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Spatial and Prediction Models for Addressing Challenges in Pediatric Tuberculosis Control and Care

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Abstract

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Tuberculosis (TB) is among the leading causes of global mortality among children <5 years. Each year, over 1 million TB cases occur among children <15 years worldwide, and nearly one quarter of those children die; approximately 80% of those deaths occur among children <5 years. Alleviating the burden of pediatric TB and mortality requires 1) enhanced efforts to prevent transmission to children and 2) treating more children for TB.

Targeting resources to children with a known TB exposure has been a cornerstone of the public health response to prevent transmission and detect cases early. Infectious adults must be diagnosed and treated earlier to prevent transmission to their child contacts. Modeling studies suggest that targeting community-level active case-finding to areas with high local transmission intensity may demonstrate population-level reductions in TB incidence. However, obtaining conclusive evidence of concentrated transmission requires access to spatial and genomic data, which is often only available under research conditions in high TB-incidence settings.

In chapter 1, I use Bayesian spatial modeling methods to probe routinely collected, age-disaggregated TB notification data to demonstrate that overrepresentation of young child cases co-locate with areas of high local transmission intensity, identified by molecular evidence of transmission from a prospective cohort study in the same setting. This finding suggests that the use of models that leverage widely available notification data should be explored as tools to target case-finding and treatment efforts in high-transmission locations to maximize the direct and indirect benefits of active

screening approaches. In chapter 2, I leverage data from a large prevalence survey to investigate a poorly understood form of TB that may frustrate symptom-based active case-finding efforts.

Given that modeling estimates suggest that 96% of global childhood mortality due to TB occurs among children not receiving antituberculosis treatment, identifying and treating more cases of pediatric TB provide an opportunity to reduce child mortality. Diagnostic tools for pediatric pulmonary TB are limited by paucibacillary disease in children as well by resource constraints in many high TB-incidence settings. This contributes to poorer treatment outcomes through missed diagnoses and treatment delays.

In chapter 3, I describe the analysis of a cohort of children being evaluated for TB from Cape Town, South Africa to demonstrate that a majority of antituberculosis treatment-decisions could be made using clinical evidence alone, without the need for additional diagnostic testing. In chapter 4, I describe the assembly of a large cohort of pediatric TB diagnostic evaluation data sourced from multiple geographically diverse, high TB-incidence settings to develop a prediction model for TB and investigate its validity and generalizability. As part of this work, I describe efforts in partnership with the World Health Organization to operationalize the prediction model as a treatment-decision algorithm to guide the evaluation of children with presumptive pulmonary TB.

Spatial and Prediction Models for Addressing Challenges in Pediatric Tuberculosis Control and Care

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Introduction

Public health priorities to reduce morbidity and mortality associated with childhood tuberculosis

Tuberculosis is among the top ten causes of global mortality among children <5 years old.

Each year, over 1 million tuberculosis cases occur among children <15 years worldwide, and nearly one quarter of those children die.[1] Approximately 80% of those deaths occur among children <5 years old.[2] This is unacceptable in the setting of effective tuberculosis treatment and prophylaxis options for children.[3-5] Current public health strategies to limit transmission to children are not on track to meet global targets set by the World Health Organization (WHO).[6,7] Additionally, underdiagnosis of pediatric tuberculosis contributes to the substantial gap between estimated and notified cases.[8] Alleviating the burden of pediatric tuberculosis and child mortality requires 1) enhanced efforts to prevent transmission to children and 2) treating more children with tuberculosis.

Interventions that limit tuberculosis transmission will disproportionately limit transmission to children.

Targeting resources to children with a known tuberculosis exposure has been a cornerstone of the public health response to prevent transmission and improve treatment outcomes.[9,10] This strategy aims to screen child contacts of infectious adults to identify and treat prevalent disease and administer effective prophylaxis to contacts without disease. Evidence from a large individual-participant meta-analysis of 137,647

tuberculosis-exposed children revealed that 83% of children <5 years who are exposed to tuberculosis and diagnosed with disease, are diagnosed within the first 90 days of baseline evaluation.[11] This contributes to the mounting evidence suggesting that earlier diagnosis and treatment of infectious adult cases will have a disproportionate effect on preventing transmission to children.[12,13]

Community-level tuberculosis screening strategies are expected to reduce transmission to children.

Community-level tuberculosis screening strategies, in which risk groups are screened to identify infectious individuals before they passively present to care, have garnered particular attention in the tuberculosis control community to reduce transmission to levels in line with global tuberculosis control goals.[6,14] Because untargeted community-level screening in high burden settings has not consistently demonstrated population-level benefits,[15-18] there has been interest in new practical approaches to focus screening to population groups among whom risk is concentrated. One such approach is to target screening to hotspots, areas in which transmission is most intense.[19] While evidence supporting the impact of targeting screening in hotspots is currently limited,[20] mathematical modeling suggests that such targeting may result in substantial population-wide reductions in transmission.[21,22]

Identifying transmission hotspots to target community-level screening may maximize its benefits.

Conclusive evidence of tuberculosis transmission hotspots typically relies on access to detailed spatial and pathogen genetic data.[23-25] While spatial information is often available in public health reporting systems (e.g. home location), resources for genetic sequencing of sufficient pathogens to infer transmission may only be available in

the context of research studies in high-transmission/resource-limited settings. Thus, methods to identify hotspots from routine tuberculosis surveillance data would be valuable.[26] However, high local tuberculosis incidence in surveillance data may not necessarily identify transmission hotspots. Patterns of tuberculosis incidence may instead reflect spatially-aggregated risk for progression of infection, migration of individuals infected with tuberculosis into the area,[27] or spatial heterogeneity in diagnostic capacity.[28] Thus, finding new ways to probe routine surveillance data to find evidence of local transmission is a priority.

The location of child cases in tuberculosis surveillance data may provide a signal for transmission hotspots to target screening and interventions to limit transmission to children.

Spatial differences in the age distribution of tuberculosis and other infectious diseases may provide a signal for local transmission intensity.[29,30] In locations where disease transmission is more intense, patients are systematically younger than in locations where disease transmission is less intense.[31] This principle underlies the use of the age-prevalence of tuberculin-skin test positivity to measure risks of infection from household and community exposure.[32,33] In particular for tuberculosis, the age-related risk of progression from infection to disease is especially high among children <5 years old, further strengthening the case that children may provide a signal for recent transmission.[34] Previous studies have suggested that areas with high childhood tuberculosis rates may correspond to areas of active transmission;[35-37] however, none have attempted to provide conclusive evidence to compare inference, and only one included covariates to account for potential non-transmission explanations of the spatial distribution of child cases.[37]

Subclinical tuberculosis may frustrate symptom-based, active case-finding targeted to areas of active tuberculosis transmission.

Tuberculosis prevalence surveys, in which all eligible individuals (regardless of symptoms) are screened for tuberculosis disease, have revealed that a large fraction of individuals with prevalent, undiagnosed tuberculosis may be "subclinical" and fail to report any classical symptom of tuberculosis.[38] Recently, others have suggested the failures of symptom-based, active case-finding to demonstrate consistent efficacy might be attributable to the potential infectiousness of individuals with subclinical tuberculosis.[39] One hypothesis is that individuals with chronic cough (for example due to pre-existing respiratory conditions, smoking, or unrelated respiratory infections) will be less likely to notice the onset of tuberculosis symptoms and more likely to transmit *M. tuberculosis* due to this persistent coughing behavior. These individuals may maintain normal activities and social behaviors, further increasing the likelihood of transmission. While the presence of chronic cough for reasons others than tuberculosis has been associated with delays to presentation and diagnosis of tuberculosis,[40-44] further understanding of the epidemiological importance of subclinical tuberculosis may enhance the impact of active case-finding on tuberculosis transmission.

Treating more children with tuberculosis provides another opportunity to reduce child mortality.

It is estimated that 96% of global childhood mortality due to tuberculosis occurs among children not receiving antituberculosis treatment.[2] The gap between estimated tuberculosis cases and cases notified to the WHO is larger for children than for adults, likely due to limitations in childhood tuberculosis diagnostics.[8,45] Unlike adult tuberculosis, childhood tuberculosis is generally paucibacillary.[46] This limits the

sensitivity of microbiological tests including diagnostics such as Xpert MTB/RIF.[47] Furthermore, obtaining specimens for microbiological confirmation for children <5 years old requires invasive sampling and resources that may only be available at referral centers.[48,49] Findings on chest radiography are less sensitive and specific among children.[50] These limitations cause delays in initiating treatment, resulting in poorer outcomes.[51]

WHO guidance suggests that children brought to healthcare services with symptoms suggestive of tuberculosis (a presumptive tuberculosis case) should be further evaluated for tuberculosis disease.[52] Once a child has been identified as a presumptive case, healthcare workers must consider whether to initiate tuberculosis treatment based upon the clinical history, physical examination, demographic data, history of recent exposure to a tuberculosis source case in the preceding 12 months, confirmatory tests for *M. tuberculosis*, chest imaging, tests of infection, and clinical follow-up where appropriate. Treatment decisions must often be made in the absence of microbiological confirmation; thus, symptoms, clinical examination, and history of close tuberculosis contact play a crucial role in the decision to initiate tuberculosis treatment.

Antituberculosis treatment decision-making at peripheral health facilities must be optimized.

Emerging evidence supports diagnosis and treatment for pediatric tuberculosis at peripheral health facilities to identify more children with tuberculosis disease and improve treatment outcomes by shortening the delay to treatment initiation.[53,54] The WHO and the International Union Against Tuberculosis and Lung Disease guidelines suggest that clinical evidence may justify treatment when microbiological testing is unavailable or in the setting of negative test results;[52,55] however, the guidelines do not

clearly describe the burden of evidence that is sufficient to initiate treatment for pediatric tuberculosis. The evidence supporting the role of symptom-based diagnosis to inform tuberculosis treatment decisions has been limited due to poorly standardized symptom and case definitions, few validation studies, and challenges in designing studies that adequately evaluate the role of individual symptoms and variable symptom combinations. Others have developed treatment decision-algorithms and scoring systems to promote rapid and uniform treatment decision-making by assigning scores to features in the diagnostic evaluation that correspond to risk for tuberculosis.[55-57]

Analysis of high-quality diagnostic evaluations data may improve treatment decision-making at peripheral health facilities among child presumptive tuberculosis cases.

The high mortality associated with untreated childhood tuberculosis requires practical guidance to identify and treat more children with tuberculosis using the best available data. Recent approaches to algorithm-building used modeling analytic methods to analyze data from diagnostic studies in order to specify which features in the diagnostic evaluation of child presumptive tuberculosis cases might be sufficient to begin treatment in the absence of bacteriological confirmation.[58] Modeling approaches to inform treatment-decision algorithm development are advantageous for being data-driven and allowing for formal validation and investigation of generalizability.

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Chapter 1

Children as sentinels of tuberculosis transmission: disease mapping of programmatic data

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ABSTRACT

Background: Identifying hotspots of tuberculosis transmission can inform spatially-targeted active case-finding interventions. While national tuberculosis programs maintain notification registers which represent a potential source of data to investigate transmission patterns, high local tuberculosis incidence may not provide a reliable signal for transmission because the population distribution of covariates affecting susceptibility and disease progression may confound the relationship between tuberculosis incidence and transmission. Child cases of tuberculosis and other endemic infectious disease have been observed to provide a signal of their transmission intensity. We assessed whether local overrepresentation of child cases in tuberculosis notification data corresponds to areas where recent transmission events are concentrated.

Methods: We visualized spatial clustering of children <5 years old notified to Peru's National Tuberculosis Program from two districts of Lima, Peru from 2005-2007 using a log-Gaussian Cox process to model the intensity of the point-referenced child cases. To identify where clustering of child cases was more extreme than expected by chance alone, we mapped all cases from the notification data onto a grid and used a hierarchical Bayesian spatial model to identify grid cells where the proportion of cases among children <5 years old is greater than expected. Modeling the proportion of child cases allowed us to use the spatial distribution of adult cases to control for unobserved factors that may explain the spatial variability in the distribution of child cases. We compare where young children are overrepresented in case notification data to areas identified as transmission hotspots using molecular epidemiological methods during a prospective study of tuberculosis transmission conducted from 2009-2012 in the same setting.

Results: Areas in which childhood tuberculosis cases are overrepresented align with areas of spatial concentration of transmission revealed by molecular epidemiologic methods.

Conclusions: Age-disaggregated notification data can be used to identify hotspots of tuberculosis transmission and suggest local force of infection, providing an easily-accessible source of data to target active case-finding intervention.

INTRODUCTION

The End TB Strategy's ambitious goals to reduce tuberculosis incidence require new interventions to interrupt transmission.[1] This has led to a renewed interest in active case-finding strategies, in which risk groups are screened to identify infectious individuals before they present to care.[2,3] Because untargeted community-based active case-finding has not consistently demonstrated population-level benefits,[4-7] there has been interest in new practical approaches to focus case-finding to population groups among whom risk is concentrated. One such approach is to target active case-finding to hotspots, areas in which transmission is most intense.[8] While evidence supporting the impact of targeting screening in hotspots is currently limited,[9] mathematical modeling suggests that such targeting can produce substantial population-wide reductions in transmission.[10,11]

Conclusive evidence of hotspot transmission typically relies on access to detailed spatial and pathogen genetic data.[12-14] While spatial information is often available in public health reporting systems (e.g. home location), in high-transmission/lower-income settings, resources for genetic sequencing of pathogens are typically only available in research studies. Thus, methods to robustly identify hotspots from routine reporting data would be valuable.[15] However given that high local rates of tuberculosis notifications may reflect spatially-aggregated risk for progression of infection, migration of individuals infected with tuberculosis into the area,[16] or spatial heterogeneity in diagnostic capacity,[17] finding new ways to probe routine surveillance data to find evidence of local transmission is a priority.

Spatial differences in the age distribution of tuberculosis cases in a single city may provide a signal for local transmission intensity.[18] In locations where disease transmission is more intense, cases are systematically younger than in locations where

disease transmission is less intense.[19] We aimed to test this previously posited, but to our knowledge yet untested, idea that areas where children are overrepresented in tuberculosis case notification data are areas where recent transmission events are concentrated. We tested this hypothesis using case notification data from Lima, Peru, where we were able to compare our inference to a prospective molecular epidemiology study conducted in the same setting several years later.[20,21] This comparison provided an opportunity to examine whether routinely-collected tuberculosis notification data can be used to identify transmission hotspots.

METHODS

Study setting and population

We examined data from all tuberculosis cases notified to Peru's National Tuberculosis Program from two of Lima's four health districts, Lima Ciudad and contiguous catchment areas of Lima Este, between January 1, 2005 and December 31, 2007. Patient demographic and clinical information was available within the notification data as well as household address, which was identified on high resolution maps created using Google Earth. Additional details of the study design and mapping procedures have been described previously.[22,23]

Our interest was in identifying areas in which young children were overrepresented in these routinely collected notification data from 2005-2007 and whether they correlated with areas identified as transmission hotspots during a prospective study of tuberculosis transmission conducted from 2009-2012.[21] The latter study included molecular epidemiological characterization of culture-positive cases of drug-susceptible and drug-resistant tuberculosis from adults older than 15 years using 24-loci mycobacterial interspersed repetitive units-variable-number tandem repeats

(MIRU-VNTR). Spatial aggregation of *Mycobacterium tuberculosis* (*M.tb*) strains identified by MIRU-VNTR genotype was presumed to indicate transmission.

Data visualization and modeling

We visualized spatial clustering of child cases <5 years old in the notification data using a log-Gaussian Cox process (LGCP) to model the intensity function driving the point process describing the distribution of child cases. We used the *lgcp* package and defined the Gaussian process with an exponential covariance function and weakly informative priors on all model parameters (details provided in the **Supplementary Information**).[24] All data visualization and analysis were performed using R 4.0.1.

Next, we aimed to determine if the clustering of child cases observed in the exploratory maps was more extreme than would be expected by chance alone. Point-level census and covariate data that may explain spatial variability in the distribution of child cases through effect on overall risk were not available for this analysis. Due to the large number of unique spatial locations observed in the data (10,198) and the well-known difficulties associated with using a Gaussian process to analyze point-referenced spatial data when the sample size is large,[25] we opted for a method that approximates the point-referenced model while offering computational improvements.[26] Specifically, we overlaid a grid on the convex hull of the case notification data and modeled the proportion of reported tuberculosis cases that occurred among children in each grid cell using a hierarchical Bayesian spatial modeling framework. We chose the grid cell sizes to be small in order to ensure that the risk within each grid cell was homogeneous and also considered multiple sizes in subsequent sensitivity analyses. As the size of the grid cells gets smaller, our approximation to the point-referenced geostatistical model improves. By modeling the proportion of the tuberculosis cases that were children (as opposed to simply modeling the number of child cases), we used the distribution of adult

cases to control for unobserved factors that may explain the spatial variability in the distribution of child cases. Under this modeling framework, we expect that the local proportion of child cases will be higher than the expected proportion of child cases over the entire study area in areas where there is local transmission. The hierarchical model structure allows us to identify where this occurs and allows us to describe the certainty with which the proportion is higher.

To do this, we use a logistic regression framework to model the grid cell-specific proportions such that:

$$Y_i|\theta_i \sim \text{Binomial}(n_i, \theta_i), i = 1, \ldots, m$$

$$\ln\left(\frac{\theta_i}{1-\theta_i}\right) = \mu + \phi_i$$

where Y_i is the number of child cases observed in grid cell *i*, n_i is the total number of child and adult cases in the grid cell, *m* is the total number of grid cells, and θ_i represents the proportion of the total cases in the grid cell that are due to children. We define child cases as those <5 years old and adult cases as those >15 years old to clearly separate recent infection among young children from more distant infection among adults (expecting that cases among older children and young adults between ages 5 and 15 represent a mix of recent infection and infection that happened earlier in their lives). We model these proportions on the logit scale as a function of an overall mean, μ (fixed effect), and a grid cell-specific deviation from that mean, ϕ_i (random effect).

We anticipate that the proportion of child cases in grid cells that are close together may be similar. To account for this potential spatial correlation and to obtain spatially smoothed risk estimates, we estimated the ϕ_i parameters using a conditional autoregressive (CAR) model such that:

$$\phi_i|\boldsymbol{\phi}_{-i}, \tau^2, \rho \sim \mathrm{N}\left(\frac{\rho\Sigma_{j=1}^{n} w_{ij}\phi_j}{\rho\Sigma_{j=1}^{n} w_{ij} + 1 - \rho}, \frac{\tau^2}{\rho\Sigma_{j=1}^{n} w_{ij} + 1 - \rho}\right)$$

where $\boldsymbol{\phi}_{-i}$ is the vector of parameters excluding ϕ_i; w_{ij} is equal to one if grid cells *i* and *j* share a common border or point and is equal to zero otherwise; τ^2 describes the variability in the ϕ_i parameters; and $\rho \in (0,1)$ describes their strength of spatial correlation. As a result, this model is flexible enough to accommodate a wide range of spatial patterns as well as the possibility that there is no spatial variability in the proportion of child cases (i.e., τ^2 near zero indicates that all ϕ_i are near zero). Additionally, examining the posterior distributions of ϕ_i allows us to determine if the grid cell proportion differs substantially from the overall mean.

We selected weakly informative prior distributions for all model parameters and used the *CAR.Leroux* function in the *CARBayes* package to obtain posterior samples for all parameters.[27] Details are provided in the **Supplementary Information**.[28] Using the posterior samples from each ϕ_i, we estimate the posterior probability that ϕ_i is larger than zero, which would suggest recent transmission based on our hypothesis.

RESULTS

Analysis of notification data

Of the total 11,711 notified tuberculosis cases over the study period, there were 332 children <5 years old, and 10,352 adults >15 years old. The LGCP modeled intensity of the cases among children <5 years old is given in **Figure 1.**

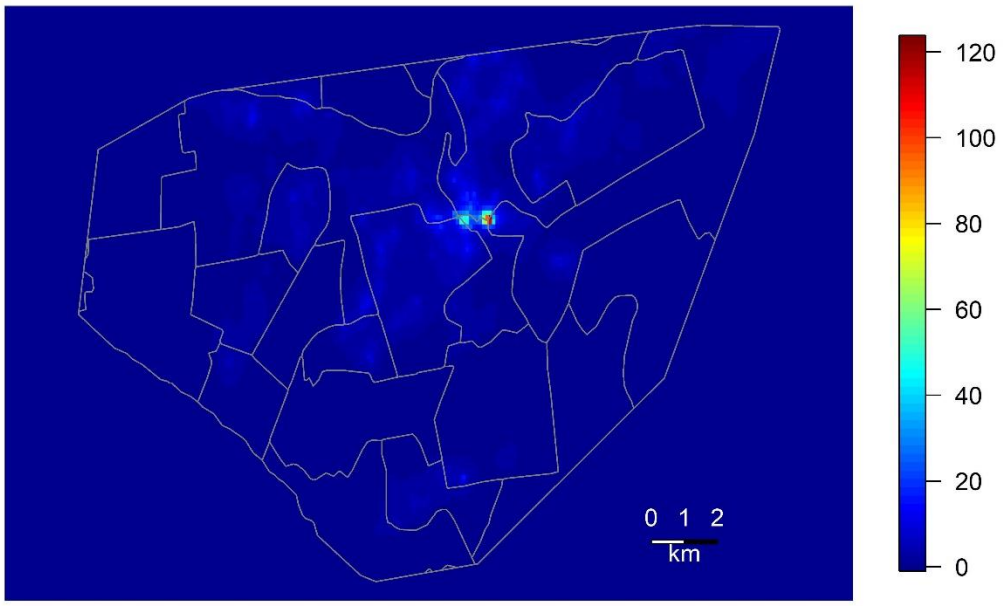

Figure 1. Disease mapping of young children in Peru's National Tuberculosis Program data.
Log-Gaussian Cox process modeled intensity of the cases of tuberculosis among children <5 years old notified to the Peru's National Tuberculosis Program within two of Lima's four health districts, Lima Ciudad and contiguous catchment areas of Lima Este, between January 1, 2005 and December 31, 2007.

We fit the hierarchical Bayesian spatial model to the case notification data collected from 2005-2007 aggregated into a 200 m x 200 m grid within the convex hull of the data. The model suggested six grid cells in which >95% of the posterior distribution of the random effect terms were above zero and an additional eight grid cells in which >90% of the posterior distribution was above zero (**Figure 2**). Examination of the posterior estimate of the spatial correlation parameter, ρ, suggested that the excess variability observed in the data was spatially structured (posterior mean 0.75, 95%

credible interval 0.24–0.98). Posterior summaries of the remaining parameters are provided in the supplementary **Table S1**.

