the lower ranges for clinical diagnosis and SOS cost did not drive the ICER under the CET, a higher TB prevalence did. At a prevalence greater than 7%, the diagnostic solution (SOS/Ultra) was below the CET of $288 (Figure 2). Also, if the LYs were not discounted, then SOS/Ultra would be cost-effective at a 3% prevalence.

Discussion

This report presents the first economic evaluation of the three novel stool processing methods. SOS/Ultra was the least costly method at $13.90 per test. When modelled for implementation in peripheral clinics in Uganda, it was cost-effective at a TB prevalence of 7% or higher. These results may be generalizable to other sub-Saharan African countries with similar TB epidemiology and costs.

The analysis had several limitations. First, there is limited data available in the literature for pediatric TB, especially for populations presenting to level 1 facilities. To address this limitation, we conducted one-way sensitivity analyses of all clinical model parameters to investigate the impact of their uncertainty on the model outputs. Also due to limited data, HIV status was not included in the model, and is likely to decrease both the performance of the SPMs and clinical diagnosis.

The performance estimates of the SPMs are from children presenting at a referral hospital and may be lower when used at level 1 facilities, where children are likely to present at an earlier stage of disease (4). Also, the added value of a microbiologically-confirmed TB diagnosis and potentially resistance detection was not considered, as the main study enrolled only drug-susceptible TB patients. If this was included, the benefits of higher adherence and detection of rifampicin resistance, and the ensuing appropriate treatment, would likely result in better outcomes. The use of stool testing at level 1 may also allow for the detection and treatment of TB at an earlier stage, preventing progression to severe disease. Thus, our model is a conservative estimate. Finally, this analysis was done from the health systems perspective and did not include patient costs or patient perspectives on stool testing.

In summary, our findings show that the diagnostic solutions will be cost-effective in settings with higher TB prevalence among children presenting for evaluation. Furthermore, the benefit of non-invasive sampling is undisputable and further supports the use of the diagnostic solutions. However, the real need for non-invasive sampling is at lower-level facilities. Further analyses are necessary to optimize screening algorithms for children with presumptive TB, to identify the most appropriate sub-population with a higher pre-test probability, where the SPMs would likely be cost-effective and model accordingly.

Tables and Figures

Table 1. Results of the micro-costing study, average cost for each SPM/Ultra test performed in a referral hospital

Cost item	SOS	SPK	OSF
Incubation/sedimentation time (minutes)	10; 10	30	30; 15
Procedure time, minutes (range)	23 (21–30)	23 (18–40)	43 (32–74)
Time of sucrose prep, minutes per aliquot	N/A	N/A	2
Cost of staff time (range)	$1.99 (1.74–2.49)	$1.99 (1.49–3.31)	$3.67 (2.65–6.13)
Consumables	$0.82	$6.16	$4.38
Xpert Ultra cartridge	$9.98	$9.98	$9.98
Invalid rate	8.7%	11.8%	10.3%
Cost of invalid-repeat testing	$1.11	$2.14	$1.86
Total, range (USD)	$13.90 (13.73–14.48)	$20.27 (17.85–21.68)	$19.89 (18.98–22.46)

Table 2. Model parameter estimates for the implementation of SOS/Ultra at level 1