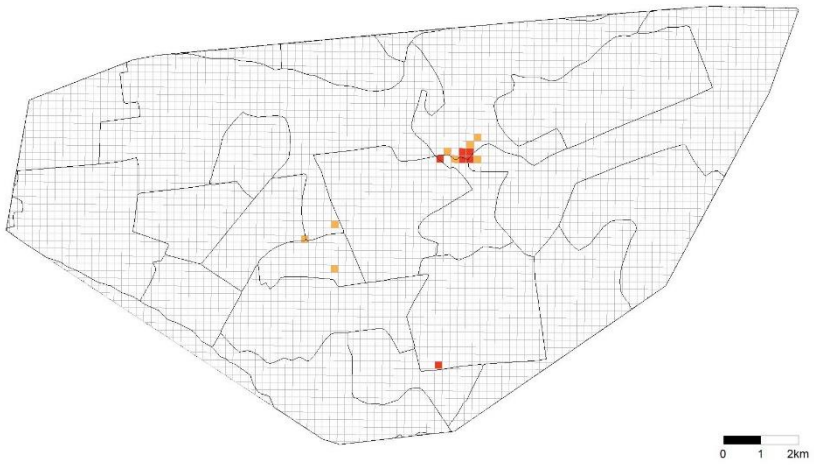

Figure 2. Identifying areas with local overrepresentation of young children in tuberculosis notification data.
Hierarchical Bayesian spatial model fit to the child cases <5 years old and adult cases >15 years old in the notification data aggregated into 200 m x 200 m grid cells overlaid on the convex hull of the data. The model suggested six grid cells (red) in which >95% of the posterior distribution of the random effect terms were above zero, and an additional eight grid cells (orange) in which >90% of the posterior distribution was above zero. The proportion of child cases in these grid cells is greater than expected over the study region, suggesting recent tuberculosis transmission based on our hypothesis.

Comparison to prospective molecular epidemiological study

Figure 3a, reproduced with permission from Zelner et al., shows areas in which there was statistically significant spatial aggregation of specific *M.tb* MIRU-VNTR genotypes, consistent with localized transmission of these strain types.[21] In **Figure 3b**, we overlay the grid from Figure 2 to demonstrate the proximity between areas where children <5 years old are overrepresented in case-notification data and areas where specific strains are concentrated. In the supplementary **Figs. S1-S2** we show that these findings are insensitive to assumed grid cell size and age cut-offs for the definitions of

young child and adult cases. **Figure 4a**, also reproduced with permission from Zelner et al., shows the spatial variation in annual per capita incidence of tuberculosis by healthcare catchment area.[21] We similarly overlay the grid from Figure 2 to create **Figure 4b** to demonstrate the proximity between areas where child cases are overrepresented and high local incidence.

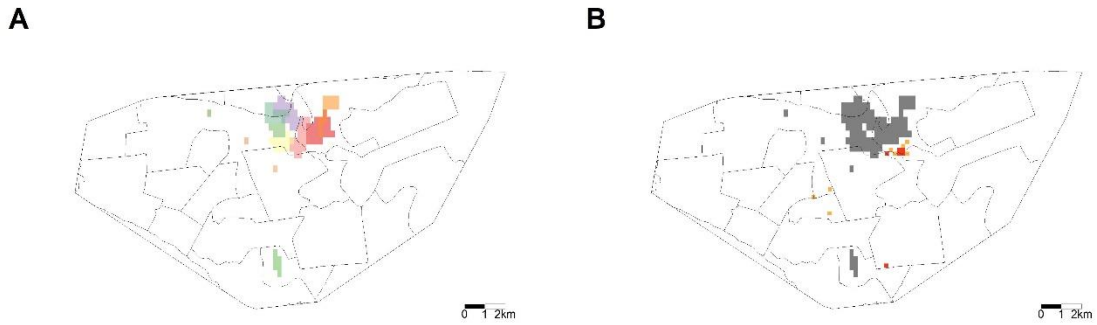

Figure 3. Comparing tuberculosis transmission inference of hotspots of active transmission.
(a) Reproduced with permission from Zelner et al. demonstrating regions (shaded) identified as tuberculosis transmission hotspots. Different color shading denotes clusters of different drug-sensitive and drug-resistant strains identified by MIRU-VNTR genotype.(21) **(b)** A grayscale reproduction of this figure is overlaid on the modeled 200 m x 200 m grid from Figure 2. We highlight those grid cells in red and orange, where the modeled proportion of child cases <5 years old is greater than expected, to demonstrate the proximity between areas with higher local childhood tuberculosis notification and areas with conclusive evidence of transmission.
Note— MIRU-VNTR, 24-loci mycobacterial interspersed repetitive units-variable-number tandem repeats.

DISCUSSION

In this paper we evaluated whether routinely-collected, age-disaggregated notification data can be used to identify hotspots of spatially concentrated tuberculosis transmission. Our analysis, based on routine data collected from 2005-2007, pinpointed

a region where child cases of tuberculosis were overrepresented relative to the number of adult cases in the area. This region was previously identified as an area of high transmission using molecular genetic data from a prospective study conducted from 2009-2012.[21] This concordance of transmission inference obtained using different methods and datasets supports the use of routinely-collected age-disaggregated notification data to identify areas of local transmission intensity.

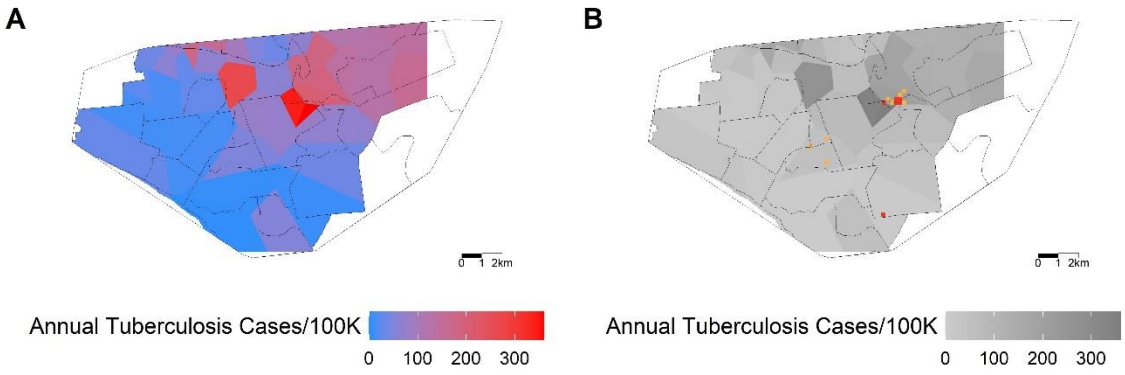

Figure 4. Comparing per capita tuberculosis incidence to putative hotspots. **(a)** Figure reproduced with permission from Zelner et al. demonstrating the spatial variation in annual per-100 thousand incidence of drug-sensitive and drug-resistant tuberculosis by healthcare catchment area.(21) **(b)** A grayscale reproduction is overlaid on the 200 m x 200 m grid from Figure 2 to demonstrate the proximity between the colored grid cells, where the modeled proportion of child cases <5 years old is greater than expected, and an area of high local incidence of tuberculosis.

Child cases have been suggested as a useful signal of transmission intensity for tuberculosis as well as other infectious disease.[29] For example, a number of studies used the age-prevalence of tuberculin-skin test positivity to measure risks of infection from household and community exposure.[30,31] Previous studies have suggested that areas with high childhood tuberculosis case notification rates may correspond to areas of active transmission;[32-34] however, only one included covariates to account for potential

non-transmission explanations of the spatial distribution of child cases.[34] Thus, our analysis is the first to provide molecular and epidemiological evidence to corroborate inferences of local tuberculosis transmission with attempts to control for unobserved, spatially heterogeneous, non-transmission factors (such as risk factors for progression of infection, migration of infected individuals into the area, and/or diagnostic capacity) that may explain the distribution of child cases.

Considering that both the routine notification data and the prospective molecular epidemiology study included tuberculosis cases separated by as many as six years, we also note that the identified hotspot appears to have been persistent over several years. This suggests that tuberculosis transmission hotspots identified from notification data may be observable for long enough periods of time to guide targeted interventions, such as spatially focused active case-finding.

It is important to note several simplifying assumptions in our analysis. Given the absence of detailed information on the distribution of covariates in the source population, we incorporated all spatial heterogeneity in the distribution of child cases into the random effect term of the model. As a result, our model necessarily attributes all spatial variability in the modeled proportions to possible recent transmission. If there are other non-transmission-related factors that impact the proportion of total cases that occurred in children, this could lead to a grid cell being incorrectly labeled as a transmission "hotspot." However, given the consistency of our results with the previous findings that more directly measure transmission, this may not be a major issue in this work. Our hierarchical Bayesian spatial modeling approach (as well as the log-Gaussian Cox process intensity modeling approach) is flexible enough to incorporate local covariate data as regression components. Future study should include such information when available.

Though we provide compelling evidence, we must be cautious interpreting that age-disaggregated data will always provide a reliable signal of transmission. Molecular evidence of transmission against which we compare transmission inference was only available for those >15 years old. Thus, we are unable to biologically link childhood cases to the identified clusters of transmission. Furthermore, accurately diagnosing tuberculosis among children is difficult. While it is clear that missing child cases in notification data likely underestimates transmission, it is unclear how false positives may affect signal detection. In addition, though we demonstrate that the putative hotspot persists over time, it is not possible to assess how mobility over the time period through which all data from these two studies was collected may affect hotspot detection. It is important to note that our findings do not imply an either-or choice between genetic and age-incidence data: future analyses exploring the impact of combining granular molecular genetic data with age-incidence data in a single model could improve the predictive capacity of such models.

This methodology may be adapted to settings in which high-resolution residence data is not readily available. For example, in settings where residential geocoding is not feasible, it may be reasonable to model the proportion of child cases in the smallest recorded unit to which the household belongs (such as modeling the proportion in the neighborhood, community, and/or administrative unit).

CONCLUSIONS

In summary, we show that age-disaggregated tuberculosis notification data may be used to investigate potential hotspots of tuberculosis transmission. This suggests that the use of models leveraging widely available data should be explored as tools for targeting case-finding and treatment efforts in high-transmission locations in the hope of maximizing the direct and indirect protective benefits of active screening approaches.

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ABBREVIATIONS

TB – tuberculosis

MIRU-VNTR – 24-loci mycobacterial interspersed repetitive units-variable number tandem repeats

M.tb – Mycobacterium tuberculosis

LGCP – log-Gaussian Cox process

CAR – conditional autoregressive

DECLARATIONS

Ethics approval and consent to participate

The study protocol for the prospective molecular epidemiology investigation was approved by the Harvard University Institutional Review Board (Ref. No 19332). The study protocol for data collection and spatial analyses of cases notified to the Peru National TB Program from 2005-2007 was approved by the Research Ethics Committee of the National Institute of Health of Peru (Ref. No 085-2007). Consent was not required as this is a secondary data analysis of previously published, de-identified data.

Consent for publication

Not applicable

Availability of data and materials

Additional data are available on reasonable request to MCB and MM. All requests for data access will need to specify the planned use of data and will require approval from MCB and MM before release.

Competing interests

The authors declare that they have no conflicts of interest.

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Authors' contributions

KG, JLW, and TC designed the study, analyzed the data, and wrote the first draft of the manuscript. JZL, MCB, CC, MFF, LL, and MBM critically revised the manuscript. MCB and MM coordinated the molecular epidemiological study which verified areas of transmission. All authors read and approved the final manuscript.

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SUPPLEMENTARY INFORMATION

Log-Gaussian Cox process details

The log-Gaussian Cox process provides an approach to model the intensity function driving spatial point processes. Examining the fitted intensity of the cases among children <5 years old provides a robust means to identify clusters of child cases. The *lgcp* package in R models the intensity function of the spatial region that contains a regular grid with a cell width chosen to be sufficiently small to approximate continuous spatial variation. We selected a cell width of 100 m, defined the Gaussian process with an exponential covariance function, and placed weakly informative priors on all model parameters as recommended by the *lgcp* Vignette. We collected 100,000 posterior samples after discarding the first 10,000 as a burn-in period, and thinned by a factor of 90 to result in 1,000 samples from which we make posterior inference. Markov-chain Monte Carlo was performed using the Metropolis-adjusted Langevin algorithm with a target acceptance probability set to 0.574, achieved by the Andrieu and Thoms algorithm as implemented by the *lgcp* package.

Hierarchical Bayesian spatial model details

Justification for small grid cell

Small grid cells ensure that the assumption of homogenous risk within the grid cell is plausible and leads to finer scale mapping of risk across the map. Additionally, smaller grid cells allow for better approximation of a model of continuous spatial variation.

Prior distribution specifications

We placed weakly informative priors on the parameter describing the fixed effect term (μ), the parameter describing variability in the random effect terms (τ^2), and the parameter describing the spatial correlation parameter (ρ) such that:

$\mu \sim \text{Normal}(0,1000)$
$\tau^2 \sim \text{Inverse Gamma}(0.01,0.01)$
$\rho \sim \text{Uniform}(0,1)$

Model interpretation

Values for ρ near zero suggest near-independence of the spatial random effects while ρ near one suggests a strong dependence on neighboring values (i.e., the conditional mean is an average of the neighboring values). We adopted the queen definition of neighbors because there was no data to suggest that grid cells sharing bordering points are not unrelated.

Model convergence and posterior parameter estimation

Model convergence was assessed using visual inspection of individual parameter traceplots and the Geweke diagnostic calculated for each parameter. Neither tool suggested obvious convergence issues (**Table S1**). In total, we collected 100,000 posterior samples after discarding the first 10,000 as a burn-in period. We further thinned the remaining samples by a factor of 10 to reduce posterior autocorrelation, resulting in 10,000 samples with which to make posterior inference.

Sensitivity Analyses

Sensitivity analysis to child and adult age cut-offs

We modeled the proportion of children of the total number of child and adult cases using different age cut-offs for both children (<2 years old, <5 years old, <15 years old) and adults (>15 years old and >25 years old). In **Fig. S1a-e**, we demonstrate that the highlighted grid cells, where the proportion of child cases is greater than expected,

continue to approximate an area with molecular evidence of transmission and our findings are insensitive to the definition of children and adults.

In **Fig. S1c** where the highlighted grid cells that represent where the proportion of cases <15 years old is greater than expected do not so clearly approximate an area with molecular evidence of transmission. This is likely because young children in notification data can only have been infected during the period that they have been alive, whereas older children in notification data represent a mix of recent infection and infection that happened earlier in their lives.

Sensitivity analysis to grid size

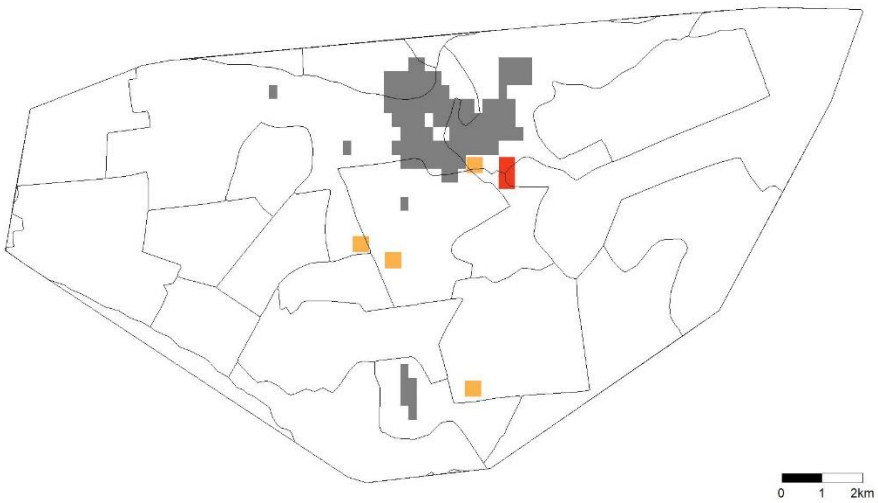
We varied the size of the grid over which we aggregated the notification data to demonstrate that our proposed method is insensitive to grid size. We demonstrate this finding in **Fig. S2a-i**, where the highlighted grid cells, representing where the proportion of child cases is greater than expected, approximate the same area—irrespective of grid size—that corresponds to an area with molecular evidence of transmission.

Table S1. Hierarchical Bayesian spatial model posterior parameter estimates
Posterior parameter estimates and model convergence diagnostics for the hierarchical Bayesian spatial CAR model specified in the main text. This model was built using case notification data collected from 2005-2007 aggregated into a 200 m x 200 m grid using age cut-offs for children as <5 years old and adults as >15 years old.

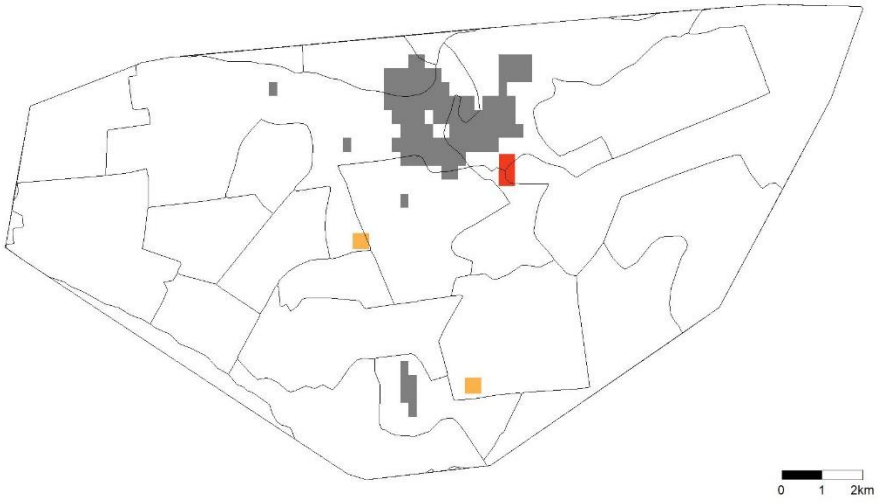
Model Parameter	Posterior Median (95% credible interval)	Effective Number of Independent Samples	Geweke Diagnostic Z-score
$\boldsymbol{\mu}$	-3.6 (-3.8 – -3.5)	475.0	-0.2
$\boldsymbol{\tau^2}$	1.3 (0.3 – 2.6)	243.6	0.1
$\boldsymbol{\rho}$	0.7 (0.2 – 1.0)	267.0	-0.3

Figure S1. Sensitivity analysis to child and adult age cut-offs. Model fit using case notification data aggregated into 400 m x 400 m grid cells using different age cut-offs to define child and adult cases as follows: **(a)** child: <5 years old, adult: >15 years old (presented in the main text); **(b)** child: <2 years old, adult: >15 years old; **(c)** child: <15 years old, adult: >15 years old; **(d)** child: <5 years old, adult: >25 years old; **(e)** child: <2 years old, adult: >25 years old. We highlight those grid cells in which >90% of the modeled posterior distribution of the random effect is above zero (orange), which includes those grid cells in which >95% of the modeled posterior distribution is above zero (red).

a)



b)



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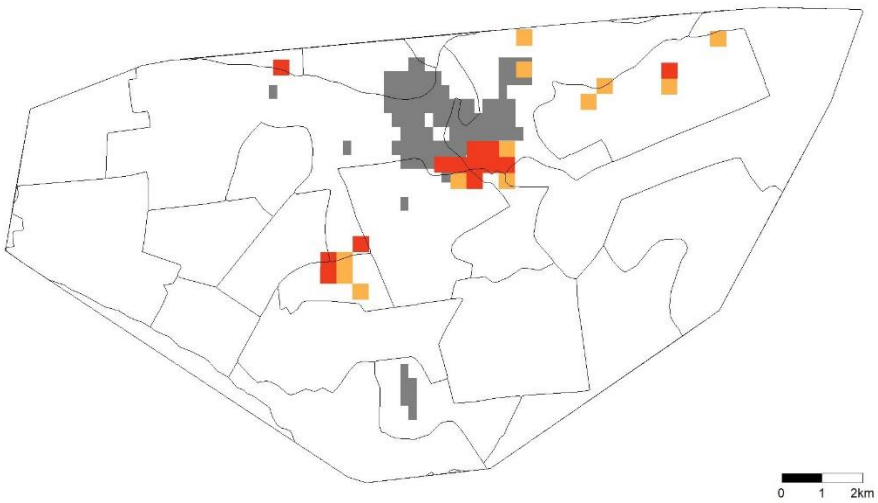
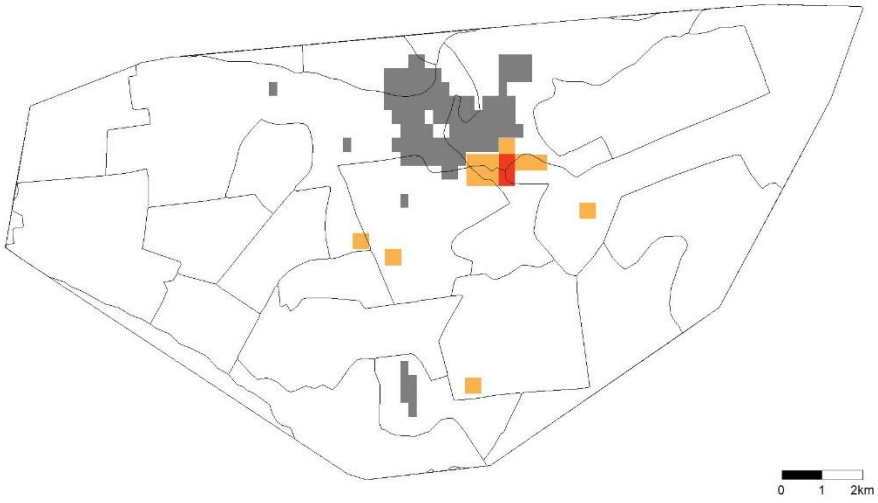


d)



e)

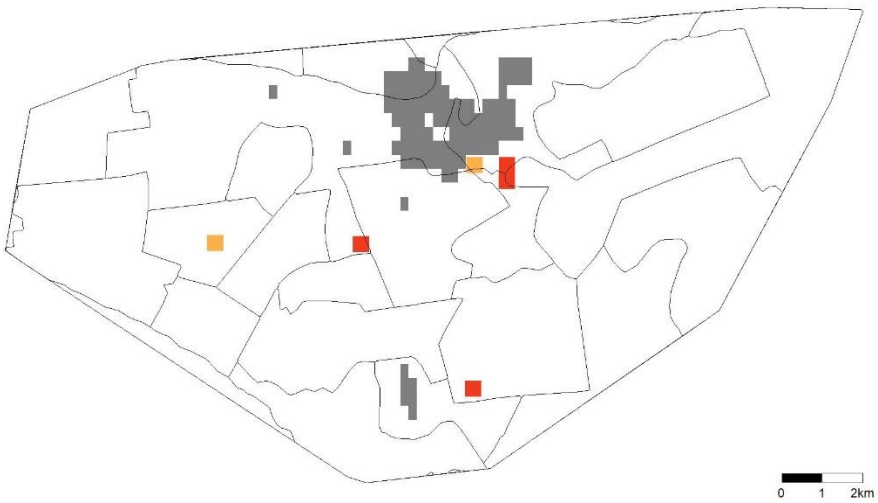
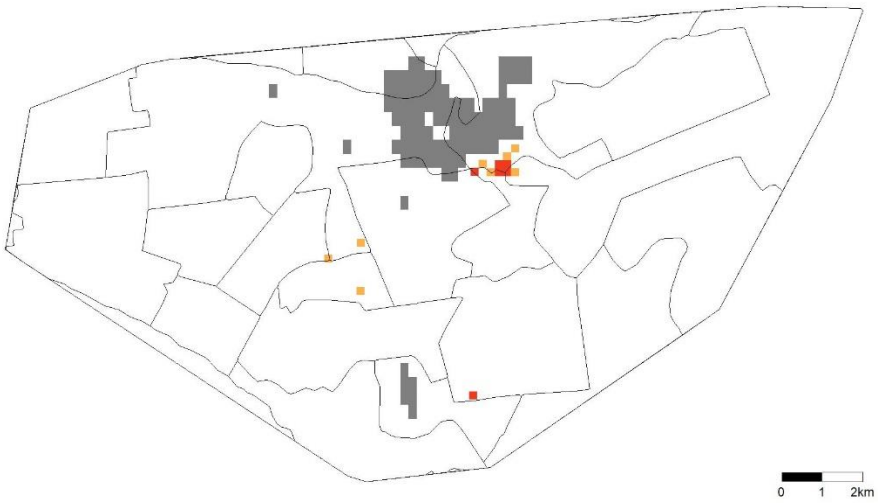
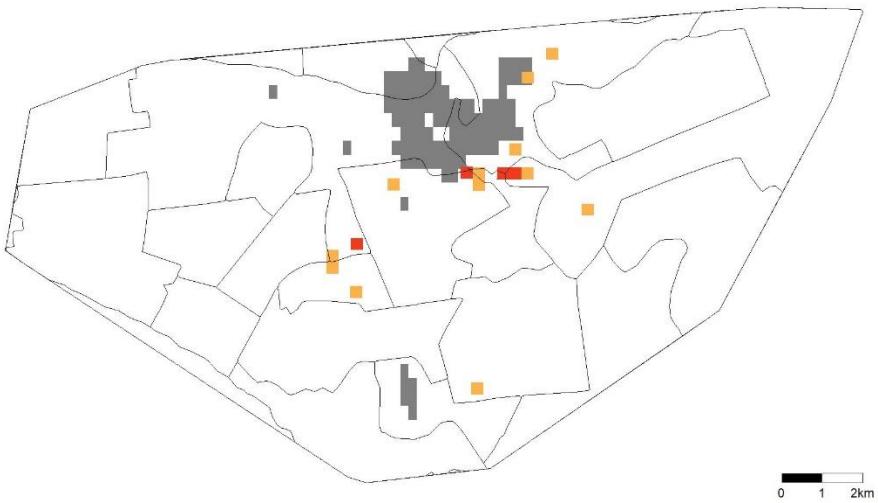


Figure S2: Sensitivity analysis to grid size. Model fit using age cut-offs of children as <5 years and adults as >15 years old on different size grids as follows: **(a)** 200 m x 200 m (presented in the main text); **(b)** 300 m x 300 m; **(c)** 400 m x 400 m; **(d)** 500 m x 500 m; (**e)** 600 m x 600 m; **(f)** 700 m x 700 m; **(g)** 800 m x 800 m; **(h)** 900 m x 900 m; **(i)** 1000 m x 1000 m. We highlight those grid cells in which >90% of the modeled posterior distribution of the random effect is above zero (orange), which includes those grid cells in which >95% of the modeled posterior distribution is above zero (red).

a)



b)



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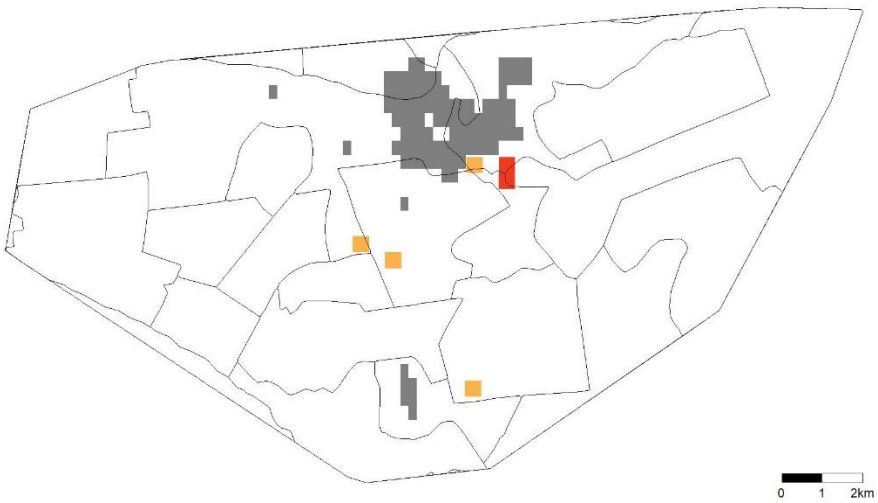
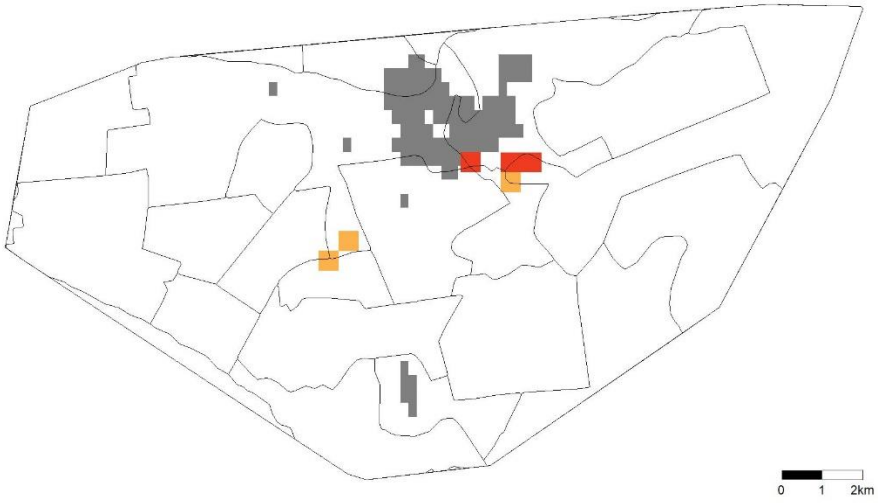
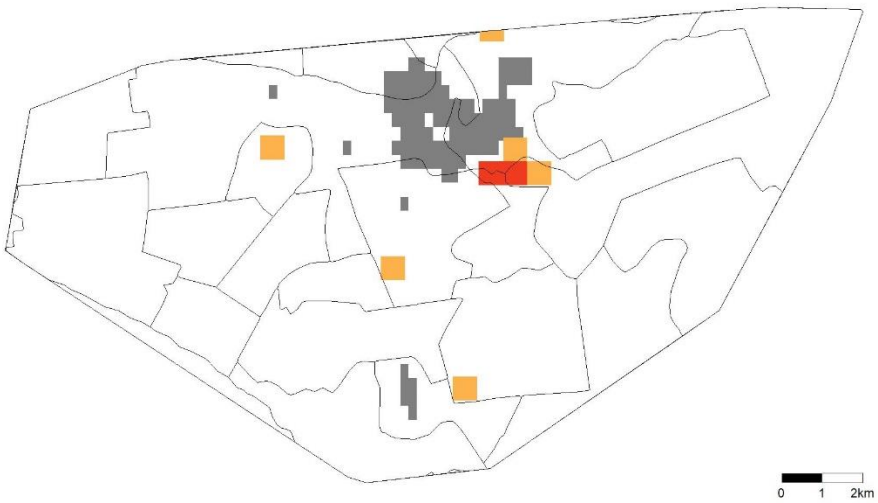


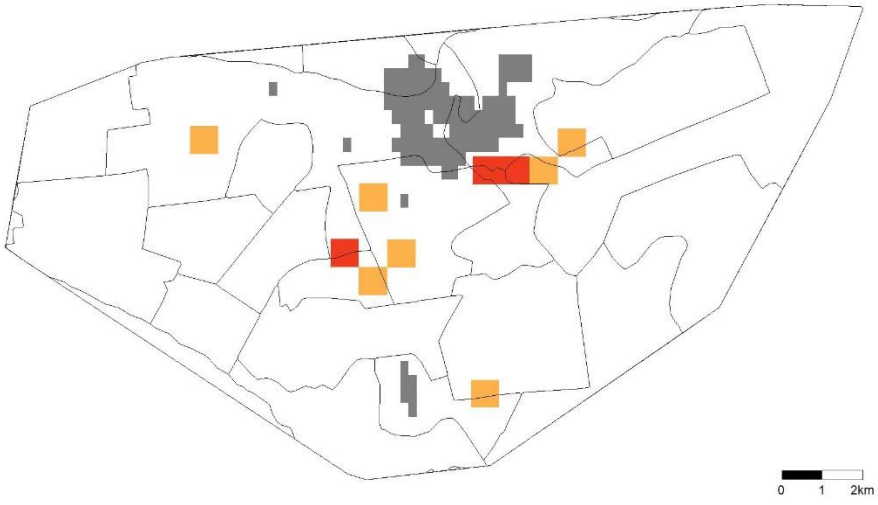
d)



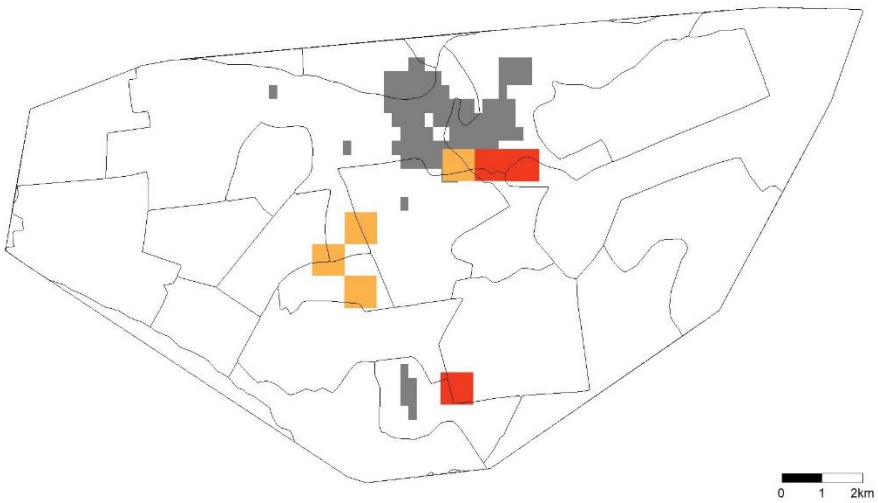
e)



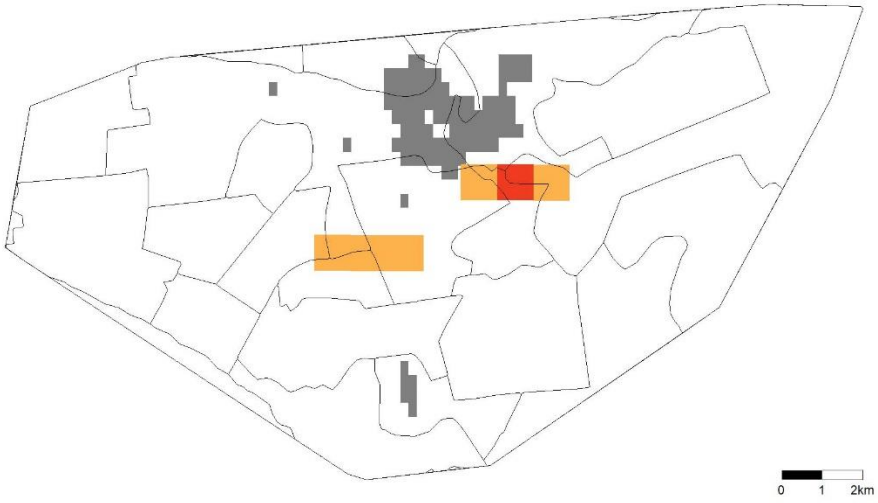
f)



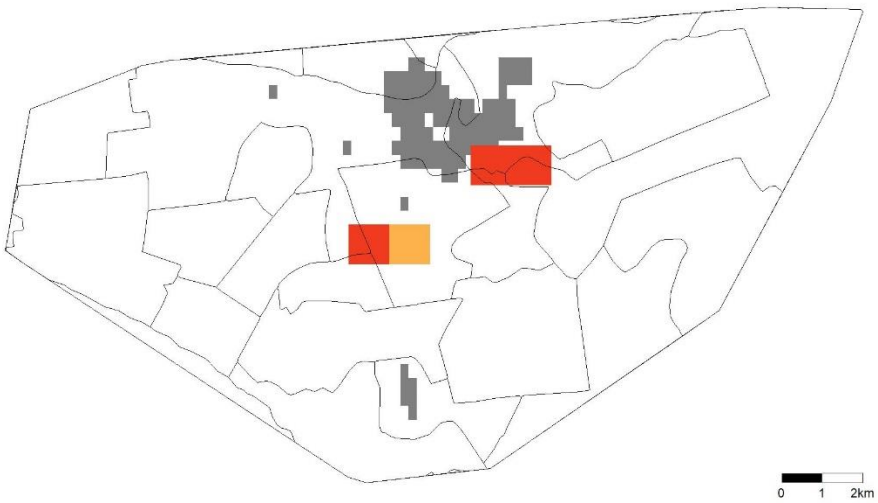
g)



h)



i)



Chapter 2

Smoking and HIV associated with subclinical tuberculosis: analysis of a population-based prevalence survey

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ABSTRACT

*Background***:** Despite multiple tuberculosis (TB) prevalence surveys reporting a relatively high frequency of bacteriologically confirmed, active TB among individuals reporting no typical symptoms of disease, our understanding of this phenomenon is limited.

*Objective***:** To quantify the epidemiological burden and estimate associations between individual-level variables and this “subclinical” presentation.

*Methods***:** We performed a secondary analysis of TB prevalence survey data from the South African communities of the Zambia and South Africa Tuberculosis and AIDS Reduction trial. Generalized estimating equations were used to estimate the association between individual-level demographic, behavioral, socio-economic, and medical variables and the risk of bacteriologically positive TB among participants not reporting any symptoms consistent with active TB.

*Results***:** The crude prevalence of TB was 2,222.1 cases per 100,000 population (95% CI 2,053.4–2,388.5); 44.7% (295/660) of all documented prevalent cases of TB were subclinical. Current tobacco smoking (OR 2.37, 95% CI 1.41–3.99) and HIV-positive status (OR 3.26, 95% CI 2.31–4.61) were significantly associated with subclinical TB.

*Conclusion***:** Individuals who smoke or have HIV may be at increased risk of active TB and not report typical symptoms consistent with disease. This suggests possible shortcomings of symptom-based case finding which may need to be addressed in similar settings.

INTRODUCTION

In 2017, only 6.4 of the estimated 10.0 million individuals with incident tuberculosis (TB) worldwide were reported to the World Health Organization (WHO).[1] Several possible mechanisms may contribute to the gap between true TB incidence and TB notifications: 1) individuals with TB may not self-present to health care providers for diagnosis due to poor self-recognition of symptoms and/or barriers to accessing healthcare; 2) individuals with TB may self-present to health care providers, but fail to be accurately diagnosed due to imperfect diagnostic practices or diagnostic tools; and 3) individuals with TB may be accurately diagnosed, but not recorded by standardized reporting systems due to imperfect administrative systems.[2]

Identifying the specific mechanisms responsible for the overall gap between estimated TB incidence and notifications has been highlighted by the WHO and the Global Fund as a major research priority,[1,3] and efforts to study leaks in the "TB care cascade" have helped to quantify deficiencies in diagnosis (mechanism 2 above)[4] and notification (mechanism 3 above).[5] TB diagnosis in most settings requires individuals to recognize their own symptoms and seek care (i.e., passive case-finding); therefore, the frequency of poor self-awareness of symptoms (mechanism 1) is challenging to quantify. TB prevalence surveys, in which all eligible individuals are screened for TB disease regardless of symptoms, have revealed that in some settings a large fraction of individuals with prevalent, undiagnosed TB may be "subclinical" and fail to report any classical symptom of TB, such as cough, fever, weight loss and night sweats. For example, analysis of national TB prevalence surveys in Asia revealed that between 40% and 79% of all individuals with prevalent TB did not report symptoms that met screening criteria.[6] It is not clear how many of individuals detected with subclinical prevalent TB would have eventually become aware of symptoms and seek care.

Esmail et al. recently suggested that the limited evidence of the benefit of active case-finding interventions using symptom-based screening for reducing TB prevalence might be attributable to individuals with subclinical TB in transmission.[7] They hypothesized that individuals with chronic cough (for example, due to pre-existing respiratory conditions, smoking, or unrelated respiratory infections) will be less likely to notice the onset of TB symptoms and more likely to transmit *Mycobacterium tuberculosis* infections due to persistent coughing behavior. Furthermore, these individuals may maintain normal activities and social behaviors, further increasing the likelihood of transmission. While the presence of chronic cough for reasons other than TB has been associated with delays in presentation and diagnosis of TB,[8–12] the epidemiological importance of subclinical TB has not yet been well-characterized.

Here we present a secondary analysis of data from TB prevalence surveys in South Africa to 1) quantify the burden of subclinical TB, and 2) estimate the association between patient-level variables and subclinical TB.

METHODS

Setting and study population

In 2010, TB prevalence surveys were conducted in eight communities in the Western Cape Province of South Africa that were part of the Zambia and South Africa Tuberculosis and AIDS Reduction (ZAMSTAR) trial. Trial communities were selected based on TB notification rates greater than 400/100,000 per annum, high human immunodeficiency virus (HIV) prevalence, and proximity to a TB diagnostic center. Community-level HIV prevalence rates did not exist at the time of site selection; however, expert opinion and available data defined all communities as having an HIV prevalence higher than provincial estimates. The detailed ZAMSTAR study design has been described previously. Below, we provide brief details relevant for this analysis.[13,14]

Data collection

TB prevalence surveys were conducted over a period of 12 months. The communities were divided into >150 clusters demarcated by census enumeration areas, and trained study personnel visited all households. Informed consent was provided by eligible adults (individuals aged ≥18 years who stayed in the household the previous night. All participants were asked to produce spot respiratory secretion samples, either spontaneously or with the help of breathing techniques. Research assistants administered a structured questionnaire to elicit demographic, behavioral, clinical, and socio-economic information (Supplementary Data S1). Participants were asked whether they had cough, fever, drenching night sweats, or weight loss at the time of survey. HIV status was determined by testing participants who provided a finger-prick sample using Determine™ HIV-1&2 test kits (Alere, Waltham, USA). Self-reported status was documented in case of participants who refused consent for HIV testing.

Case definitions

A case of bacteriologically confirmed TB (confirmed TB) was defined as a participant who produced a respiratory sample resulting in a positive culture for *M. tuberculosis*.[13] A subclinical case of TB (subclinical TB) was defined as a participant with bacteriologically confirmed TB who did not report any of the symptoms specified by the WHO for diagnosis of TB: cough, 1 month of fever, weight loss, and night sweats.[15] A symptomatic case of TB (active TB) was defined as a participant with bacteriologically confirmed TB by culture who reported at least one symptom. No TB was defined as having no microbiologic evidence of *M. tuberculosis* on culture.

Data analysis

Crude prevalence of TB was calculated among the entire study population, the population reporting no symptoms associated with TB, and the population reporting at least one of the symptoms associated with TB.

Multivariate generalized estimating equations (GEE) were used to provide population-average estimates of odds ratios (OR) between individual-level variables and the risk of bacteriologically positive TB among participants who did not report any symptoms consistent with TB at the time of the prevalence survey. We included basic demographic (age, sex, race), socio-economic (education, occupation), behavioral (tobacco smoking, alcohol use), and health (previous TB, HIV infection, diabetes) data that have well-documented associations with risk of TB.[16]

Because data collected by cluster violates the independence assumptions made by regression, we selected GEEs and specified an exchangeable correlation structure. GEEs provide reasonable estimates of the log(OR) and standard errors when the number of clusters is large.[17] Variables with $P < 0.5$ after a Bonferroni Correction for multiple comparisons testing were considered to be significantly associated with culture-positive TB. A complete case analysis was performed in order to fit the model. Analyses were performed using R v3.3.2 programming software (R Computing, Vienna, Austria) using the 'geepack' package geeglm function for the GEEs.[18]

Ethics

Approval for this analysis was given by Stellenbosch University, Tygerberg, South Africa (N17/09/084). Yale University Institutional Review Board, New Haven, CT, USA, exempted this study from a full board review, as the Yale-based investigators did not have identifying data. Approval for the ZAMSTAR trial was given by the Health Research Ethics Committees of Stellenbosch University, the University of Zambia

(Lusaka, Zambia), and the London School of Hygiene & Tropical Medicine (London, UK). Written informed consent was provided by participants during the prevalence surveys. Participants did not give consent for data to be shared.

RESULTS

Of the 32,792 eligible adults providing consent to participate in the ZAMSTAR trial prevalence survey in South Africa (78% of those approached), 99.9% (32,770/32,792) had recorded data on age and sex. Evaluable respiratory secretions were obtained from 91.6% (30,017/32,770) of those providing consent. There were 300 participants receiving TB treatment at the time of the survey who were excluded from this analysis.

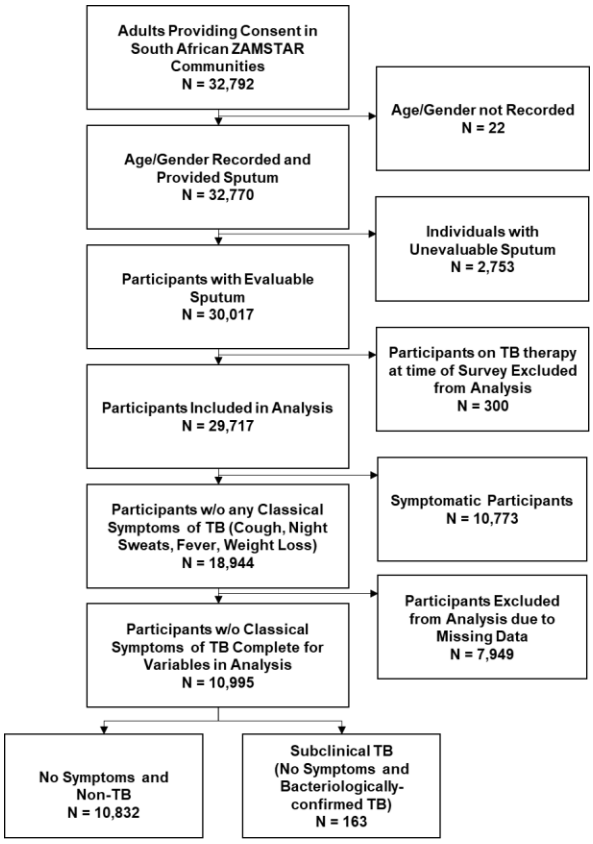

Figure 1. Flow diagram of participants included in this analysis.
Note: ZAMSTAR—Zambia and South Africa Tuberculosis and AIDS, Reduction TB—tuberculosis.

Of the surveyed participants, 64% (18,944/29,717) reported no symptoms associated with TB (as defined above), and the remaining 36% (10,773/29,717) reported at least one symptom consistent with TB (**Figure 1**).

The crude prevalence of TB among those not on treatment within the South African ZAMSTAR trial communities was 2,222.1 cases per 100,000 (*n* = 660 cases, 95% CI 2,053.4–2,388.5 per 100,000). Of the total number of bacteriologically confirmed cases of prevalent TB, 44.7% (295/660) were subclinical. The crude prevalence of TB among participants reporting no symptoms was 1,557.2 per 100,000 (*n* = 295, 95% CI 1,381.0–1,733.5 per 100,000). The crude prevalence of TB among participants reporting symptoms was 3,388.1 per 100,000 (*n* = 365, 95% CI 3,046.4–3,729.8 per 100,000). Demographic breakdown of the data for both the symptomatic and asymptomatic populations and the prevalence of bacteriologically confirmed TB within the levels of each variable are given in **Table 1**. Among the participants not reporting any symptoms, data on all modeled variables were available for 58% (10,995/18,944). The primary source of missing data was HIV-status—7,809 participants did not undergo HIV testing or report HIV status. The proportion of younger males among participants excluded from the analysis was higher than the proportion among participants included in the complete case analysis. Full description of the differences can be found in Supplementary **Table S1**.