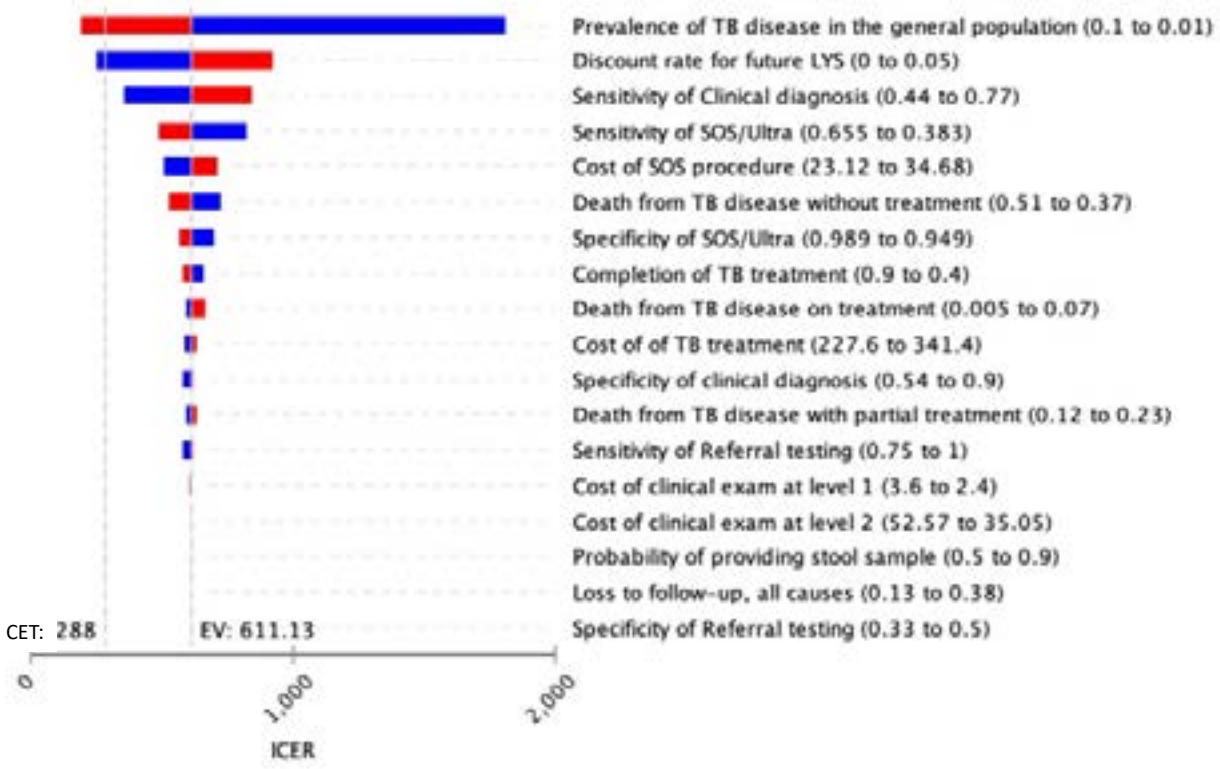
Parameter	Base Case	Sensitivity Range	Reference
Clinical			
Prevalence of TB disease	0.03	0.01–0.10	(5–8)
Sensitivity of SOS/Ultra	0.52	0.38–0.66	H2H study
Specificity of SOS/Ultra	0.97	0.95–0.99	H2H study
Provide stool sample	0.70	0.50–0.90	(9–11)
Sensitivity of Clinical Diagnosis	0.68	0.44–0.77	(12)
Specificity of Clinical Diagnosis	0.80	0.54–0.90	(12)
Sensitivity of referral testing	0.95	0.75–1.0	(12–14)
Specificity of referral testing	0.41	0.33–0.5	(12–14)
Probability of Completing Treatment	0.70	0.45–0.90	(15–17)
Probability of Death with Untreated TB	0.44	0.37–0.5	(18)
Probability of Death with partially treated TB	0.17	0.12–0.23	(18)
Probability of Death with Treated TB	0.02	0.007–0.07	(18)

Parameter	Base Case	Sensitivity Range	Reference
Lost to Follow-up	0.22	0.13–0.38	(19, 20)
Self-Cure	0.30	0.30–0.50	(21)
Probability of Death from other causes	0.003		(22)
Life Expectancy, Uganda (years)	68		(22)
Discount rate	0.03	0.00–0.05	(23)
Cost (USD)			
Clinical visit, level 1	3.00	2.40–3.60	(24)
SOS/Ultra testing:			
• Stool collection	1.67		(25)
• Sample transport	1.33		(26)
• Stool processing only (excluding Ultra cost)	3.92		Table 1
• Xpert Ultra	21.98		(26)
Total cost of SOS/Ultra testing	28.90	23.12–34.68	
Referral testing:			
• Clinical visit, level 2	4.00		(24)
• Chest X-ray	13.45		(27)
• Hospitalization	9.50		(24)
• Gastric aspirate	4.38		(25)
• Xpert Ultra	21.98		(26)
Total cost of referral testing	53.31	35.05–52.57	
TB treatment	284.50	227.60–341.40	(28)