Multivariate analysis on sufficiently complete cases (**Table 2**) found current tobacco smoking (OR 2.37, 95% CI 1.41–3.99) and HIV-positive status (OR 3.26, 95% CI 2.31–4.61) to be independently associated with an increased risk of subclinical TB. Participants in the 30–34 years age group were less likely to have subclinical TB (OR 0.45, 95% CI 0.24–0.84). History of tobacco smoking was not significant after correcting for multiple hypothesis testing (OR 1.68, 95% CI 1.04–2.71).

Table 1. Demographic breakdown of all participants in the eight South African ZAMSTAR trial communities (including participants with missing data) grouped by presence of symptoms and showing prevalence of bacteriologically confirmed TB. Note: ZAMSTAR—Zambia and South Africa Tuberculosis and AIDS, Reduction TB—tuberculosis, HIV—human immunodeficiency virus.

Variable	No TB with no classical symptoms of TB at time of survey	TB case with no classical symptoms of TB at time of survey	Crude subclinical TB point prevalence (/100 000)	No TB with symptoms at the time of survey	TB case with symptoms at the time of survey	Crude symptomatic TB point prevalence (/100 000)
Total population, *n*	18 649	295	1 557.2	10 408	365	3 388.1
Male sex, *n*	6 923	129	1 829.3	3 949	181	4 382.6
Age group, years						
18–24	2 268	30	1 305.5	1 041	25	2 345.2
25–29	1 250	18	1 419.6	626	20	3 096.0
30–34	944	19	1 973.0	504	25	4 725.9
35–39	729	19	2 540.1	453	23	4 831.9
40–49	907	24	2 577.9	645	48	6 926.4
50–59	470	11	2 286.9	405	23	5 373.8
≥60	351	8	2 228.4	272	17	5 882.4
Missing	4	0	0	3	0	0
Female sex, *n*	11 726	166	1 395.9	6 459	184	2 769.8
Age group, years						
18–24	3 698	55	1 465.5	1 609	45	2 720.7
25–29	2 162	32	1 458.5	1 026	37	3 480.7
30–34	1 567	12	760.0	797	22	2 686.2
35–39	1 211	15	1 223.5	653	14	2 099.0
40–49	1 568	19	1 197.2	1 068	29	2 643.6
50–59	896	16	1 754.4	750	24	3 100.8
≥60	619	17	2 673.0	550	13	2 309.1
Missing	5	0	0	6	0	0
Ethnicity						
Non-Black	1 714	26	1 494.3	854	48	5 321.5
Black	16 935	269	1 563.6	9 554	317	3 211.4
Tobacco smoking						
Never smoker	14 794	204	1 360.2	7 222	212	2 851.8
Ex-smoker	2 330	52	2 183.0	1 965	103	4 980.7
Current smoker	1 525	39	2 493.6	1 221	50	3 933.9
Alcohol use						
Never	10 944	144	1 298.7	4 992	112	2 194.4
Daily	340	11	3 133.9	305	16	4 984.4
Occasional	6 594	121	1 801.9	4 420	197	4 266.8
Ex-drinker	771	19	2 405.1	691	40	5 472.0
Previously infected with TB						
No	16 849	252	1 473.6	8 648	274	3 071.1
Yes	1 794	43	2 340.8	1 756	91	4 926.9
Missing	6	0	0	4	0	0
Diabetes						
No	17 552	279	1 564.7	9 307	338	3 504.4
Yes	1 097	16	1 437.6	1 101	27	2 393.6
HIV status						
Negative	9 356	110	1 162.1	5 710	173	2 940.7
Positive	1 484	53	3 448.3	1 230	76	5 819.3
Missing	7 809	132	1 662.3	3 468	116	3 236.6
Final year of education						
None/Grade 1/Grade 2	841	23	2 662.0	715	34	4 539.4
Grade 3–Grade 6	1 938	54	2 710.8	1 410	55	3 754.3
Grade 7–Grade 10	6 671	113	1 665.7	4 142	167	3 875.6
Grade 11–Grade 12	8 332	97	1 150.8	3 755	101	2 619.3
College/university	867	8	914.3	386	8	2 030.5
Occupation at year of survey						
None or own land	7 485	137	1 797.4	4 340	172	3 812.1
Occasional	1 071	22	2 012.8	1 164	41	3 402.5
Employed	6 462	93	1 418.8	3 070	101	3 185.1
Unable to work	325	8	2 402.4	264	17	6 049.8
Student	2 536	27	1 053.5	1 174	26	2 166.7
Homemaker	770	8	1 028.3	396	8	1 980.2

Table 2. Multivariate analysis of predictors of bacteriologically confirmed TB among those participants not reporting any current symptoms of TB*

* Only variables with sufficiently complete data were included in this analysis.

† Indicates significance with P < 0.05 and Bonferroni Correction allowing for 10% false-discovery rate.

Note: TB—tuberculosis, OR—odds ratio, CI—confidence interval, HIV—human immunodeficiency virus.

	OR	95% CI	*P* value
Baseline	0.02	0.01–0.04	<0.001
Sex			
Male			
Female	0.91	0.63–1.31	0.615
Age group, years			
18–24			
25–29	0.87	0.54–1.41	0.572
30–34	0.45	0.24–0.84	0.012†
35–39	1.12	0.67–1.86	0.665
40–49	0.82	0.46–1.44	0.488
50–59	1.14	0.58–2.24	0.706
≥60	0.71	0.29–1.74	0.453
Race			
Other			
Black	1.11	0.66–1.85	0.696
Tobacco smoking			
Never smoker			
Ex-smoker	1.68	1.04–2.71	0.032
Current smoker	2.37	1.41–3.99	0.001†
Alcohol use			
Never			
Daily	0.50	0.13–1.96	0.321
Occasional	1.09	0.75–1.59	0.657
Ex-drinker	1.34	0.69–2.58	0.385
Previously infected with TB			
No			
Yes	1.13	0.73–1.74	0.585
Diabetes			
No			
Yes	1.22	0.69–2.15	0.500
HIV status			
Negative			
Positive	3.26	2.31–4.61	<0.001†
Final year of education			
None/Grade 1/Grade 2			
Grade 3–Grade 6	0.70	0.32–1.52	0.363
Grade 7–Grade 10	0.78	0.38–1.60	0.501
Grade 11–Grade 12	0.61	0.29–1.30	0.204
College/university	0.76	0.27–2.20	0.618
Occupation at year of survey			
None or own land			
Occasional	0.96	0.51–1.81	0.889
Employed	0.84	0.57–1.23	0.359
Unable	1.27	0.43–3.78	0.666
Student	0.81	0.44–1.48	0.487
Home-maker	0.41	0.13–1.31	0.131

DISCUSSION

In our study population (*n* = 29,717), 44.7% of participants with bacteriologically confirmed prevalent TB did not report any classical TB symptom during the standard screening interview; this is consistent with several other large-scale prevalence studies reporting high burdens of subclinical disease.[6]

A growing body of evidence supports the notion that subclinical disease may be a useful category within the continuum of TB infection and suggests that disease course after infection may include a subclinical state.[19,20] History of smoking and HIV infection are well-known to be associated with active TB disease; these findings are reflected in the subclinically infected individuals in this analysis. This perhaps suggests that subclinical disease may be a subset of active TB disease. Analysis of the symptomatic group (data not shown) did indicate that smoking and HIV infection in the ZAMSTAR survey were also associated with TB disease; however, in the case of smoking, the association was not as strong as with TB disease in the subclinical asymptomatic group. Our analysis of ZAMSTAR prevalence data was not powered to compare the associations.

Molecular and mathematical evidence suggests that it may be useful to think of subclinical TB as distinct from active TB.[20–25] A recent meta-analysis of active case-finding interventions revealed that these interventions have generally failed to show either reductions in community incidence or improvement in individual patient outcomes, although such case-finding lead to earlier disease detection among individuals screened.[26] Dowdy et al. used a model that included subclinical disease to demonstrate the potential limitations of symptom-based screening and to suggest how active case-finding strategies may improve control, especially if those not reporting classical symptoms could be identified.[22] However, the impact of such strategies will depend on

quantities for which we currently have little data, such as the relative infectiousness of individuals with bacteriologically confirmed TB that do not have symptoms compared with those who have symptoms, and the natural history of subclinical TB.

Given the nature of the cross-sectional ZAMSTAR prevalence data, information on whether individuals with subclinical TB progressed to symptomatic TB was unavailable. A cohort study may be able to provide insight into determinants of subclinical TB and disease progression; however, the natural history of subclinical TB is challenging to investigate due to ethical concerns of withholding treatment from individuals with bacteriological confirmation. Historical cohorts from the pre-anti-TB chemotherapeutic era may inform the natural history if symptomatic and asymptomatic individuals were investigated for bacteriological confirmation of TB with follow-up. Narrowing uncertainty around key parameters related to infectiousness of subclinical TB may inform more effective interventions; for example, if individuals with subclinical disease remain in this health state for long periods of time and are likely to transmit *M. tuberculosis*, active-case finding interventions to identify individuals with subclinical disease would be especially attractive.

Our analysis supports Esmail et al.'s hypothesis that behaviors and health conditions that mask recognition of classical TB symptoms, such as smoking, may inform the design of active case-finding interventions with greater impact. Since upper respiratory infections and chronic cough associated with cigarette smoking may impede self-recognition of TB symptoms and delay healthcare seeking, the strong association between subclinical TB and current cigarette smoking shown in our analysis is potentially significant.[27,28] For example, our findings support the possibility of further probing for details about symptoms possibly relating to TB among individuals who smoke and do not report symptoms upon initial screening. Our analysis of the

ZAMSTAR trial TB prevalence survey allows us to assess the relationship between smoking behaviors and current TB, therefore avoiding potential recall bias that limit retrospective studies that assess smoking behaviors after a TB diagnosis has been made or among symptomatic individuals seeking a diagnosis.

The ZAMSTAR trial prevalence data provides compelling evidence that HIV infection is also independently associated with subclinical TB. Crude HIV prevalence in the South African ZAMSTAR trial communities, based on individuals who consented to give blood for HIV testing or self-report HIV status in the TB prevalence survey, was about 16,100 per 100,000; however, HIV status was missing for more than one third of the population. Previous studies of TB among HIV-positive individuals have identified subclinical disease in these populations, and have posited that subclinical presentation may be related to atypical disease associated with immune suppression.[23,29–31] Our study further supports the importance of screening for TB among individuals infected by HIV in high TB-HIV co-burden settings, and that such screening may need to be more comprehensive than an assessment of symptoms through questionnaires.

Limitations

Our ability to assess the presence of symptoms was based on several questions related to the presence of any cough, fever, weight loss and drenching night sweats (**Supplementary Data S1**). While responses by surveyed participants to these questions may accurately reflect their ability to recognize their current symptoms, it is not clear whether additional questioning could have revealed the presence of worsening baseline cough or other potential signs of TB.

Our analysis is also limited by substantial missing data, especially related to HIV infection, which may introduce bias. Given that younger adult males are known to have a higher prevalence of active TB, it will be important to investigate potential reasons for the

lack of data on HIV status to enhance the strength of future study of subclinical infection.[1]

Radiological data were not available for analysis. Previous studies have shown that radiological findings are variable in the context of subclinical infection,[23,29,32] which is significant, given that many prevalence surveys and diagnostic algorithms rely on the presence/absence of such findings.

CONCLUSION

Nearly 45% of participants with bacteriologically confirmed TB in the South African ZAMSTAR trial TB prevalence surveys denied experiencing any of classical symptoms of TB. Among those participants for which we had sufficiently complete data, current smoking was independently associated with a greater than two-fold odds, and HIV infection was independently associated with a greater than three-fold odds of subclinical TB. These findings confirm the importance of new approaches for detecting disease among individuals with atypical presentation or among individuals who may have other explanations for their symptoms, which can impede self-recognition of TB. While this study provides additional support for claims of the potential importance of subclinical disease, the epidemiological significance of subclinical disease remains unclear, and studies which can address the natural history of subclinical disease and the transmission potential of individuals with subclinical TB will be valuable.

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CONFLICTS OF INTEREST

None declared.

Supplementary Table 1:
Comparison of participants without symptoms sufficiently complete for multivariate analysis against those excluded from the analysis due to missing data. Males were more likely to be excluded from the analysis than females; other than sex, the distributions of variables among those included in our analysis were similar to those excluded.

		Data Included in Analysis[a]		Data Excluded from Analysis[a]	
Population Total		10995		7949	
Gender	Male	3464	31·5%	3588	45·1%
	Female	7531	68·5%	4361	54·9%
Age Group	18-24	3426	31·2%	2625	33·1%
	25-29	2060	18·7%	1402	17·7%
	30-34	1528	13·9%	1014	12·8%
	35-39	1170	10·6%	804	10·1%
	40-49	1471	13·4%	1047	13·2%
	50-59	789	7·2%	604	7·6%
	60+	551	5·0%	444	5·6%
Male Age Group	18-24	1039	30·0%	1259	35·1%
	25-29	620	17·9%	648	18·1%
	30-34	477	13·8%	486	13·6%
	35-39	368	10·6%	380	10·6%
	40-49	496	14·3%	435	12·1%
	50-59	265	7·7%	216	6·0%
	60+	199	5·7%	160	4·5%
Female Age Group	18-24	2387	31·7%	1366	31·4%
	25-29	1440	19·1%	754	17·3%
	30-34	1051	14·0%	528	12·1%
	35-39	802	10·6%	424	9·7%
	40-49	975	12·9%	612	14·0%
	50-59	524	7·0%	388	8·9%
	60+	352	4·7%	284	6·5%
TB-status	Negative	10832	98·5%	7817	98·3%
	Positive	163	1·5%	132	1·7%
Race	Non-Black	1257	11·4%	483	6·1%
	Black	9738	88·6%	7466	93·9%
Tobacco Smoking	Never smoker	8773	79·8%	6225	78·3%
	Ex-smoker	1527	13·9%	855	10·8%
	Current smoker	695	6·3%	869	10·9%
Alcohol Use	Never	6473	58·9%	4615	58·1%
	Daily	179	1·6%	172	2·2%
	Occasional	3837	34·9%	2878	36·2%
	Ex-drinker	506	4·6%	284	3·6%
Previously Infected w/ TB	No	9763	88·8%	7338	92·4%
	Yes	1232	11·2%	605	7·6%
Diabetes	No	10218	92·9%	7613	95·8%
	Yes	777	7·1%	336	4·2%
HIV Status	No	9458	86·0%	8	100·0%
	Yes	1537	14·0%	0	0·0%
Final Year of Education	None/Grade 1/Grade 2	458	4·2%	406	5·1%
	Grade 3 - Grade 6	1116	10·2%	876	11·0%
	Grade 7- Grade 10	3912	35·6%	2872	36·1%
	Grade 11 - Grade 12	4959	45·1%	3470	43·7%
	College/University	550	5·0%	325	4·1%
Occupation at Year of Survey	None or Own Land	4666	42·4%	2956	37·2%
	Occasional	682	6·2%	411	5·2%
	Employed	3627	33·0%	2928	36·8%
	Unable to Work	175	1·6%	158	2·0%
	Student	1338	12·2%	1225	15·4%
	Home-Maker	507	4·6%	271	3·4%

a = Percentages given as a total of the entire population of participants included in the analysis or participants excluded in the analysis

Supplementary Appendix 1:
Structured individual and household questionnaires used in the Zambia South Africa TB and AIDS reduction trial prevalence survey[1] to elicit demographic, behavioral, clinical, and socioeconomic information. Trained research assistants administered these questionnaires in the trial participants' households.

Individual Questionnaire

SECTION 1

ALL QUESTIONS IN THIS SECTION MUST BE ANSWERED

HOUSEHOLD BARCODE

Q01_INC	**Interviewer's code**	
Q02_DAT	**Date today**	D D M M Y Y Y Y
Q03_SEN	**Serial Number**	
Q05_HOH	**Are you the Head of Household?**	No 0 / Yes 1
Q06_SEX	**Sex**	M 1 / F 2
Q07_AGE	**Age**	
Q08_MAR	**Married to**	
Q09_DIS	**Disability?**	No Disability 1; Sight(blind/ severe visual impairment) 2; Hearing (deaf/ profoundly hard of hearing) 3; Communication(speech impairment) 4; Physical(needs wheelchair/ crutches) 5; Mental disability 6
Q10_CON	**Consent**	No 0 / Yes 1 / Absent 2 / Excluded 3
Q04_IND	**Individual Barcode (If Consent = Yes)**	

ONLY CONTINUE IF CONSENT IS GIVEN

SECTION 2A – FILL THIS AND SUBSEQUENT SECTIONS IN ONLY IF PERSON HAS GIVEN CONSENT

I would like to ask you some questions

Q11_DOB	**Date of Birth** (01/01/1800 if unknown) **If not known, what was your age in Q11_1_DOB years at your last birthday?** (999 if unknown)	D D M M Y Y Y Y

Q12_YLC How many years have you lived in this community?
Write down actual number, zero if less than one year)

Q13_RAC What is your race?
Select only one option

Black	1
Coloured	2
Indian/Asian	3
White	4
Other	5

Q14_COB What is your country of birth?
(Drop down menu with SADC countries and few other Africa countries)

Q15_HZS Before this survey, have you heard of or been involved with ZAMBART/ZAMSTAR (DTTC/ ZAMSTAR for SA)

No	Yes
0	1

Q16_CMS What is your current marital Status?
If married, Divorced or widowed, continue, If never married go to Q18

Never married	1
Currently married or living as married	2
Divorced or Separated	3
Widowed	4

Q17_AFM Age at first marriage? (years)

Q18_MOY What has been your main occupation during the past year?

Unemployed/working on own land	1
Occasional/seasonal employment	2
Employed (Formal employment or self employed making money)	3
Unable to work	4
Student	5
Housewife/ home-maker	6

I would like to ask you about smoking

Q19 Have you ever smoked

Y	N

Q19_1 How old were you when you first started regular cigarette smoking?
(Record Age - X Years old)

Q19_2 If you have stopped smoking, how old were you when you stopped? X years old
(If the participant has not stopped smoking, record as 999)

Q19_3 On average over the entire time that you smoke(d), about how many cigarettes per week do (did) you smoke?

Q19_4 On average over the entire time that you smoke(d), do (did) you primarily smoke manufactured or hand rolled cigarettes

M	HR

I would like to ask you about your current drinking habits

Q20_CDH How would you classify your drinking habits?

Have never drunk	1
Daily drinker	2
Occasional drinker	3
Ex-drinker	4

Now I will ask questions about your education

Q21_HEA What is the highest level of education you have attained?

No Formal Education	0
Grade 1-12(Indicate actual grade)Note Grade 8-12 is also Form 1 –form 5	
College	20
University	30

If has attended school, continue, if No formal education go to Q23

Q21_1_FBS Have you ever attended a faith-based school

No	Yes	Unknown

If has attended school, continue, if No formal education go to Q23

Q22_YES When was the last year you were enrolled in School/College/University? Enter 9999 if year is not known

Y	Y	Y	Y

Q23_OCC Please state main occupation at age 15 years?

Unemployed/ working on own land	1
Seasonal/Occasional employment	2
Employed (formal employment or self employed earning money)	3
Unable to work	4
Student	5
Housewife/home-maker	6
Can't remember	-5

I would like to ask you about your health. (Current TB questions)

Q24_CTB Are you currently on TB treatment? Probe and be sure only conventional treatment (on ATT)

No	Yes
0	1

(If yes continue, If No go to Q35)

Q25_FPS Where did you first present for your symptoms?

Government/Community clinic	1
Private Clinic/hospital	2
Government Provincial/District hospital	3
Pharmacy	4

Private Doctor	5
Traditional Healer	6
ZAMSTAR/DTTC Sputum collection point	7

Q26_TCA Is TB treatment card available? (confirm by seeing the card)
If yes continue, If No go to Q31

No	Yes
0	1

Q27_DTS **Date treatment started**

D	D	M	M	Y	Y	Y	Y

Q28_TTN **TB treatment Number (from treatment card)**

Q29_CAT **Category of TB as recorded on card?**

Sputum smear Positive	1
Sputum smear Negative	2
Extrapulmonary	3
Unknown/not recorded	-5

Q30_TTC **TB treatment Centre(as written on card)**

ASK QUESTION 31 TO 34 IF TB TREATMENT CARD NOT AVAILABLE

Q31_MST Which month did you start treatment

January	1
February	2
March	3
April	4
May	5
June	6
July	7
August	8
September	9
October	10
November	11
December	12
Unknown	-5

Q32_SPT Was the sputum smear positive for TB?

No	Yes	Unk
0	1	-5

Q33_RTF Where are you receiving your TB treatment from?

Government/Community clinic	1
Private Clinic/hospital	2
Government Provincial/District hospital	3
Pharmacy	4
Private Doctor	5

Q34_TTC **TB treatment Centre**

Questions about previous TB treatment

Previous TB treatment

Q35_TTB Have you ever been on TB treatment before?
If yes continue, if no go to Q37

No	Yes	Unk
0	1	-5

Q36_HMT How many times?

Once	1
Twice	2
Three times	3
More than three times	4
Unknown	-5

I would like to ask about your current state of health

Q37_CHC Do you currently have a cough?
If yes continue, if no go to Q47

No	Yes
0	1

Q38_WBC How many weeks have you been coughing?

< 1 week	1
1 week	2
2 weeks	3
3 weeks	4
4 weeks	5
5 weeks	6
6 weeks	7
7 weeks	8
8 weeks (2 months)	9
3 – 6 months	10
> 6 months	11
Unknown	-5

Q39_CPS Do you currently produce sputum

No	Yes
0	1

Q40_CCB Do you currently cough up blood?

No	Yes
0	1

Q41_CAC	Did you consult anybody for this cough? If yes continue, if no go Q47	No	Yes
		0	1

Q42_GHF	Where did you go for help first?	
	Government /Community clinic	1
	Private clinic/hospital	2
	Government Provincial/ District hospital	3
	Pharmacy	4
	Private Doctor	5
	Traditional healer	6
	ZAMSTAR/DTTC Sputum collection point	7

If 1, 2, 3 go to Q44

Q43_GCP	If pharmacy/private/tradition healer, did you ever go to a government/community/sputum collection point	No	Yes
		0	1
Q44_ASS	Did anyone ask for sputum samples? **If yes continue, if no go to Q 47**	No	Yes
		0	1
Q45_DGS	If yes, did you give sputum? **If yes continue, if no go to Q47**	No	Yes
		0	1

Q46_RES	What was the result?	
	Negative for TB	0
	Positive for TB	1
	Unknown/can't remember	-5

Other symptoms

Q47_CCP	Do you currently have chest pains?	No	Yes
		0	1
Q48_CHF	Do you currently have fever?	No	Yes
		0	1
Q49_DNS	Do you currently have drenching night sweats?	No	Yes
		0	1
Q50_LWU	In the last month have you lost weight unintentionally?	No	Yes
		0	1
Q51_DBB	Do you currently have difficulty breathing or shortness of breath?	No	Yes
		0	1

Now I will ask questions about Diabetes and HIV

Q52_THD	Have you ever been told you have diabetes **If Yes continue, if No go to Q55**	No	Yes
		0	1
Q53_CAT	If yes, are you currently on any treatment for diabetes? **If yes continue If no go to Q55**	No	Yes
		0	1

Q54_TON	What treatment are you on?	
	Dietary only	1

Tablets	2
Insulin injections	3

Q55_KHS Do you know your HIV status?

No	Yes
0	1

Q56_DHS Are you willing to disclose your HIV status?
If yes continue, if not willing to discuss and male go to Q60.

No	Yes
0	1

Q57_HIV What is your HIV status?

Negative	0
Positive	1

If HIV status is Positive, continue, if negative and male go to Q60

Q58_ART Are you on Antiretroviral treatment(ART)
If yes continue, if no and male go to Q60

No	Yes
0	1

Q59_LAR How long have you been on ART? Write down actual number of months

Ask question 60 and 61 only to males

Q60_CIR Are you circumcised?
If yes continue, if no go to Q62

No	Yes	Unk
0	1	-5

Q61_WCI When were you circumcised?

0-10 years	1
10-15 years	2
15 – 20 years	3
>20 years	4

	Interview's code	Date								Signature
		d	d	m	m	y	Y	y	y	
Interviewer										
Field manager										
1st data entry										
2nd data entry										

THANK YOU FOR YOUR HELP

Individual Barcode

SECTION 2 B

MEASUREMENTS

Q01_INC	**Counselor's code**	
Q01_INC	**Nurse's code**	
Q02_DAT	**Date today**	D D M M Y Y Y Y
Q62_WEI	**Weight? Record weight in Kilograms (one decimal point) If not done, write 999.9**	. Kg
Q63_HEI	**Height? Record weight in centimeters If not done, write 999**	cm
Q64_ABC	**Abdominal Circumference? Record in centimeters If not done, write 999**	cm

SECTION 3

RECORD BLOOD SUGAR AND HIV RESULTS HERE

Q65_BLG **Blood Glucose.** — Write actual Results below: .

Q65_1_LAG **When did you last have anything to eat or drink (except water)?.** — Write Number of hours ago

Q66_HIV_DET **HIV Test result (Determine).**

Negative	0
Positive	1
Not Done	-5

Q67_HIV_UNI **Confirmatory HIV Test result (Unigold/Sensa)**

Negative	0
Positive	1
Not Done	-5

Q68_KHS **Does study participant want to know his/her HIV Result?**

No	Yes
0	1

Q68_1_GHRR HIV test results given to study participant?

No	Yes
0	1

Q69_HIV_ORA Oral HIV Test

Negative	0
Positive	1
Not Done	-5

THANK YOU FOR YOUR HELP

	Interview's code	Date								Signature
		d	d	m	m	y	Y	y	Y	
Interviewer										
Field manager										
1st data entry										
2nd data entry										

Household Questionnaire

ALL QUESTIONS IN THIS SECTION MUST BE ANSWERED
Administer questionnaire to head of household or any responsible adult who is available

HOUSEHOLD BARCODE

Q01_INC	Interviewer's code	
Q02_DAT	Date today	D D M M Y Y Y Y
Q03_HOH	Are you the Head of Household?	No: 0 / Yes: 1

ALL QUESTIONS IN THIS SECTION MUST BE ANSWERED

Household questions to be asked

Q04_HHH In your Household is there (Check every option)

	No	Yes
Electricity	0	1
A radio/radio cassette	0	1
A television	0	1
A refrigerator/freezer	0	1
A bicycle	0	1
A motorcycle	0	1
A car	0	1
A domestic worker not related to household head	0	1
A mobile phone	0	1
A landline (non mobile telephone)	0	1

Q05_WOL Do members of your household work on their or the family's agriculture land?

No	Yes
0	1

Q06_WAT What is the main source of DRINKING WATER for this household (check only one option)

Piped water inside the residence	1
Piped water in the yard	2
Piped water from a public tap	3
Protected well	4
Unprotected shallow well	5
Traditional well	6
Bore hole	7
River, stream, lake etc	8
Other	9

Q07_TOI What is the main type of TOILET facility for this household? (Check only one option)

Private flush toilet	1
Shared flush toilet	2

Pit Latrine without ventilation	3
VIP Latrine	4
None- use bush/field	5
Bucket system	6
Chemical	7
Other	9

Q08_DWE **Which of the following types best describes the main dwelling unit that this household occupies?**

House/brick structure on own stand(single unit)	1
Townhouse/cluster/semidetached house(multiunit residential)	2
Traditional dwelling/hut/structure made from traditional material	3
Flat in block of flats	4
Brick house/flat/room in backyard	5
Informal dwelling or shack in back yard	6
Informal dwelling or shack not in backyard. (informal squatter settlement)	7
Caravan/Tent	8
Worker's hostel	9
Other	99

Q09_HMR **Number of persons per sleeping room** ____

Q10_FLO **What is the main type of flooring for this household?**

(Check only one option)

Dirt/earth	1
Wood, plank	2
Parquet, lino	3
Cement	4
Tile flooring	5
Other	9

Q11_HEA **What type of fuel does your household mainly use to keep warm inside the house during winter?**

(Check only one option)

Nothing	0
Electricity	1
Liquefied Petroleum Gas	2
Kerosene/Paraffin	3
Charcoal	4
Wood	5
Other	9

Q12_FFC **What type of fuel does your household mainly use for cooking?**

(Check only one option) If charcoal or wood continue, else go to Q14

No cooking is done	0
Electricity	1
Gas	2
Paraffin	3

Charcoal	4
Wood	5
Other	9

Q13_ TOS **What type of stove is usually used for cooking?**

Open fire	1
Surrounded fire	2
Stove with combustion chamber	3
Two or three pot stove	4
Sunken pot stove	5

Q14_WCH **Where does cooking mainly happen?**

(Check only one option)

Indoors in main house	1
Indoors separate building	2
Outdoors	3

Q15_RON **Did your household have to rely on any of the following in the last 18 months?**

(Each item must be answered)

	No	Yes
Relief food, free food from government and other bodies	0	1
Reducing number of meals or food in-take	0	1
Borrowing cash (e.g. kaloba, borrowing from friends etc)	0	1
Sale of assets	0	1
Sending household members away	0	1

Q16_HUN **During the past three months, did it happen even once that you or any member of your family experienced hunger because you did not have any food to eat?**

No	0
Yes	1
Unk	-5

	Interviewer's Code	Date								Signature
		d	d	m	m	y	y	y	y	
Interviewer										
Field Manager										
1st data entry										
2nd data entry										

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Chapter 3

Development of a treatment-decision algorithm for HIV-uninfected children evaluated for pulmonary tuberculosis

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ABSTRACT

Background: Limitations in the sensitivity and accessibility of diagnostic tools for childhood tuberculosis contribute to the substantial gap between estimated cases and cases notified to national tuberculosis programs. Thus, tools to make accurate and rapid clinical diagnoses are necessary to initiate more children on antituberculosis treatment.

Methods: We analyzed data from a prospective cohort of children <13 years being routinely evaluated for pulmonary tuberculosis in Cape Town, South Africa from March 2012 to November 2017. We developed a regression model to describe the contributions of baseline clinical evaluation to the diagnosis of tuberculosis using standardized, retrospective case definitions. We included results from baseline chest radiography and Xpert MTB/RIF to the model to develop an algorithm with at least 90% sensitivity in predicting tuberculosis.

Results: Data from 478 children being evaluated for pulmonary tuberculosis were analyzed (median age: 16.2 months, interquartile range: 9.8-30.9); 242 (50.6%) were retrospectively classified with tuberculosis, of which 104 (43.0%) were bacteriologically-confirmed. The area under the receiver operating characteristic curve for the final model was 0.87. Clinical evidence identified 71.4% of all tuberculosis cases in this cohort, and inclusion of baseline chest radiography results increased the proportion to 89.3%. The algorithm was 90.1% sensitive and 52.1% specific, and maintained a sensitivity of above 90% among children <2 years or with low weight-for-age.

Conclusions: Clinical evidence alone was sufficient to make most clinical antituberculosis treatment decisions. The use of evidence-based algorithms may improve decentralized, rapid treatment-initiation, reducing the global burden of childhood mortality.

INTRODUCTION

Each year, 1.2 million children are estimated to develop tuberculosis, and about one quarter of those children die.[1] This places tuberculosis in the top ten causes of mortality among children under 5 worldwide. Globally, over 96% of deaths in children with tuberculosis occur among those not receiving treatment.[2]

Childhood tuberculosis is generally paucibacillary, limiting the sensitivity of bacteriologic tests including rapid molecular diagnostics such as Xpert MTB/RIF (Xpert).[3] Findings on chest radiography (CR) are similarly less sensitive among children.[4] In addition to diagnostic limitations, accessing these tests may be challenging—especially in low- and middle-income countries that bear the greatest burden of tuberculosis.[5] These limitations in sensitivity and accessibility contribute to the substantial gap between the estimated 1.2 million annual incident cases of childhood tuberculosis and the approximate 500,000 annual cases notified to the World Health Organization (WHO).[1]

Decentralized diagnosis and treatment for childhood tuberculosis may reduce the risk of untreated tuberculosis and improve treatment outcomes by shortening the delay to treatment initiation.[6-10] To that end, the WHO and the International Union against Tuberculosis and Lung Disease suggest treating children for whom there is sufficient clinical evidence of tuberculosis, even in the absence of further diagnostic investigation;[11,12] however, it is not clear what clinical evidence is sufficient to start treatment. Practical, data-driven treatment-decision algorithms could help support more effective and uniform treatment decision-making at peripheral health facilities.[13]

A recent study among children living with HIV demonstrated that antituberculosis treatment-decisions may be made using clinical evidence alone.[14] We present a complementary study, in which we analyze data from HIV-uninfected children from a

well-characterized prospective cohort of young children routinely evaluated for pulmonary tuberculosis in Cape Town, South Africa. We aimed to investigate the relative contributions of baseline clinical characteristics, baseline CR, and baseline Xpert to the diagnosis of childhood pulmonary tuberculosis in a high-tuberculosis burden setting. We used this evidence to develop a practical algorithm to assist in making sensitive and rapid antituberculosis treatment-initiation decisions.

METHODS

Participants

Children <13 years old routinely evaluated for pulmonary tuberculosis were prospectively identified for participation in a diagnostic study.[15-17] Children were recruited from inpatient wards and emergency rooms at Tygerberg Hospital and Karl Bremer Hospital, referral hospitals in Cape Town, South Africa, from March 2012 to November 2017. Eligibility criteria reflected the WHO and national criteria for the evaluation of childhood tuberculosis and were any of the following: cough ≥2 weeks, unexplained fever ≥1week, poor growth/weight loss over the preceding three months, or cough <1 week with a known tuberculosis exposure in the previous 12 months, positive tuberculin skin test (TST), or CR suggestive of tuberculosis as evaluated by study physicians. Children were not eligible if they had received antituberculosis treatment for >1 day or had extrapulmonary tuberculosis without also being evaluated for pulmonary tuberculosis.

Procedures and definitions

At the time of enrollment each participant underwent a standardized clinical examination performed by study physicians; TST; bacteriological testing for *Mycobacterium tuberculosis* (*M.tb*) using acid-fast bacilli smear microscopy, Xpert, and Mycobacteria Growth Indicator Tube (MGIT) liquid culture from a minimum of two

respiratory specimens (one specimen of either gastric aspirate for children <5 years or spontaneously produced sputum for older children able to expectorate, and one specimen of induced sputum); and anteroposterior and lateral CR. CR was read by two independent pulmonology and/or pediatric tuberculosis experts blinded to the clinical history using a standardized evaluation tool. Some children underwent additional sampling for other respiratory specimens for *M.tb* confirmation, including nasopharyngeal aspirate and stool, as part of investigational sub-studies. At two months, all study participants were evaluated irrespective of tuberculosis diagnosis at baseline. All children with an ongoing suspicion for tuberculosis, regardless of the decision to treat for tuberculosis, had respiratory samples taken during follow up at 1, 2, and/or 6 months or as clinically needed for smear microscopy, MGIT, and Xpert. Data were dual-entered into standard case report forms. Managing clinical teams made the decision to treat.

Study participants were retrospectively classified by the study team as having confirmed, unconfirmed, or unlikely tuberculosis using standardized clinical case definitions developed for the evaluation of diagnostics for childhood pulmonary tuberculosis (supplemental Table S1).[18] These definitions considered clinical history from baseline evaluations, immunological evidence of *M.tb* infection, consistency of CR with tuberculosis as evaluated by experts blinded to the clinical history, confirmation of *M.tb* from Xpert or MGIT from respiratory specimens collected at baseline or in follow-up, and follow-up evaluation to assess for resolution or persistence of symptoms. All available information was used to inform classification of tuberculosis using these definitions.

Given the epidemiological difference in the risk of tuberculosis and severe forms of disease,[19] we defined two risk-groups in our population: higher-risk children <2 years

of age or with a weight-for-age Z-score of <-2, and lower-risk children ≥2 years of age and with a weight-for-age Z-score of ≥-2.

Statistical analysis

We used logistic regression to develop a model to predict confirmed and unconfirmed tuberculosis restricted to data from the baseline evaluation of children with complete predictor information. We identified candidate predictors from the baseline clinical evaluation (the initial clinical history and physical examination) used in previous scoring systems to diagnose childhood pulmonary tuberculosis, as well as from a nested case-control analysis of our data, where we defined cases as having any bacteriological confirmation of *M.tb* over the study period and controls as those retrospectively classified as unlikely tuberculosis with the additional requirement that they completed the study without ever receiving antituberculosis treatment.

We carried out backward variable selection from the full model containing only predictors from the baseline clinical evaluation to develop the first model (clinical model). We used an inclusion p-value cutoff informed by variable degree-of-freedom as per Akaike information criterion in model selection.[20] We added results from the baseline CR and Xpert performed on all respiratory specimens collected at baseline only to obtain the second model (investigational model). Though MGIT culture is more sensitive for *M.tb* than Xpert, we include Xpert in our models given improved accessibility in many settings and shorter time-to-result.

All predictors were binary variables to reflect their presence or absence in the child except cough duration, which we categorized as no cough or cough <1 week, 1-2 weeks, 2-3 weeks, or >3 weeks. A list of all relevant candidate predictors and their

definitions as relevant to this study are provided in the supplementary information. Analysis was performed using R version 4.0.1.

Given that a positive Xpert result was sufficient to classify a child as having tuberculosis by the reference standard, coefficient and standard error estimates for the investigational model were obtained using Firth's logistic regression using function 'brglm' in R package *brglm.* We examined separation by plotting the receiver operating characteristic (ROC) curve for each model and assessing the area under the ROC curve (AUC) using the R package *pROC*. We used the function 'roc.test' to compare whether the models had statistically significant AUCs using DeLong's test for correlated ROC curves. We used leave-one-out cross-validation using function 'cv.glm' in the R package *boot* to assess out-of-sample predictive performance.

Treatment-decision algorithm development

We scaled the coefficient estimates for the parameters in each model such that a score of >100 constituted a sensitivity of at least 90% to diagnose pulmonary tuberculosis, consistent with the WHO target product profile of a community-based triage test to identify tuberculosis (scaling methodology described in the supplementary information).[21] To develop a treatment-decision algorithm, we examined how study participants met criteria for diagnosis disaggregated by contribution from baseline clinical evidence, baseline CR consistent with tuberculosis, and baseline Xpert on respiratory specimens.

Ethical considerations

Data collection and analysis was approved by the Stellenbosch University Health Research Ethics Committee (Ref No. N11/09/282). Written informed consent for study participation was obtained from parents or legal caregivers, and written assent was

obtained from children 7 years and above. This analysis was approved via expedited review by the Yale Institutional Review Board (Ref No. 2000028046) and did not require specific consent as it was a secondary analysis of previously collected data.

RESULTS

Population

Data were available for 608 children who completed evaluation for the prospective study, of which 478 HIV-uninfected participants had sufficiently complete data for this analysis (Figure 1). Two hundred and forty-two (50.6%) children were retrospectively classified as having confirmed or unconfirmed pulmonary tuberculosis using the clinical case definitions, and 104 of these (43.0%) were bacteriologically-confirmed. See supplemental Table S2 for differences between population included/excluded from this analysis due to missing variables.

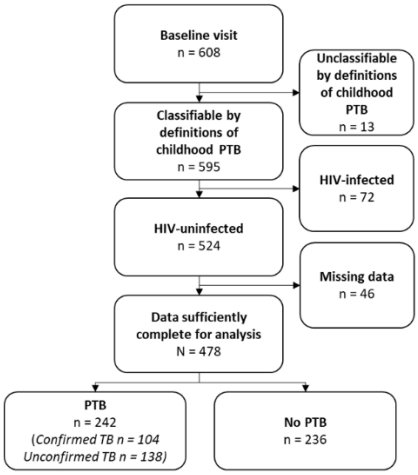

Figure 1. Flow diagram demonstrating participant eligibility for this analysis.[17]

Table 1 describes the demographics and candidate predictors for children with sufficiently complete data for this analysis. Of 478 children, 223 (46.7%) were female, the median age was 16.2 months (interquartile range [IQR]: 9.8 - 30.9), and the median weight-for age Z-score was -1.58 (IQR: -2.7 - -0.7). We classified 378 children (79.1%)

as at higher-risk for tuberculosis and severe disease. Descriptions of these higher- and lower-risk subpopulations are provided in the supplemental Tables S3 & S4**.**

Table 1. Description of demographics and candidate predictors from clinical evaluation and diagnostic imaging/testing of HIV-uninfected participants with sufficiently complete data for this analysis.

	Children, No. (%)[b]	
Variable	Tuberculosis (n = 242)	Not Tuberculosis (n = 236)
Demographics		
Sex		
Male	127 (52)	128 (54)
Female	115 (48)	108 (46)
Age, median (IQR), mo	18.09 (10.14–32.1)	15.28 (9.36–27.52)
Age group, y		
0–1	15 (64)	161 (68)
2–4	60 (25)	62 (26)
≥5	27 (11)	13 (6)
Weight-for-age *z* score , median (IQR)	−1.71 (−3.01 to −0.66)	−1.46 (−2.47 to −0.69)
Weight-for-age *z* score below −2	105 (43)	92 (39)
Clinical history at baseline		
Cough duration, wk		
No cough	46 (19)	55 (23)
<1	74 (31)	97 (41)
1–2	43 (18)	32 (14)
2–3	23 (1)	16 (7)
>3	56 (23)	36 (15)
Fever	147 (61)	105 (44)
Failure to thrive/weight loss	111 (46)	87 (37)
Poor appetite	137 (57)	122 (52)
Lethargy	104 (43)	74 (31)
History of tuberculosis contact	128 (53)	55 (23)
Clinical examination at baseline		
Lymphadenopathy	151 (62)	145 (61)
Stridor	6 (2)	3 (1)
Wheeze	55 (23)	58 (25)
Hepatomegaly	42 (17)	19 (8)
Splenomegaly	19 (8)	6 (3)
Diagnostic testing/imaging at baseline		
CR findings consistent with pulmonary tuberculosis at baseline	131 (54)	22 (9)
Xpert-confirmed *Mycobacterium tuberculosis* on respiratory specimens at baseline	62 (26)	0 (0)
Retrospective clinical case definitions		
Confirmed tuberculosis	104 (43)	0 (0)
Unconfirmed tuberculosis	138 (57)	0 (0)
Unlikely tuberculosis	0 (0)	236 (0)

Prediction modeling

The predictors selected from baseline clinical evidence for inclusion in the final model were cough duration, fever, failure to thrive/weight loss, lethargy, history of tuberculosis exposure, and hepatomegaly. We added results from baseline CR and baseline Xpert to create the investigational model. Odds ratios, 95% confidence intervals, and p-value of the predictors included in the clinical and investigational models along with AUC and leave-one-out cross-validation for each model are provided in Table

2, and the ROC curves for the models are presented in Figure 2. The clinical and investigational models had statistically different AUCs of 0.75 and 0.87 respectively (P-value < 0.001).

Table 2. Prediction models of baseline clinical history and physical evaluation with/without diagnostic imaging/microbiological investigation.

	Clinical Model: Clinical Evidence Only			Investigational Model: Clinical Evidence + CR + Xpert		
Predictor	OR	95% CI (0.025–0.975)	*P* Value	OR	95% CI (0.025-0.975)	*P* Value
Intercept	0.22	0.12-0.37	.00	0.10	0.04-0.18	<.01
Cough duration, wk						
No cough	Reference	…	…	Reference	…	…
<1	0.68	0.39-1.19	.18	0.62	0.31-1.18	.15
1–2	1.51	0.78-2.97	.22	1.29	0.59-2.85	.52
2–3	2.29	1.01-5.29	.05	1.35	0.48-3.76	.56
>3	2.27	1.20-4.35	.01	2.48	1.19-5.49	.02
Fever present						
No	Reference	…	…	Reference	…	…
Yes	1.89	1.24-2.90	.01	1.69	1.03-2.88	.04
Failure to thrive/weight loss						
No	Reference	…	…	Reference	…	…
Yes	1.66	1.10-2.54	.02	1.80	1.10-3.04	.02
Lethargy						
No	Reference	…	…	Reference	…	…
Yes	1.40	0.90-2.18	.14	1.68	0.98-2.97	.06
History of tuberculosis exposure						
No	Reference	…	…	Reference	…	…
Yes	5.13	3.33-8.05	.01	6.99	4.20-13.00	<.01
Hepatomegaly						
No	Reference	…	…	Reference	…	…
Yes	2.62	1.38-5.13	.01	1.18	0.52-2.71	.69
Baseline CR findings consistent with pulmonary tuberculosis					…	…
No	…	…	…	Reference	…	…
Yes	…	…	…	9.38	5.22-19.45	<.01
Baseline respiratory specimens positive for *Mycobacteriun tuberculosis with* Xpert						
No	…	…	…	Reference	…	…
Yes	…	…	…	90.41	10.69-Inf	<.01
Leave-one-out cross-validation	0.21	…	…	0.15	…	…
Area under the ROC curve	0.75	…	…	0.87	…	…

Treatment-decision algorithm

The probability threshold of the investigational model was set at 0.25 to classify tuberculosis with 90.1% sensitivity and 52.1% specificity. At this threshold, 173 (71.5%) of the 242 children with a diagnosis of tuberculosis could be identified using clinical evidence (Figure 3). Among those children not identifiable by clinical evidence, an additional 43 were identified by CR. Inclusion of chest radiography results after clinical evidence increased the proportion of tuberculosis identified to 89.3%. Figure 4 shows the treatment-decision algorithm built from the investigational model**.** This algorithm

failed to diagnose 24 children with tuberculosis (described in supplemental Table S5). The sensitivity and specificity compared to the retrospective reference standard for baseline CR alone was 0.54 and 0.91 and respectively 0.26 and 1.0 for baseline Xpert alone.