Table 3. Costs and effectiveness per life year saved of the SOS/Ultra versus status quo at level 1 facilities

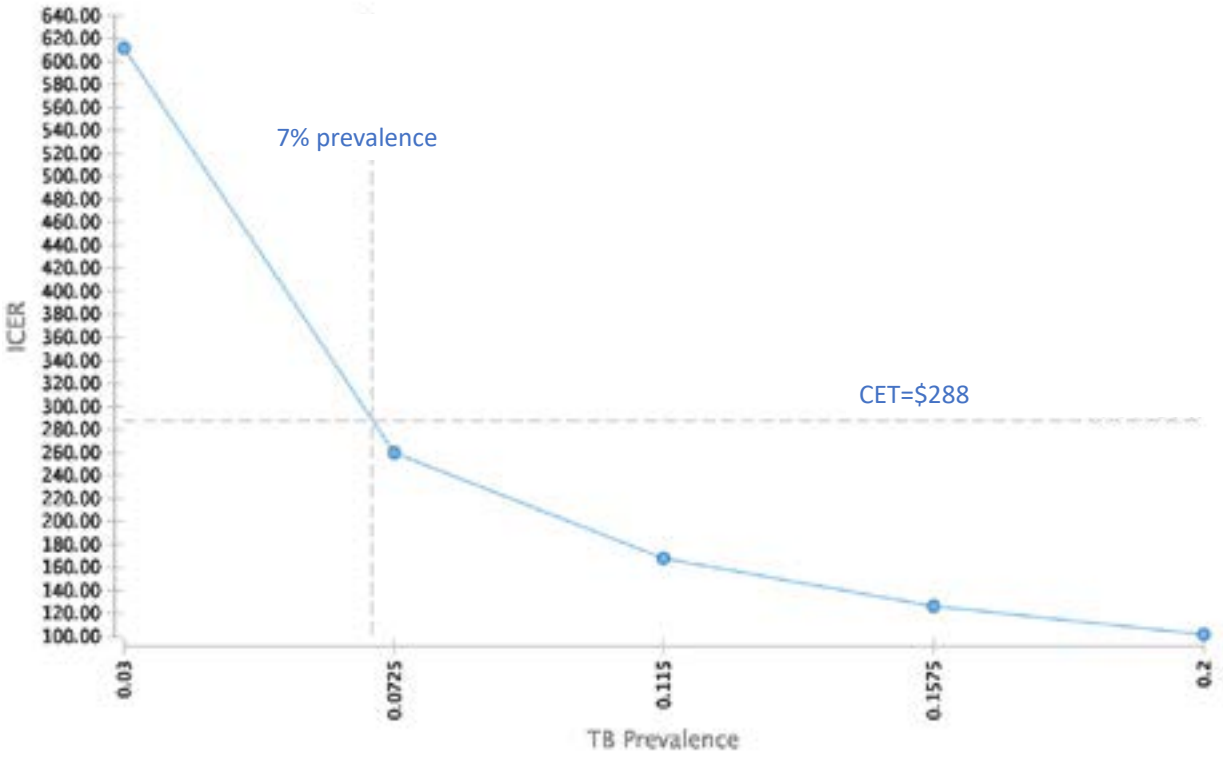
Strategy	Cost	Incremental Cost (USD)	Effectiveness (LYs)	Incremental effectiveness (LYs)	ICER (USD)
Status quo	58.70		28.6829		
SOS/Ultra	82.74	24.04	28.7223	0.0393	611.13

Figure 1. One-way sensitivity analysis comparing SOS/Ultra to status quo for all parameters



Each bar indicates how the range of the parameter changes the ICER. Red=high value of the range; blue=low value; expected value (EV)=base case.

Figure 2. One-way sensitivity analysis of TB prevalence



Varying prevalence of TB disease from 3% to 20% impacts ICER relative to the CET.

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Costing analysis of integrated treatment-decision algorithms for children under 10 years

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Background

This report presents data to inform the updated guidelines for the management of tuberculosis in children, specifically regarding the use of integrated treatment-decision algorithms for the diagnosis of pulmonary TB in children aged below 10 years.

The objective of this analysis is to provide costing estimates for the following treatment-decision algorithms: Union desk guide (1), Cape Town cohort (2), and PAANTHER study (3). This analysis did not aim to evaluate the clinical accuracy of the algorithms.

Methods

Algorithms studied

Each algorithm follows a sequence of evaluations, such as physical examination and Chest X-ray (CXR), until either a decision to initiate TB treatment is reached or other clinical management is indicated. The algorithms differ by the order in which the evaluations are performed, and the number of steps needed to reach the treatment decision. In general, when a patient tests positive or reaches a certain threshold at an evaluation step, they proceed to treatment. As the goal of the algorithms is to have the highest possible sensitivity and enable a rule-out when negative, a negative result on any of the components of the algorithm leads to further steps until a positive result (false or true positive) is reached, or the algorithm ends.

Because HIV status is an important consideration in TB diagnosis, the algorithms were analyzed separately by HIV status. While the Union Desk Guide considers both HIV-negative and HIV-positive status in its algorithm, the PAANTHER (HIV-positive) and Cape Town (HIV-negative) algorithms are specific to respective HIV-status in children.

Study design & population

The setting used for the analysis was primary health clinics (level 1 facilities) in Uganda. Uganda was chosen as a country that is representative for the region and similar to most high-burden countries with limited access to diagnostic tools in peripheral settings, where the algorithms are intended for use.

Each algorithm was converted into a decision tree model, and it was necessary to make assumptions about the clinical pathway and availability of resources. The first step of the Union algoriths is sputum Xpert testing, and due to the difficulty obtaining sputum samples from young children in level 1 facilities, we assumed only 30% had a sample collected. The patients without a sputum sample would follow the same steps as those with a negative result. Also for the Union HIV-negative algorithm, assessment of contact history, physical examination, and CXR are presented in one step. However, due to limited access to X-ray at level 1 facilities, we assumed that children would only be referred for CXR later if necessary. Similarly, in the PAANTHER algorithm, CXR, Xpert, and ultrasonography are presented in one step. We assumed the evaluations would be done sequentially, and the majority would have CXR due to the limited use of ultrasound for pediatric TB.

The models simulated a hypothetical cohort of 10,000 presumptive TB patients (i.e. those with TB symptoms such as prolonged cough, fever, or poor growth/weight loss) who are under age 10 presenting to level 1 facilities in Uganda. We factored the costs of HIV testing, initial clinical examination, and additional clinical and diagnostic evaluations as specified by the algorithm (e.g. additional physical exam, Xpert Ultra testing, CXR, ultrasound). Clinical and epidemiological estimates relevant for each decision node were obtained from the literature or expert advice (Table 1).

The outcomes tracked in our model were the total cost for evaluating a cohort of 10,000 presumptive TB patients, the number of TB cases diagnosed, and the cost per TB case diagnosed for each algorithm. One-way sensitivity analyses were done to explore how the range of the parameters impacted the cost outcomes.

Costing

Cost estimates were obtained from the literature for model parameters (Table 1). All costs were calculated from a health system perspective and converted to 2020 United States dollars (USD). The cost for sputum collection was calculated as an age-weighted average cost of collecting two samples per child.