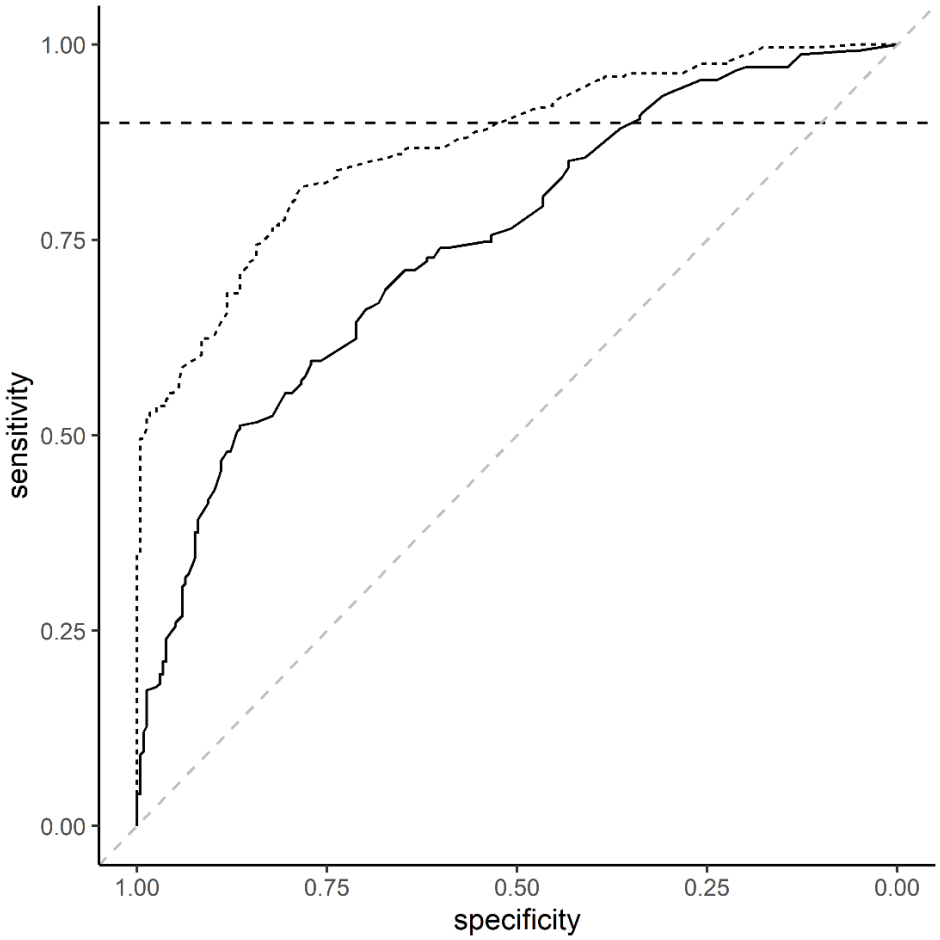

Figure 2. Receiver operating characteristic curves of the clinical model (solid line) including the features form the baseline clinical evidence (cough duration, fever, failure to thrive/weight loss, lethargy, a history of tuberculosis exposure, and hepatomegaly) and the investigational model (dotted line) considering baseline clinical evidence, baseline chest radiography, and Xpert MTB/RIF from respiratory specimens collected at baseline. The horizontal dashed line is drawn at a sensitivity of 90%.

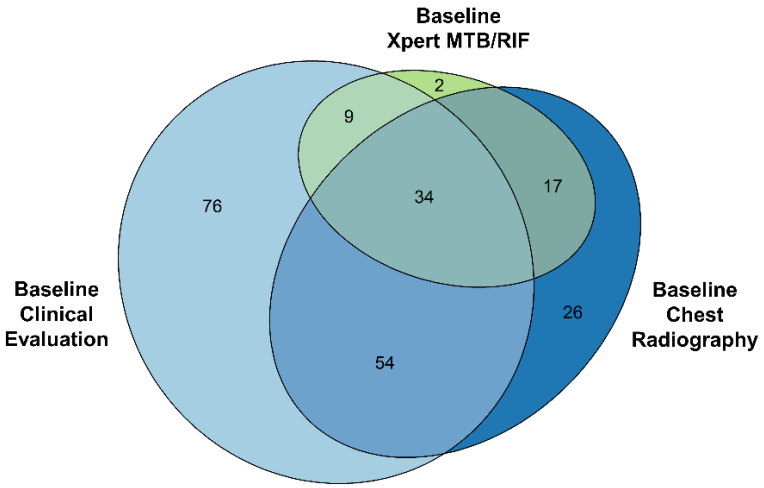

Figure 3. Venn diagram depicting how the 242 participants with tuberculosis in this cohort met criteria to be classified as having tuberculosis by the investigational model. Criteria was met by having sufficient evidence from baseline clinical evaluation, having baseline chest radiography consistent with pulmonary tuberculosis, and/or having Xpert MTB/RIF-confirmed M.tb from respiratory specimens collected at baseline. Note that 24 participants classified as having tuberculosis by the reference standard were missed by the investigational model.

Table 3 demonstrates the sensitivity, specificity, positive predictive value, and negative predictive value of the algorithm in the higher- and lower-risk subpopulations. The algorithm had a sensitivity and specificity of 91.8% and 51.6% respectively among higher-risk children and 83.3% and 53.8% respectively among lower-risk children.

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value of the algorithm developed from the investigational model including baseline clinical evidence, chest radiography, and Xpert MTB/RIF given for the subpopulations of children at higher- and lower-risk for tuberculosis and severe disease.

Risk for Tuberculosis and Severe Disease	Sensitivity, %	Specificity, %	PPV, %	NPV, %
High risk (age <2 y or weight-for-age *z* score below −2)	91.8	51.6	66.7	85.6
Low risk (age ≥2 y and weight-for-age *z* score of at least −2)	83.3	53.8	62.5	77.8

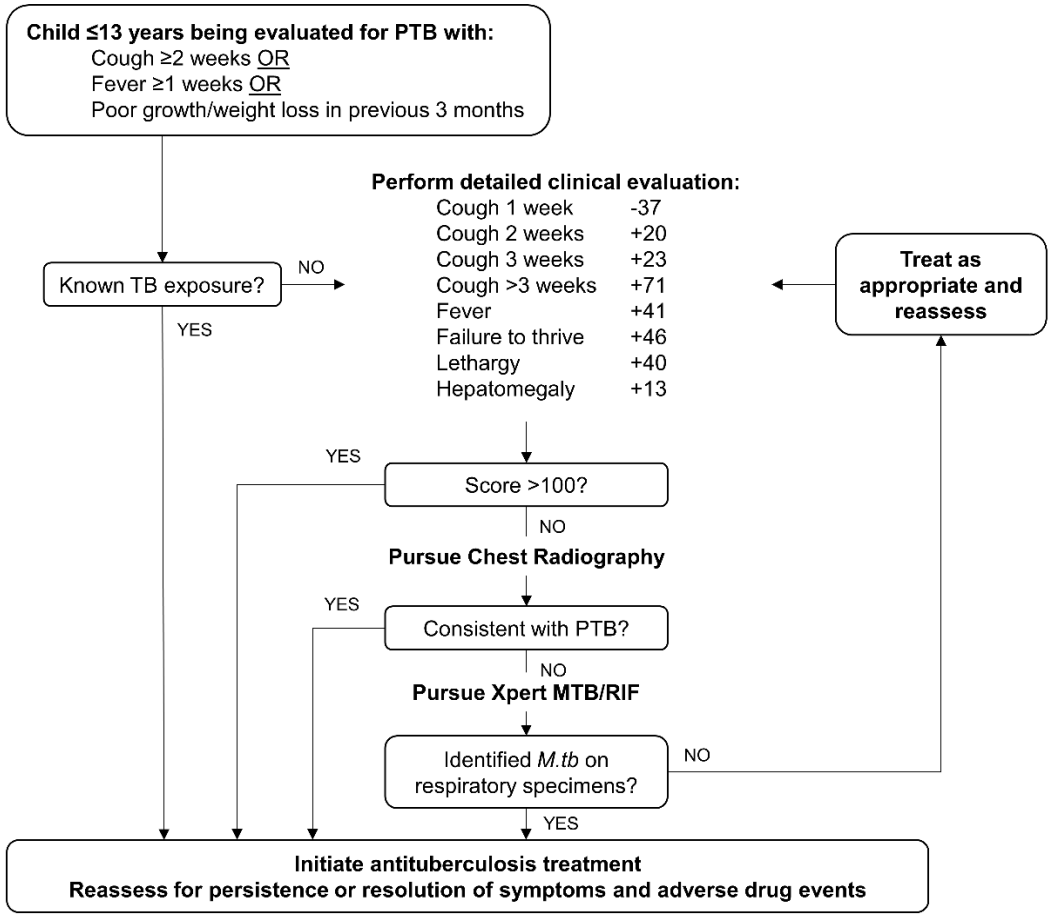

Figure 4. Treatment-decision algorithm developed from the investigational model which includes baseline clinical evidence, baseline chest radiography, and Xpert MTB/RIF from respiratory specimens collected at baseline.

The algorithm built from the clinical model including only clinical evidence is shown in supplemental Figure S1, with a sensitivity of 90.5% and specificity of 33.9% (supplemental Figure S2 and supplemental Table S6).

DISCUSSION

Our analysis of a well-characterized, prospective cohort of young children evaluated for pulmonary tuberculosis demonstrates that a detailed clinical history and physical examination is sufficient to initiate treatment in most HIV-uninfected children. In our setting, CR and Xpert only impacted the decision to treat a minority of children with

symptoms suggestive of pulmonary tuberculosis. This suggests that diagnostic testing/imaging may be reserved for those children who do not meet criteria for treatment-initiation based on clinical evidence alone. We used these findings to construct a data-driven algorithm to promote sensitive and rapid antituberculosis treatment-initiation.

While the WHO does not define the target sensitivity and specificity of diagnostic tools for childhood tuberculosis as compared to a composite reference standard, we fixed the sensitivity of our algorithm at 90% to be consistent with both the WHO-defined target for a community-based triage and the algorithm-building approach adopted by Marcy and colleagues.[14,21] Our specificity fell short of the WHO-proposed target; however, given the severe consequences of failing to diagnose and treat a case of childhood tuberculosis, we elected to prioritize sensitivity over specificity.

Our results highlight the importance of a detailed clinical history and physical examination in making treatment-initiation decisions for childhood tuberculosis. We identified clinical evidence suggestive of childhood pulmonary tuberculosis that is consistent with the literature,[14,22-25] and we quantitatively described their contribution to diagnosis. This analysis demonstrates that incorporating additional clinical characteristics may improve the specificity of treatment decisions without a substantial sacrifice in sensitivity among children identified by the WHO symptom screen. Additionally, this approach allows health workers to identify those children with sufficient clinical evidence to begin antituberculosis treatment without the need for additional diagnostic imaging/testing. This supports rapid treatment-initiation in settings where access to diagnostic imaging/testing is limited, as well where negative results from available tests may not change management.

Our analysis suggests pursuing CR prior to Xpert among those children who do not meet criteria to receive antituberculosis treatment using clinical evidence alone. This is reasonable given the accessibility of CR in many settings and its utility in identifying other pathology not related to tuberculosis. Additionally, it does not require any invasive sampling procedures that may be needed to obtain samples from young children for microbiological confirmation. We note that the contribution to diagnosis that we present for CR in this analysis may be optimistic, given that high quality images were obtained in a tertiary care setting with expert readings that may be unavailable in some high-burden, low-resource settings.[26] Prospective investigation into the use of standardized digital CR and enhanced reader training will be important to understand the use of CR in childhood tuberculosis diagnosis in settings with limited resources.[27] Furthermore, inclusion of specific findings on CR may increase the specificity of our algorithm.[4]

Though we demonstrate that well-collected respiratory specimens for Xpert performed at baseline do not substantially improve our algorithm, we note that Xpert may provide important information on guiding treatment selection in settings where drug resistance is a concern. However, it is important to note that lack of access to microbiological testing and negative test results should not prevent children from accessing antituberculosis treatment when clinical criteria are met. Furthermore, while drug-resistant tuberculosis transmission is an important public health concern, the relative importance of microbiological tests in children should be informed by the local epidemiology of drug-resistant tuberculosis transmission.[28] Given limitations in the sensitivity of microbiological testing among children, obtaining a detailed exposure history that includes the drug susceptibility test profile of any potential source cases remains critical.

Good performance of this algorithm among younger or low weight-for-age children is encouraging, given a higher risk of severe tuberculosis in this group. The children missed by this algorithm were generally older, had a higher weight-for-age Z-score, and had a shorter cough duration. We believe that increased sensitivity of treatment decisions, rather than precise diagnosis, is likely to have a greater impact on child mortality given the high proportion of young children who are undiagnosed. It may be necessary to accept some overtreatment with relatively safe antituberculosis therapy to reduce the preventable morbidity and mortality of untreated tuberculosis.[29,30] Diagnostic vigilance and careful follow-up are critically important for all children, regardless of the initial treatment-initiation decision, to consider competing diagnoses and monitor for adverse drug events.

Although TSTs were used to establish the reference standard, we chose not to include it in our analysis due to the many participants with missing TST data (120/478) due to global tuberculin stockouts during the study. While immunological testing for *M.tb* infection may improve the specificity of the algorithms, limitations in sensitivity among young and malnourished children and lack of accessibility at peripheral health centers may discourage their inclusion in treatment-decision algorithms.[31]

A source of potential bias in this analysis arises from the fact that the clinical evaluation, CR results, and Xpert results are included as predictors in the model and as components of the clinical reference standard. We believe that this may not be a major issue in this study given the high degree of microbiological confirmation. This is further supported by the similar operational characteristics of the algorithms in the nested case-control subpopulation as compared to in the development cohort (supplemental Tables S7 & S8). Additionally, we must be careful not to overinterpret the generalizability of these algorithms that were built from a cohort that was pre-screened for tuberculosis and

sourced from a tertiary care center. While the entry criteria for this development cohort reflects the WHO criteria for investigation for tuberculosis and a low value for cross-validation suggest generalizability and external validity, the positive predictive value of these algorithms may be lower where the baseline prevalence of tuberculosis is lower. Further evidence is required to determine the pre-test probability of tuberculosis in children identified as having a positive WHO symptom screen across different settings, as this would have implications for the performance of this treatment-decision algorithm. Furthermore, randomized, interventional investigation is necessary to evaluate the morbidity and mortality impact of using data-driven, treatment-decision algorithms to guide antituberculosis treatment initiation in different settings.

This analysis outlines an approach to interpret clinical data to inform treatment-initiation decisions for children being evaluated for pulmonary tuberculosis. It is important to recognize that this algorithm is context-specific and translation to other settings should be undertaken cautiously. Ideally, treatment-decision algorithms should be constructed locally to reflect the site-specific epidemiology, the quality and accessibility of diagnostic imaging and testing, and the relative consequence of overtreatment versus untreated child tuberculosis. Furthermore, these algorithms should be revised and recomputed as circumstance change—for example, as local capacity to incorporate additional tools changes or as improved diagnostic tools are discovered. Implementation of treatment-decision algorithms must include programmatic support and mentorship for the healthcare providers to use them effectively, as well as additional resources to support the families of the children initiated onto treatment.[7]

We demonstrate that algorithms that incorporate evidence from a detailed clinical history and physical examination could play an important role in guiding sensitive treatment-initiation decisions for most children being evaluated for pulmonary

tuberculosis. Data-driven treatment algorithms provide an important framework to consider the contribution of additional investigation, after detailed clinical evaluation. Algorithms that support rapid, decentralized antituberculosis treatment decision-making are important tools to reduce the burden of childhood tuberculosis morbidity and mortality.

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AUTHOR CONTRIBUTION

KSG and JAS conceptualized and designed the study with input from JLW and TC. EW, MMvdZ, MP, and ACH collected the data from the original diagnostic study. KSG and JAS verified the underlying data. KSG, JLW, TC, and JAS analyzed and interpreted the data. KSG wrote the first draft of the manuscript. All authors critically reviewed and approved the final manuscript.

CONFLICT OF INTEREST

We declare no competing interests.

SUPPLEMENTARY INFORMATION

Available data for predictors in model and their definition

Data from the baseline clinical evaluation (clinical history and physical examination) that were available for inclusion as predictors of tuberculosis included the following: fever, cough duration, failure to thrive/weight loss, lethargy, poor appetite, history of a known exposure to someone with tuberculosis, peripheral lymphadenopathy, hepatomegaly, splenomegaly, wheeze, and stridor. Definitions of select variables are presented below:

- Cough duration was recorded in days and collapsed into the following categories: no cough, cough <1 week, cough 1-2 weeks, cough 2-3 weeks, cough >3 weeks.
- Failure to thrive/weight loss was defined as poor growth over the preceding three months or having a weight-for-age z-score <-2 in the absence of previous weight measurements.
- History of exposure to tuberculosis was defined as having a family member in the same household with tuberculosis or exposure for ≥4 hours with someone who had tuberculosis.

Scaling coefficients to form a score for treatment-decision algorithm

A general form of a multivariate logistic regression equation is given as follows:

$$\text{logit}(p) = \beta_0 + \beta_1 * x_1 + \beta_2 * x_2 + \cdots + \beta_n * x_n$$

Where p is the probability of tuberculosis, $x_{1\ldots n}$ refers to the predictors and $\beta_{1\ldots n}$ refers to the coefficients describing the relationship between the predictor and the logit-transformed probability. We fit the prediction model to the data, and we identified the probability corresponding to classification of tuberculosis with at least 90% sensitivity compared to the retrospective reference standard. We obtained a threshold probability by subtracting the intercept from the logit-transformed probability corresponding to diagnosis with 90% sensitivity. We scaled the threshold to 100 by multiplying by a

scaling factor, and we multiplied the coefficients for each predictor by that scaling factor to obtain the score for that predictor. Thus, the score for each individual meeting entry criteria was obtained by summing the scaled coefficients for each factor present in the patient, and a total score of >100 constituted a diagnosis of tuberculosis using this treatment-decision algorithm.

Table S1. Retrospective case definitions of childhood intrathoracic tuberculosis adapted from Graham et al.[1]

Case Definition	Criteria
Confirmed tuberculosis	Bacteriological confirmation obtained *M.tb* must be confirmed (culture or Xpert MTB/RIF from at least one respiratory specimen by expectoration, sputum induction, gastric aspirate, nasopharyngeal aspirate, string test, or other relevant respiratory specimens or stool)
Unconfirmed tuberculosis	Bacteriological confirmation NOT obtained AND at least 2 of the following: - Symptoms/signs suggestive of TB (defined in Graham et al.)[18] - Chest radiograph consistent with TB - Close TB exposure or immunologic evidence of *M.tb* infection - Positive response to TB treatment (requires documented positive clinical response on TB treatment) o With *M.tb* infection ▪ Immunological evidence of Mtb infection (TST and/or IGRA positive) o Without *M.tb* infection ▪ No immunological evidence of *M.tb* infection
Unlikely tuberculosis	Bacteriological confirmation NOT obtained AND criteria for “unconfirmed tuberculosis” NOT met o With *M.tb* infection ▪ Immunological evidence of *M.tb* infection (TST and/or IGRA positive) o Without *M.tb* infection ▪ No immunological evidence of *M.tb* infection

M.tb – *Mycobacterium tuberculosis*, TB – tuberculosis, TST – tuberculin skin test, IGRA – interferon-gamma release assay.

Table S2. Differences in demographic and candidate predictors from clinical evaluation and diagnostic imaging/testing between the participants in/excluded from analysis due to missing values for variables of interest.

		Included in Analysis (n=478)		Excluded for MV (n=46)		MV
		n or Median	% or IQR	n or Median	% or IQR	
Demographic	Sex					
	Male	255	0.53	27	0.59	0
	Female	223	0.47	19	0.41	0
	Age (months)	16.21	9.82 to 30.9	12.47	7.89 to 26.56	0
	0-1 years	316	0.66	34	0.74	0
	2-4 years	122	0.26	10	0.22	0
	5 years and older	40	0.08	2	0.04	0
	Weight (Z-score for age)	-1.58	-2.69 to -0.67	-1.74	-2.4 to -0.6	0
	Z-score < -2	197	0.41	18	0.39	0
Clinical History at Baseline	Cough Duration					5
	No cough	101	0.21	8	0.17	
	Cough < 1 week	171	0.36	19	0.41	
	Cough 1-2 weeks	75	0.16	5	0.11	
	Cough 2-3 weeks	39	0.08	1	0.02	
	Cough > 3 weeks	92	0.19	8	0.17	
	Fever	252	0.53	30	0.65	0
	Failure to thrive/weight loss	198	0.41	20	0.43	0
	Poor appetite	259	0.54	26	0.57	0
	Lethargy	178	0.37	23	0.5	0
	History of tuberculosis contact	183	0.38	11	0.24	0
Clinical Examination at Baseline	Lymphadenopathy	296	0.62	28	0.61	0
	Stridor	9	0.02	1	0.02	0
	Wheeze	113	0.24	16	0.35	0
	Hepatomegaly	61	0.13	6	0.13	0
	Splenomegaly	25	0.05	2	0.04	0
Diagnostic Testing/Imaging at Baseline	Chest radiography consistent with PTB	153	0.32	2	0.04	41
	Xpert-confirmed *M.tb* on respiratory specimens	62	0.13	4	0.09	0
Retrospective Clinical Case Definitions	Confirmed TB	104	0.22	7	0.15	0
	Unconfirmed TB	138	0.29	12	0.26	0
	Unlikely TB	236	0.49	27	0.59	0

MV – missing values, IQR – interquartile range, PTB – pulmonary tuberculosis, Xpert – Xpert MTB/RIF, *M.tb* – *Mycobacterium tuberculosis*, TB – tuberculosis.

Table S3. Description of demographics and candidate predictors from clinical evaluation and diagnostic imaging/testing of the subpopulation at higher-risk for tuberculosis and severe disease as defined as being <2 years old or having a weight-for-age Z-score of <2.

		TB (n=194)		Not TB (n=184)	
		n or Median	% or IQR	n or Median	% or IQR
Demographic	Sex				
	Male	102	0.53	103	0.56
	Female	92	0.47	81	0.44
	Age (months)	13.72	8.32 to 22.42	12.91	7.63 to 18.17
	0-1 year	155	0.8	161	0.88
	2-4 years	28	0.14	18	0.1
	5 years and older	11	0.06	5	0.03
	Weight (Z-score for age)	-2.13	-3.28 to -0.96	-1.98	-2.86 to -0.97
	Z-score < -2	105	0.54	92	0.5
Clinical History at Baseline	Cough Duration				
	No cough	37	0.19	43	0.23
	Cough < 1 week	58	0.3	77	0.42
	Cough 1-2 weeks	37	0.19	26	0.14
	Cough 2-3 weeks	12	0.06	10	0.05
	Cough > 3 weeks	50	0.26	28	0.15
	Fever	116	0.6	81	0.44
	Failure to thrive/weight loss	97	0.5	80	0.43
	Poor appetite	100	0.52	99	0.54
	Lethargy	83	0.43	66	0.36
	History of tuberculosis contact	109	0.56	40	0.22
Clinical Examination at Baseline	Lymphadenopathy	113	0.58	106	0.58
	Stridor	5	0.03	3	0.02
	Wheeze	51	0.26	50	0.27
	Hepatomegaly	40	0.21	17	0.09
	Splenomegaly	18	0.09	5	0.03
Diagnostic Testing/Imaging at Baseline	Chest radiography consistent with PTB at baseline	103	0.53	17	0.09
	Xpert-confirmed *M.tb* on respiratory specimens at baseline	50	0.26	0	0
Retrospective Clinical Case Definitions	Confirmed TB	80	0.41	0	0
	Unconfirmed TB	114	0.59	0	0
	Unlikely TB	0	0	184	1

TB – tuberculosis, IQR – interquartile range, PTB – pulmonary tuberculosis, Xpert – Xpert MTB/RIF, M.tb – *Mycobacterium tuberculosis*.

Table S4. Description of demographics and candidate predictors from clinical evaluation and diagnostic imaging/testing of the subpopulation at lower-risk for tuberculosis and severe disease as defined as being ≥2 years old and having a weight-for-age Z-score of ≥2.

		TB (n=48)		Not TB (n=52)	
		n or Median	% or IQR	n or Median	% or IQR
Demographic	Sex	25	0.52	25	0.48
	Male	23	0.48	27	0.52
	Female	45.5	31.92 to 74.81	44.11	31.99 to 53
	Age (months)	0	0	0	0
	0-1 year	32	0.67	44	0.85
	2-4 years	16	0.33	8	0.15
	5 years and older	-0.79	-1.32 to -0.21	-0.63	-1.34 to 0.2
	Weight (Z-score for age)	0	0	0	0
	Z-score < -2				
Clinical History at Baseline	Cough Duration	9	0.19	12	0.23
	No cough	16	0.33	20	0.38
	Cough < 1 week	6	0.12	6	0.12
	Cough 1-2 weeks	11	0.23	6	0.12
	Cough 2-3 weeks	6	0.12	8	0.15
	Cough > 3 weeks	31	0.65	24	0.46
	Fever	14	0.29	7	0.13
	Failure to thrive/weight loss	37	0.77	23	0.44
	Poor appetite	21	0.44	8	0.15
	Lethargy	19	0.4	15	0.29
	History of tuberculosis contact	38	0.79	39	0.75
Clinical Examination at Baseline	Lymphadenopathy	1	0.02	0	0
	Stridor	4	0.08	8	0.15
	Wheeze	2	0.04	2	0.04
	Hepatomegaly	1	0.02	1	0.02
	Splenomegaly				
Diagnostic Testing/Imaging at Baseline	Chest radiography consistent with PTB at baseline	28	0.58	5	0.1
	Xpert-confirmed *M.tb* on respiratory specimens at baseline	12	0.25	0	0
Retrospective Clinical Case Definitions	Confirmed TB	24	0.5	0	0
	Unconfirmed TB	24	0.5	0	0
	Unlikely TB	0	0	52	1

TB – tuberculosis, IQR – interquartile range, PTB – pulmonary tuberculosis, Xpert – Xpert MTB/RIF, *M.tb* – *Mycobacterium tuberculosis*.

Table S5. Description of demographics and candidate predictors from clinical evaluation and diagnostic imaging/testing of the 24 participants with tuberculosis missed by the treatment-decision algorithm built from the investigational model using initial evaluation data only.

		n or Median	% or IQR
Demographic	Sex		
	Male	16	0.67
	Female	8	0.33
	Age (months)	25.84	14.06 to 33.64
	0-1 year	10	0.42
	2-4 years	13	0.54
	5 years and older	1	0.04
	Weight (Z-score for age)	-1.13	-2.29 to -0.33
	Z-score < -2	9	0.38
Clinical History at Baseline	Cough Duration		
	No cough	5	0.21
	Cough < 1 week	11	0.46
	Cough 1-2 weeks	3	0.12
	Cough 2-3 weeks	0	0
	Cough > 3 weeks	5	0.21
	Fever	11	0.46
	Failure to thrive/weight loss	10	0.42
	Poor appetite	16	0.67
	Lethargy	11	0.46
	History of tuberculosis contact	0	0
Clinical Examination at Baseline	Lymphadenopathy	17	0.71
	Stridor	0	0
	Wheeze	1	0.04
	Hepatomegaly	2	0.08
	Splenomegaly	0	0
Diagnostic Testing/Imaging at Baseline	Chest radiography consistent with PTB at baseline	0	0
	Xpert-confirmed *M.tb* on respiratory specimens at baseline	0	0
Retrospective Clinical Case Definitions	Confirmed TB	5	0.21
	Unconfirmed TB	19	0.79
	Unlikely TB	0	0

TB – tuberculosis, IQR – interquartile range, PTB – pulmonary tuberculosis, Xpert – Xpert MTB/RIF, *M.tb* – *Mycobacterium tuberculosis*.

Table S6. Sensitivity, specificity, positive predictive value, and negative predictive value of the algorithm developed from the clinical model given for the subpopulations of children at higher- and lower-risk for tuberculosis and severe disease.

	Sensitivity	**Specificity**	**PPV**	**NPV**
High-Risk Children				
< 2 years old or weight-for-age Z-score < -2	92.8%	34.3%	59.8%	81.8%
Low-Risk Children				
≥ 2 years old and weight-for-age Z-score ≥ -2	81.3%	32.7%	52.7%	65.4%

PPV – positive predictive value, NPV – negative predictive value.

Table S7. Description of demographics and candidate predictors from clinical evaluation and diagnostic imaging/testing of the nested case-control subpopulation. Cases were defined as children with any bacteriological-confirmation over the study period and controls were defined as children retrospectively classified as "unlikely tuberculosis" without ever receiving antituberculosis treatment.

		TB (n=104)		Not TB (n=184)	
		n or Median	% or IQR	n or Median	% or IQR
Demographic	Sex				
	Male	48	0.46	100	0.54
	Female	56	0.54	84	0.46
	Age (months)	18.56	9.4 to 47.43	15.85	9.15 to 31.51
	0-1 year	60	0.58	119	0.65
	2-4 years	25	0.24	52	0.28
	5 years and older	19	0.18	13	0.07
	Weight (Z-score for age)	-1.83	-2.92 to -0.94	-1.44	-2.44 to -0.49
	Z-score < -2	48	0.46	71	0.39
Clinical History at Baseline	Cough Duration				
	No cough	16	0.15	29	0.16
	Cough < 1 week	32	0.31	80	0.43
	Cough 1-2 weeks	22	0.21	28	0.15
	Cough 2-3 weeks	12	0.12	15	0.08
	Cough > 3 weeks	22	0.21	32	0.17
	Fever	65	0.62	81	0.44
	Failure to thrive/weight loss	47	0.45	67	0.36
	Poor appetite	60	0.58	97	0.53
	Lethargy	48	0.46	53	0.29
	History of tuberculosis contact	51	0.49	45	0.24
Clinical Examination at Baseline	Lymphadenopathy	65	0.62	114	0.62
	Stridor	2	0.02	2	0.01
	Wheeze	21	0.2	43	0.23
	Hepatomegaly	22	0.21	14	0.08
	Splenomegaly	13	0.12	5	0.03
Diagnostic Testing/Imaging at Baseline	Chest radiography consistent with PTB at baseline	80	0.77	17	0.09
	Xpert-confirmed *M.tb* on respiratory specimens at baseline	62	0.6	0	0
Retrospective Clinical Case Definitions	Confirmed TB	104	1	0	0
	Unconfirmed TB	0	0	0	0
	Unlikely TB	0	0	184	1

TB – tuberculosis, IQR – interquartile range, PTB – pulmonary tuberculosis, Xpert – Xpert MTB/RIF, *M.tb* – *Mycobacterium tuberculosis*.

Table S8. Sensitivity and specificity of the algorithms developed from the clinical model (evidence from baseline clinical evaluation only) and the investigational model (evidence from baseline clinical evaluation, baseline chest radiography, and baseline Xpert MTB/RIF on respiratory specimens) from the nested case-control subpopulation.

	Sensitivity	**Specificity**
Clinical model	88.5%	32.6%
Investigational model	95.2%	51.1%

Figure S1. Treatment-decision algorithm developed from the clinical model using baseline clinical evidence only.
PTB – pulmonary tuberculosis, TB – tuberculosis.

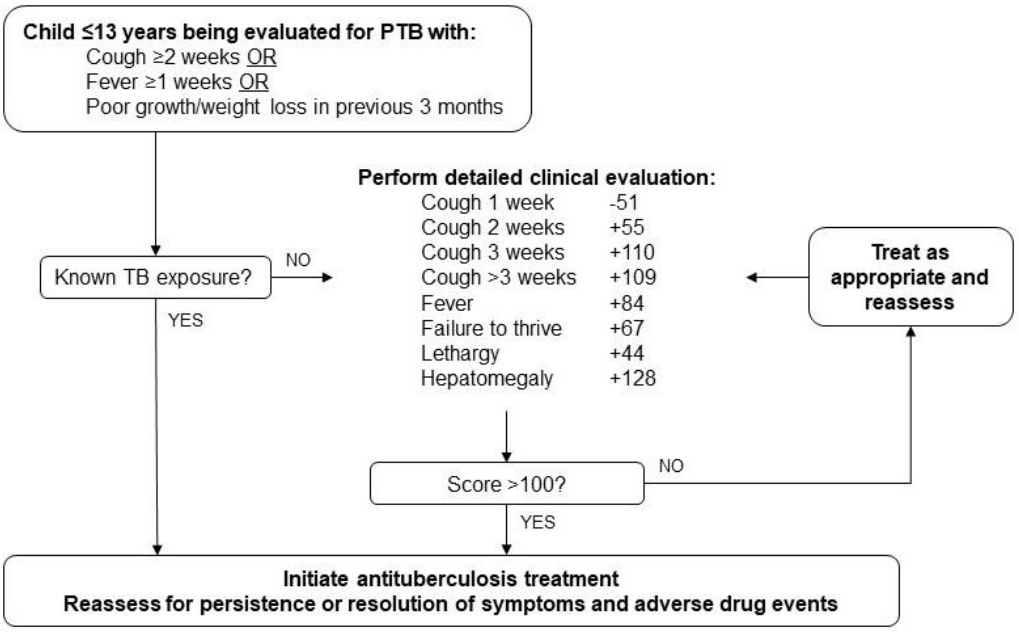
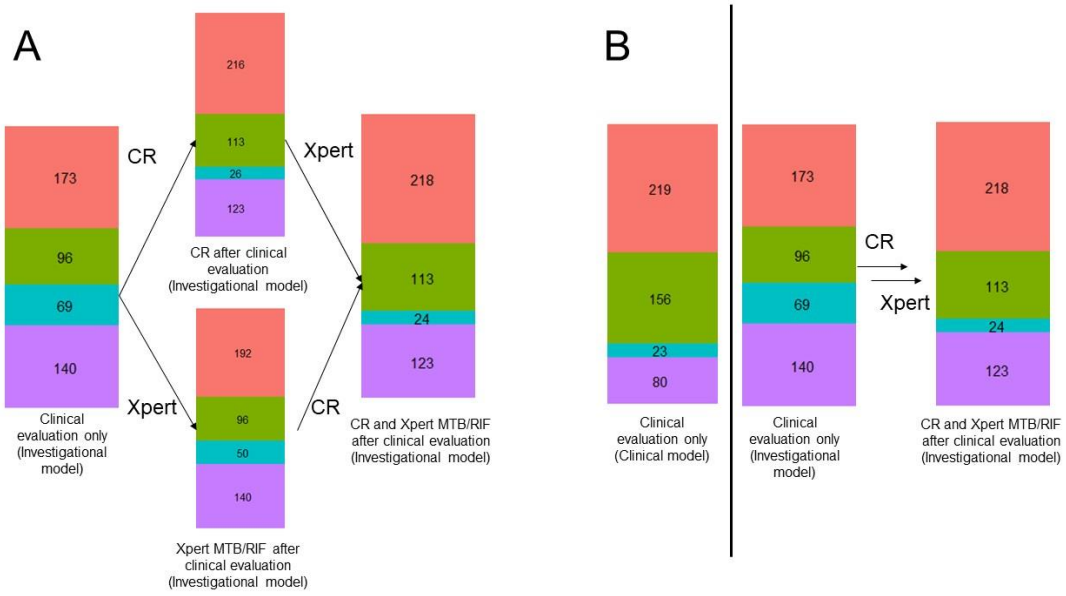


Figure S2. A) Depicts the changes in true positive (red), false positive (green), true negative (purple), and false negative (blue) over the steps of the algorithm built from the investigational model after clinical evaluation followed by CR then Xpert or Xpert then CR. CR reduces the false negative more than Xpert when performed first after clinical evaluation. B) Using the treatment-decision algorithm built from the clinical model, clinical evidence alone results in a sensitivity and specificity of 90.5% and 52.1% respectively. Using the treatment-decision algorithm built from the investigational model, meeting a score of >100 from clinical evidence alone has a sensitivity of 71.5% and specificity of 59.3%. Those participants not meeting criteria based on clinical evidence alone are investigated further by CR and/or Xpert to result in the overall investigational model algorithm sensitivity and specificity of 90.1% and 52.1% respectively. We suggest use of the clinical model algorithm in settings where CR and Xpert are not available to maintain algorithm sensitivity of at least 90%.
TP – true positive, FP – false positive, TN – true negative, FN – false negative, CR – chest radiography, Xpert – Xpert MTB/RIF.



SUPPLEMENTARY REFERENCE

1. Graham SM, Cuevas LE, Jean-Philippe P, et al. Clinical case definitions for classification of intrathoracic tuberculosis in children: an update. *Clin Infect Dis* 2015; **61**: s179-87.

Chapter 4

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

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ABSTRACT

*Background***:** Identifying children with pulmonary tuberculosis (PTB) is challenging due to the paucibacillary nature of childhood tuberculosis and concentration of resources and expertise to diagnose in tertiary or referral healthcare centers. Moving treatment initiation decisions to peripheral healthcare settings may improve outcomes by increasing treatment detection and reducing delays. Treatment-decision algorithms may empower providers in these settings by relating information gained in the evaluation into an assessment of tuberculosis disease risk. Recent advances in algorithm development have used prediction modeling approaches; however, studies that have done so are small and provide limited insight into generalizability. We describe the assembly of a large, individual participant dataset (IPD) from child presumptive PTB cases to develop a new data-driven algorithm.

*Methods***:** Studies enrolling presumptive PTB cases aged <10 years old were identified through referral from experts in pediatric TB and a World Health Organization (WHO) call for data. We used clinical evaluation, bacteriology, and imaging IPD to retrospectively evaluate the performance of existing treatment-decision algorithms for PTB. We then used this IPD to develop a logistic regression model to predict PTB and investigated generalizability using an internal-external cross-validation framework.

*Findings***:** IPD from 4,718 children (38.3% with bacteriologically-confirmed and unconfirmed PTB) were received from 13 studies in high TB-incidence settings. Existing algorithms were found to have heterogeneous performance in classifying PTB. We developed a prediction model with a sensitivity of 85% [95% credible interval (CrI): 0.78-0.91] and specificity of 37% [95% CrI: 0.22-0.55] in classifying PTB with similarly heterogeneous performance. With guidance from WHO, we operationalized this model as a treatment-decision algorithm to guide evaluation of children with presumptive PTB in peripheral health centers.

*Interpretation***:** We present a pragmatic and transparent approach for the development of a data-driven algorithm, that can be revised as better data and technologies become available. Treatment decision-algorithms represent an important tool that could, in combination with improved health system investment, reduce child mortality.
*Funding***:** World Health Organization, US National Institutes of Health

INTRODUCTION

Mycobacterium tuberculosis (*Mtb*) is a leading cause of mortality among young children, with estimates suggesting that nearly a quarter of a million children (<15 years) die due to tuberculosis (TB) each year.[1] *Mtb* is responsible for ~2.5% of the 6 million deaths that occur in children <5 years old annually.[2] Modeling suggests that that 96% of child mortality due to TB occurs among children not on treatment.[3] The World Health Organization (WHO) estimates suggest that nearly 50% of TB among children is undiagnosed, with an even greater proportion undiagnosed among children <5 years old.[1] Thus, efforts to improve TB case detection among children represents an important opportunity to reduce the global burden of child mortality.[4]

Identifying children with TB can be challenging, in part as disease among younger children (<10 years) tends to be paucibacillary, resulting in low sensitivity of bacteriological investigations.[5] Furthermore, collection of respiratory specimens from children who are unable to expectorate is invasive and requires resources that are generally concentrated in tertiary or referral healthcare centers.[6] Thus, symptoms, clinical examination, and history of *Mtb* exposure play a crucial role in the decision to initiate TB treatment. However, expertise and resources to make clinical diagnoses and/or initiate TB treatment are similarly concentrated at tertiary or referral centers. This can lead to delays in care-seeking and treatment initiation, which are known to be associated with worse outcomes.[7,8] Moving treatment initiation decisions to more peripheral healthcare settings may increase case detection and reduce child TB mortality.

Treatment-decision algorithms or scores (referred to as algorithms in this article) aim to empower healthcare workers in primary and peripheral health settings to make treatment decisions for children with presumptive TB by relating information gained in

the evaluation of children into an assessment of TB disease risk.[9] A study in Uganda demonstrated that adopting an algorithmic approach improved case-detection in primary and peripheral health settings.[10] Other groups have developed algorithms to guide the evaluation of children with TB,[11,12] including an attempt by the International Union Against TB and Lung Diseases to operationalize previous WHO guidance.[13] Many of these algorithms have been developed using expert opinion and have not been validated.

There have been several recent attempts to develop algorithms using modeling approaches, in which data from diagnostic TB evaluations of children or adults are used to quantify the contribution of different characteristics to generate an algorithm.[14-16] These data-driven approaches are more transparent and offer greater potential for formal validation. While these approaches represent an important advance, previous modeling studies have been small and have not allowed for assessment of generalizability. In this study, we aimed to assemble individual patient-level data from children with presumptive pulmonary TB from multiple cohorts in geographically diverse, high TB-incidence settings. We then sought to use this individual patient data (IPD) to evaluate the performance of diagnostic algorithms used in practice and cited in the literature, as well as to develop a new data-driven algorithm. We further aimed to operationalize this new algorithm to make it relevant for primary care settings to enable inclusion into the updated 2022 WHO consolidated guidelines on tuberculosis in children and adolescents and the accompanying operational handbook.[17,18]

METHODS

Establishment of individual-participant data

In collaboration with the Secretariat of the Child and Adolescent Tuberculosis Working Group at the WHO, we identified potential sources for IPD from studies carried

out within a geographically diverse set of high TB-burden countries. Studies were eligible for inclusion if they consecutively enrolled children <10 years old brought to healthcare facilities for clinical evaluation and meeting established criteria as a presumptive pulmonary TB case.[19] Investigators were identified to join this collaborative group through referral from experts in the field of pediatric TB and from responses to the WHO Public Call for Data on the Management of Children with TB in July 2020.

After identification of eligible primary studies, we requested IPD including details from the initial clinical history and physical examination, readings from initial chest x-ray, results from rapid confirmatory tests for *Mtb* performed on samples collected at the initial encounter, and a final classification of pulmonary TB (that may have included data collected from subsequent encounters). A full list of variables requested is provided in supplemental Appendix A. Unpublished data meeting eligibility criteria for this analysis were also acceptable. All data assembly and analysis described in this manuscript were carried out using R software. To account for the uncertainty associated with missing variables, we used 2-level multiple imputation by chained equations (MICE) implemented in the *MICE* package to generate 100 imputed datasets (additional details in supplemental Appendix B.[20]

Existing algorithm evaluation

We identified existing algorithms used to guide the evaluation of children with presumptive pulmonary TB through a literature search and through consultation with members of the WHO Guideline Development Group formed to oversee the development of the 2022 WHO consolidated guidelines on the management of TB in children and adolescents. We retrospectively evaluated the performance of these algorithms to inform treatment decisions using the IPD data from the baseline investigation, against the final classification of TB, using both confirmed and all TB

(confirmed and unconfirmed) as the reference standards. We used the "reitsma" function from the *mada* package to pool study-level sensitivity and specificity using a bivariate model (additional details in supplemental Appendix C).[21,22]

Prediction model development and validation

We used logistic regression to develop a model to predict TB using baseline evaluation data available in the IPD. We included all variables for which there was <50% missing in the IPD to predict the binary outcome of TB, considering both all TB versus unlikely TB. To account for possible heterogeneity in the relationship between the predictors and the outcome among the different studies comprising the IPD, we used the "metapred" function in package *metamisc* to fit the model at the level of each study comprising the IPD and then pooled the study-level parameter coefficients and their respective standard error estimates to generate a prediction model.[23,24] To account for the uncertainty introduced by missing data, we generated a prediction model (as described before) from each of the 100 imputed datasets and used established methods to pool the parameter coefficient and standard error estimates to generate a final, single prediction model.[25]

We used an internal-external cross-validation framework to validate the prediction model by investigating discrimination and calibration.[23] This framework uses a leave-one-study-out approach, building a model on n-1 studies (n being the total number of studies included in the IPD) and validating performance on the remaining n^{th} study, repeating this such that n models have been built on n sets of n-1 studies and validated on the holdout study. Specifically, we examined the c-statistic (also known as the area under the receiver operating characteristic curve) to understand whether there were studies in which the model had better or worse discrimination between TB and non-TB; and we examined the observed: expected (O:E) slope as a measure of calibration to

assess whether there were studies in which the model over- or under-classified TB. Empiric evidence has shown that this internal-external cross-validation approach is a more efficient use of available IPD to build prediction models as compared to methods that arbitrarily divide into training and test sets. As above, we accounted for uncertainty introduced by missing data, by pooling the c-statistic and O:E slope estimates from each of the multiply imputed datasets.

Algorithm development

To generate an algorithm that was easily implementable in settings without advanced computational power, we scaled the coefficient estimates for the parameters in each of the final prediction models to develop a score such that a score of >10 corresponded to classification of TB at fixed sensitivities of 90%, 85%, 80%, 75%, and 70%. Additional details describing this method are specified in the supplemental Appendix D. To estimate the sensitivity and specificity of the scaled score in classifying TB (all TB vs. unlikely TB), study-level sensitivities and specificities were pooled using the bivariate model of Reitsma et al. (implemented in the *mada* package) accounting for uncertainty introduced by imputation of missing data.[21,22]

In conjunction with the Secretariat of the WHO Child and Adolescent TB Working Group, we convened panel of experts to advise on the development of algorithms from these prediction models. The composition of this panel is provided in the supplemental Appendix E. Specifically, we sought advice on: 1) which features to include in the model that are clinically relevant and easy to assess in peripheral health settings, 2) modifications required to implement the models at peripheral health centers, given development had used data from tertiary levels of care, and 3) selection of a performance target for the final algorithm.

Ethics

This analysis was approved by the Stellenbosch University Health Research Ethics Committee (Ref No. X21/02/003) and the Yale Institutional Review Board (Ref No. 2000028046) and did not require specific consent as it was a secondary analysis of previously collected data. Collaborating investigators provided evidence of ethical approval for original data collection.

ANALYSIS

Data Assembly

Eighteen studies were identified as having potentially appropriate data; two of these studies were unable to provide data in the necessary timeline and an additional three studies did not meet the inclusion criteria (**Figure 1**). This led to 4,718 IPD records from children <10 years old with presumptive pulmonary TB from 13 studies,[26-39] of which, 1,811 (38.3%) were found to have TB (541 confirmed, 1,270 unconfirmed), 2,818 (59.7%) were found not to have TB, and 89 (1.9%) were not given a final classification of TB (**Table 1**). The data were predominantly collected from tertiary and referral settings.