Results

The model results for the total cost of screening, number of TB cases diagnosed, and cost per case for each algorithm are shown in Table 2. At a TB disease prevalence of 3%, 300 true TB cases would be present in the cohort of 10,000 patients. The Cape Town algorithm diagnosed the most TB patients (294), followed by PAANTHER (289), Union HIV-positive (275), and Union HIV-negative algorithm (213).

The costs were highest for the Union HIV-negative algorithm, at $2,079 per TB patient diagnosed and $442,840 for evaluating the entire cohort. The three other algorithms had very similar cost per TB case diagnosed, at around $1,300. The total cost for the Cape Town HIV-negative algorithm was $402,537. The Union HIV-positive ($376,363) and PAANTHER HIV-positive ($376,258) had nearly identical total costs.

In a one-way sensitivity analysis of TB prevalence, the cost per TB patient diagnosed decreased similarly for all algorithms as the prevalence increases (Figure 1). As there are more cases of disease in the population being evaluated, a higher proportion of patients would test positive at each step and forgo additional evaluations, reducing the cost.

For the Union algorithms that rely on sputum testing at the first step, the proportion of patients with a sample collected was the main driver of cost. The Cape Town and PAANTHER algorithms start with clinical evaluation and CXR, which have lower specificity than Xpert. If the higher range of the specificity estimates for CXR and clinical diagnosis are used, fewer children receive a false-positive diagnosis and more receive a true-negative diagnosis. This results in more children having a negative result at the initial step, necessitating additional testing. Thus, higher specificity of CXR and clinical diagnosis would result in higher costs for these algorithms.

Discussion

This analysis provides the first cost estimates to guide decision-making on the use of diagnostic algorithms for evaluating young children with presumptive TB. The algorithms with fewer steps to reach a treatment decision have the lowest cost. The two HIV-positive algorithms have nearly identical costs. Of the HIV-negative algorithms, the Cape Town cohort had the lower cost. These results may be generalizable to other sub-Saharan African countries with similar TB epidemiology and costs.

The analysis had several limitations. The process of modelling the algorithms required assumptions on how the clinical pathway would be followed and access to diagnostic procedures. There is limited data available in the literature for pediatric TB clinical parameters, especially for populations presenting to level 1 health facilities. We therefore conducted one-way sensitivity analyses to examine the uncertainty of all the parameters. In addition, the analysis only included costs from the health system perspective. The inclusion of patient costs would presumably favor algorithms with more sensitive diagnostics upfront (e.g. Union) as it would reduce recurrent visits and the associated costs to patients. Furthermore, the models did not consider loss to follow-up, which would likely be higher in algorithms starting with less sensitive tests (Cape Town and PAANTHER) that require multiple visits. Lastly, the costs associated with over-treatment of patients incorrectly diagnosed with TB was not included.

In conclusion, the algorithms with the fewest steps have the lowest cost occurring to the health care system. At a higher prevalence of TB disease, the difference in cost between the algorithms decreases. However, uncertainty in the clinical estimates and assumptions in modelling limit the generalizability and strength of conclusions. Including patient costs as part of implementation programs would be informative.

Tables and Figures

Table 1. Model parameter estimates for level 1 facilities in Uganda

Clinical Parameter	HIV-negative		HIV-positive		Reference
	Base Case	Range	Base Case	Range	
Prevalence of TB Disease	0.03	0.01–0.10	0.03	0.01–0.10	(4–6)
Proportion with sputum sample	0.30	0.15–0.40	0.30	0.15–0.40	(4)
Clinical Diagnosis, sensitivity	0.74	0.65–0.90	0.56*	0.45–0.70	(7–10)
Clinical Diagnosis, specificity	0.80	0.54–0.90	0.62*	0.50–0.89	(7–10)
Chest X-ray, sensitivity	0.67	0.58–0.89	0.61*	0.47–0.74	(11–13)
Chest X-ray, specificity	0.55	0.31–0.67	0.50*	0.30–0.60	(11–13)
Xpert Ultra, sensitivity	0.73	0.65–0.80	0.64*	0.44–0.80	(14–16)
Xpert Ultra, specificity	0.97	0.96–0.98	0.98*	0.93–1.0	(14–16)
Ultrasound, sensitivity	-	-	0.35	0.29–0.42	(3)
Ultrasound, specificity	-	-	0.86	0.80–0.91	(3)
Reported TB contact, TB case	0.40	0.30–0.55	0.40	0.30–0.55	(17)
Reported TB contact, TB-neg	0.25	0.05–0.30	0.25	0.05–0.30	(15)

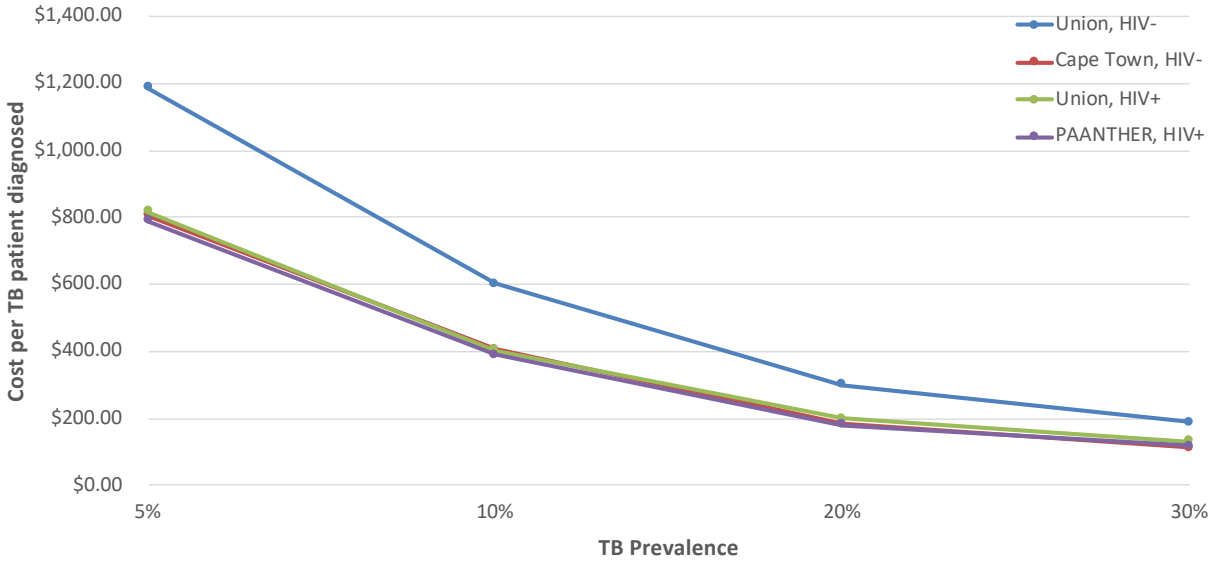
Cost Parameter	Base case	Range	Reference
Clinical visit, level 1	$3.00	2.40–3.60	(18)
HIV testing	$6.00	4.80–7.20	(19)
Chest X-ray	$13.45	10.76–16.14	(20)
Ultrasound	$11.71	9.37–14.05	(21)
Xpert Ultra	$21.98	17.58–26.38	(22)
Collection of sputum samples	$21.99	17.59–23.99	(18, 22, 23)

* HIV-specific clinical estimates were used where data was available.

Table 2. Costs for screening cohort of 10,000 presumptive TB patients at 3% prevalence

Algorithm	Total cost for screening	Number of TB patients diagnosed	Cost per TB case diagnosed
Union, HIV-negative	$442,840	213	$2,079.06
Cape Town, HIV-negative	$402,537	294	$1,369.17
Union, HIV-positive	$376,363	275	$1,368.59
PAANTHER, HIV-positive	$376,258	289	$1,301.93

Figure 1. Sensitivity analysis of varying TB prevalence on cost per TB case diagnosed



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