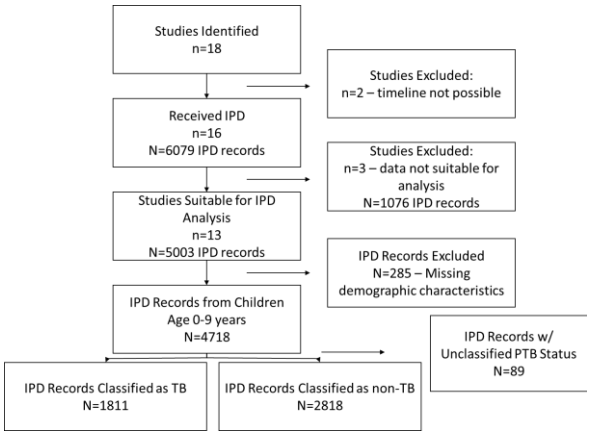

Figure 1. Studies involved and data contributed to IPD. Flow-diagram demonstrating how the eighteen studies that were identified as having potentially appropriate data for this analysis led to inclusion of 4,718 IPD records from children <10 years old with presumptive pulmonary TB (1,811 [38.3%] were found to have either bacteriologically-confirmed TB or unconfirmed TB). Note that 285 IPD records from eligible studies were excluded due to missing age. TB – tuberculosis, IPD – individual participant data, PTB – pulmonary tuberculosis.

Table 1. Characteristics of studies contributing to IPD. Study-level descriptions of data included in the IPD. HIV – human immunodeficiency virus, SAM – severely acutely malnourished, TB- tuberculosis, BD – Bangladesh, BR – Brazil, KE – Kenya, MM – Myanmar, Multi – Multi-country study (includes Burkina Faso, Cameroon, Vietnam, and Cambodia), MZ – Mozambique, PK – Pakistan, UG – Uganda, VN – Vietnam, ZA – South Africa.

Study	Size N	Age histogram 0-10 ,months	<2 years old N (%)	HIV N (%)	SAM N (%)	Confirmed TB N (%)	Unconfirmed TB N (%)	Unlikely TB N (%)	TB status unknown N (%)
Aurilio/2020/BR	50		21 (0.42)	6 (0.12)	0 (0)	9 (0.18)	11 (0.22)	24 (0.48)	6 (0.12)
Bonnet/**/UG	217		157 (0.72)	70 (0.32)	108 (0.5)	12 (0.06)	58 (0.27)	125 (0.58)	22 (0.1)
Garcia/2020/MZ	142		59 (0.42)	70 (0.49)	27 (0.19)	5 (0.04)	28 (0.2)	109 (0.77)	0 (0)
Giang/2015/VN	113		86 (0.76)	0 (0)	8 (0.07)	20 (0.18)	77 (0.68)	16 (0.14)	0 (0)
Hamid/2019/PK	445		41 (0.09)	0 (0)	26 (0.06)	0 (0)	29 (0.07)	416 (0.93)	0 (0)
Kabir/2020/BD	402		219 (0.54)	0 (0)	93 (0.23)	63 (0.16)	36 (0.09)	303 (0.75)	0 (0)
LopezVarela/2015/MZ	789		549 (0.7)	104 (0.13)	68 (0.09)	13 (0.02)	128 (0.16)	648 (0.82)	0 (0)
Marcy/2016/Multi	338		78 (0.23)	338 (1)	64 (0.19)	41 (0.12)	155 (0.46)	142 (0.42)	0 (0)
Myo/2018/MM	223		72 (0.32)	27 (0.12)	46 (0.21)	27 (0.12)	84 (0.38)	112 (0.5)	0 (0)
Orikiriza/2018/UG	338		124 (0.37)	101 (0.3)	41 (0.12)	12 (0.04)	145 (0.43)	167 (0.49)	14 (0.04)
Song/2021/KE	300		146 (0.49)	73 (0.24)	8 (0.03)	31 (0.1)	65 (0.22)	170 (0.57)	34 (0.11)
South_Africa_UCT	766		362 (0.47)	137 (0.18)	32 (0.04)	189 (0.25)	274 (0.36)	303 (0.4)	0 (0)
Walters/2017/ZA	595		389 (0.65)	70 (0.12)	18 (0.03)	119 (0.2)	180 (0.3)	283 (0.48)	13 (0.02)

Though each study was required to include children with presumptive pulmonary TB, there were heterogeneities in the inclusion criteria, definitions of variables, and reference classification of TB. Details describing heterogeneities and the imputation models to handle missing data are provided in the supplemental Appendices F-J.

Existing algorithm performance evaluation

We retrospectively evaluated the performance of eight existing algorithms to guide treatment decision-making for presumptive pulmonary TB in children;[10,13-15,40-43] one of these algorithms was evaluated only on data from children living with HIV,[14] and another was evaluated only on data from children without HIV.[15] The data to develop these latter two algorithms were included in the IPD; thus, their data were excluded from the evaluation of the respective algorithms. We had to make modifications to the

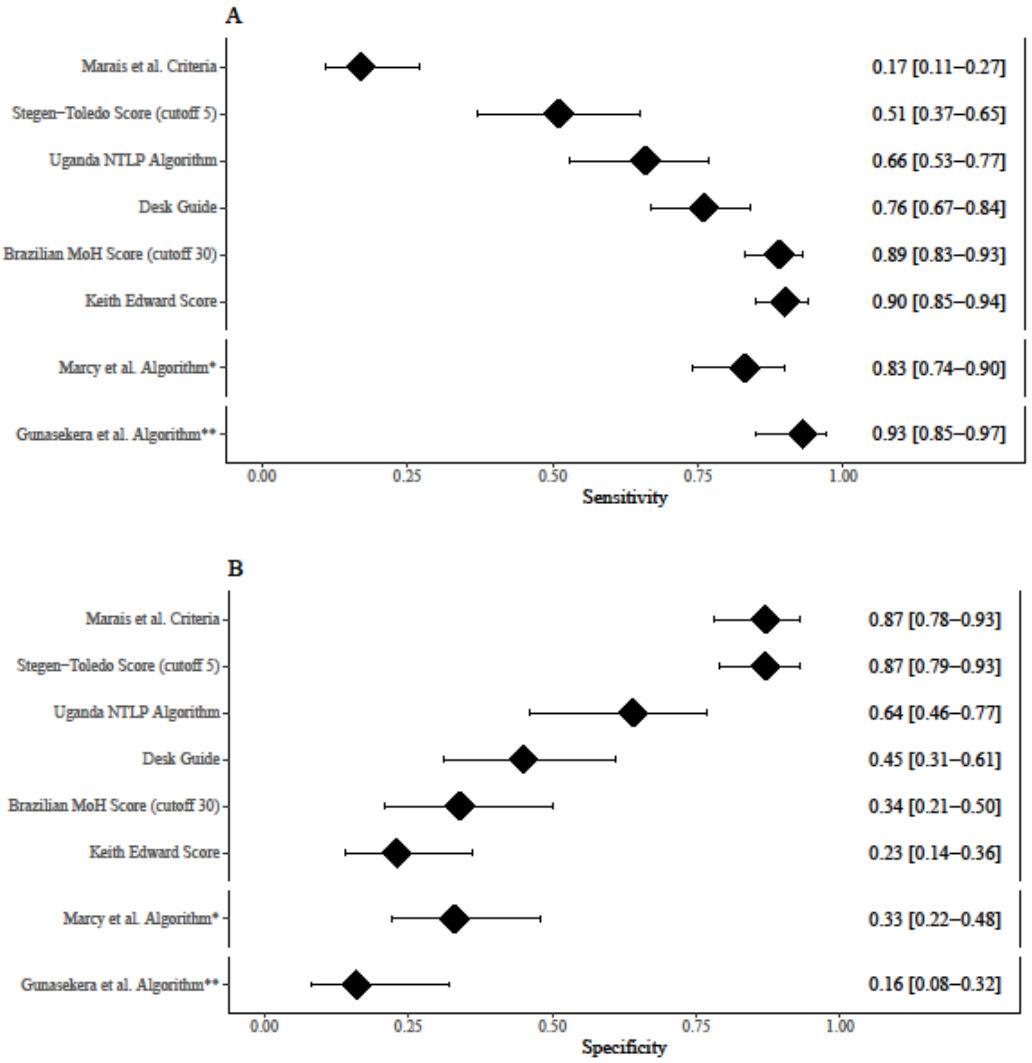

Figure 2. Performance of existing algorithms at classifying TB. Retrospective estimates of the pooled **(a)** sensitivity and **(b)** specificity of eight algorithms to guide treatment decision-making for children with presumptive pulmonary TB, had they been used to evaluate the children for whom we have IPD records. The reference classification of pulmonary TB included bacteriologically-confirmed pulmonary TB as well as unconfirmed pulmonary TB. Modifications were made to the algorithms to maximize the use of the available IPD. TB – tuberculosis, IPD – individual participant data, HIV – human immunodeficiency virus, BD – Bangladesh, BR – Brazil, KE – Kenya, MM – Myanmar, Multi – (PAANTHER) Multi-country study (includes Burkina Faso, Cameroon, Vietnam, and Cambodia), MZ – Mozambique, PK – Pakistan, UG – Uganda, VN – Vietnam, ZA – South Africa, MoH – (Brazil) Ministry of Health, NTLP – (Uganda) National TB and Leprosy Program.
*Performance estimates of the Marcy et al. Algorithm were derived from only HIV-positive children in the IPD that excludes data form the Marcy/2016/Multi cohort (from which the algorithm was developed)
**Performance estimates of the Gunasekera et al. Algorithm were derived from only HIV-negative children in the IPD that excludes data from the Walter/2017/ZA population (from which the algorithm was developed).

algorithms to evaluate their performance, given that not all features were available in the IPD (details describing these modifications are provided in the supplemental Appendix K). The overall performance of these algorithms is shown in **Figure 2**; the study-level performance of each algorithm can be found in the supplemental Appendix L. A sensitivity analysis evaluating algorithm performance to discriminate confirmed TB from unlikely TB (excluding unconfirmed TB from this analysis) demonstrated generally higher sensitivities and comparable specificities to the performance in the entire dataset including those with unconfirmed TB; these results are provided in the supplemental Appendix M.

Prediction model development and validation

The variables included in the prediction model included features from the baseline clinical evaluation and baseline chest x-ray findings that were recommended by the panel of experts to advise on algorithm development. The model fit with odds ratios and 95% confidence intervals (CI) are displayed in **Table 2**. The panel also recommended building a model including only features from the baseline clinical evaluation (without chest x-ray findings). We present the model fit with odds ratios and 95% CI of this model in supplemental Appendix N.

The summary estimate of the c-statistic for the prediction model including chest x-ray features was 0.71 [95% CI: 0.66-0.76]; the c-statistic in each of the holdout studies is included in **Figure 3a**. The summary estimate of the O:E slope for the prediction model was 0.90 [95% CI: 0.28-2.98]; the O:E in each of the holdout studies is included in **Figure 3b**.

Algorithm Development

The scaled prediction coefficient scores corresponding to classification of TB with respective sensitivities of 90%, 85%, 80%, 75%, and 70% can be found in supplemental

Appendix O. The study-level and summary performance of these scores in classifying TB can be found in supplemental Appendix P.

Table 2. Estimates of logistic regression prediction model developed from IPD. Odds ratio with 95% confidence interval and p-value estimates for each parameter included in the logistic regression prediction model. The model parameter estimates account for potential clustering at the study-level as well as uncertainty introduced by missing data. IPD – individual participant data, OR – odds ratio, CXR – chest x-ray.

		OR	2.5%ile	97.5%ile	P-value
	(Intercept)	0.147	0.075	0.285	0.000
Cough duration ≥ 2 weeks (Absence is no cough or <2 weeks)	Absent	--	--	--	--
	Present	1.185	0.913	1.537	0.856
Fever duration ≥ 2 weeks (Absence is no fever or <2 weeks)	Absent	--	--	--	--
	Present	1.568	1.178	2.087	0.245
Lethargy	Absent	--	--	--	--
	Present	1.282	1.016	1.618	0.663
Weight loss	Absent	--	--	--	--
	Present	1.251	0.970	1.615	0.746
History of known TB exposure	Absent	--	--	--	--
	Present	4.195	2.385	7.377	0.000
Hemoptysis	Absent	--	--	--	--
	Present	1.404	0.690	2.857	0.788
Night sweats	Absent	--	--	--	--
	Present	1.224	1.022	1.465	0.709
Peripheral lymphadenopathy	Absent	--	--	--	--
	Present	1.422	1.141	1.772	0.353
Temperature >38	Absent	--	--	--	--
	Present	1.004	0.776	1.299	1.000
Tachycardia	Absent	--	--	--	--
	Present	1.159	0.879	1.529	0.896
Tachypnea	Absent	--	--	--	--
	Present	0.949	0.766	1.176	0.983
Cavities on baseline CXR	Absent	--	--	--	--
	Present	1.600	0.898	2.849	0.527
Intrathoracic lymphadenopathy on baseline CXR	Absent	--	--	--	--
	Present	4.323	2.727	6.854	0.000
Opacities on baseline CXR	Absent	--	--	--	--
	Present	1.540	1.022	2.320	0.452
Miliary infiltrate on baseline CXR	Absent	--	--	--	--
	Present	3.558	1.761	7.191	0.000
Pleural effusion on baseline CXR	Absent	--	--	--	--
	Present	1.899	1.217	2.964	0.128

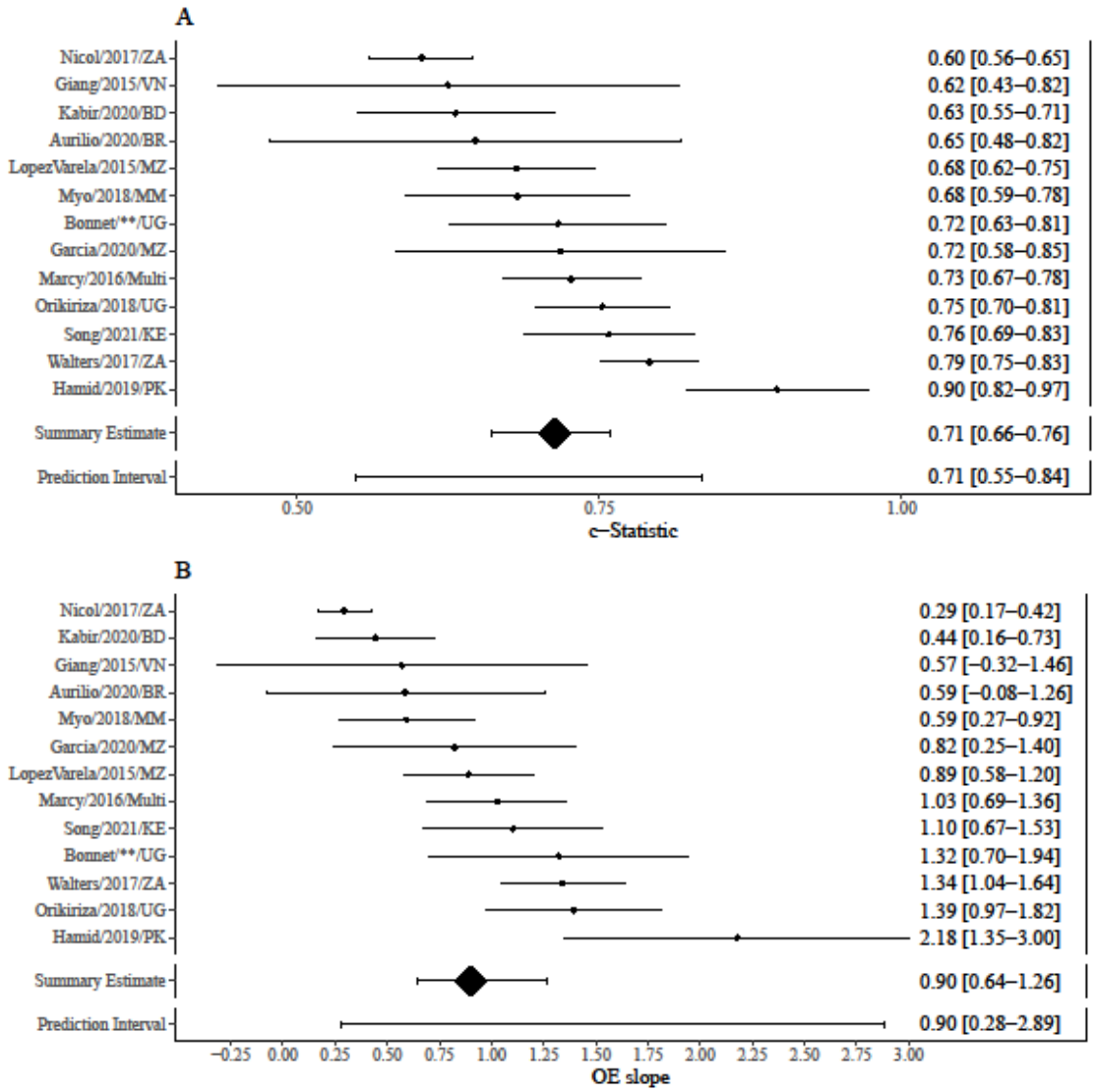

Figure 3. Calibration and discrimination of prediction model to classify TB. Study-level and pooled estimates of the (a) discrimination (c-statistic) and (b) calibration (O:E slope) of the prediction model developed from the IPD in classifying TB using an internal-external cross-validation framework (reference standard: bacteriologically-confirmed pulmonary TB and unconfirmed pulmonary TB). c-Statistic – concordance statistic, O:E – observed: expected slope, IPD – individual participant data, TB – tuberculosis, BD – Bangladesh, BR – Brazil, KE – Kenya, MM – Myanmar, Multi – Multi-country study (includes Burkina Faso, Cameroon, Vietnam, and Cambodia), MZ – Mozambique, PK – Pakistan, UG – Uganda, VN – Vietnam, ZA – South Africa.

Given that the prediction models were developed on IPD largely sourced from tertiary and referral healthcare settings and that the models are intended to be used in primary and peripheral healthcare settings, the panel recommended additional selection steps prior to using the prediction model. Specifically, it was recommended to stratify

children by risk of mortality and progression of TB disease. Higher-risk children, defined as children <2 years old, severely acutely malnourished, and/or living with HIV, would enter the prediction model at the time of initial evaluation; the remaining lower-risk children would be followed-up in 1-2 weeks, and only those with persistent/worsening symptoms at follow-up would enter the prediction model. This stratification was intended to enrich the probability of TB among the population of children proceeding through the algorithm to the model such that the probability would more closely reflect the preselected population producing the data from which the prediction model was built while balancing the consequences of untreated TB among high-risk children.

To balance the consequences of untreated TB versus the consequences of overtreatment, the panel recommended selecting a sensitivity threshold of 85% in classifying TB (all TB vs. unlikely TB), resulting in the development of a score with a sensitivity of 0.85 [95% credible interval (CrI): 0.78-0.91] and a specificity of 0.37 [95% CrI: 0.22-0.55] (**Figure 4**). A sensitivity analysis of the performance of this score in classifying confirmed TB vs. unlikely TB (excluding unconfirmed TB from this analysis) demonstrated a sensitivity of 0.88 [95% CrI: 0.81-0.92] and specificity of 0.38 [95% CrI: 0.23-0.55] (supplemental Appendix Q).

Under the same sensitivity threshold of 85%, the score developed from the model that including only features from the baseline clinical evaluation (without chest x-ray findings) had a sensitivity of 0.84 [95% CrI: 0.76-0.89] and specificity of 0.30 [95% CrI: 0.20-0.44] in classifying all TB vs. unlikely TB, and sensitivity of 0.86 [95% CrI: 0.78-0.91] and specificity of 0.30 [95% CrI: 0.20-0.44] in classifying confirmed TB vs. unlikely TB (excluding unconfirmed TB from this analysis; see supplemental Appendix R).

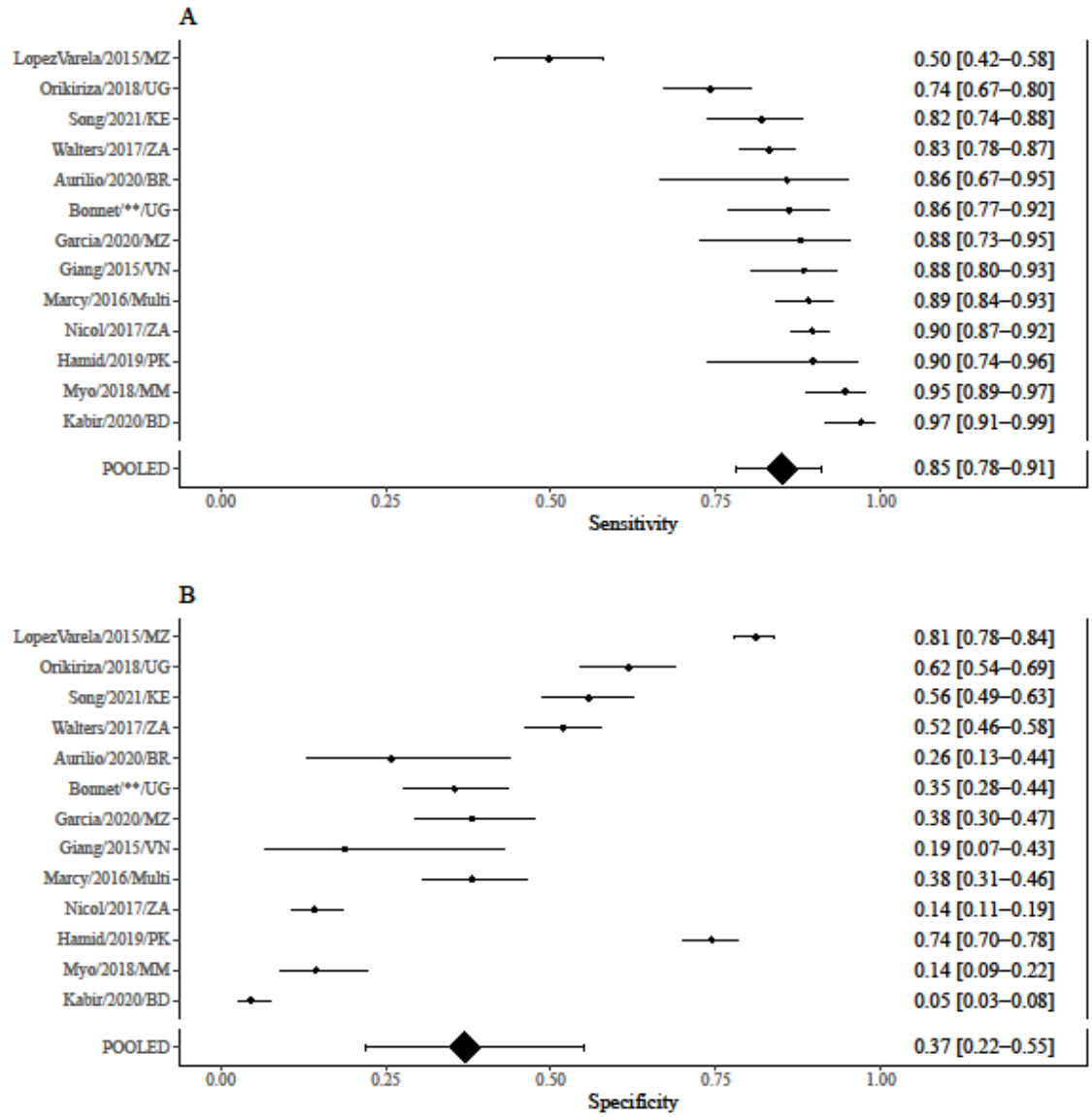

Figure 4. Performance of scaled scores from prediction model to classify TB with 85% sensitivity. Study-level and pooled estimates of the (a) sensitivity and (b) specificity of classifying TB (reference standard: bacteriologically-confirmed pulmonary TB and unconfirmed pulmonary TB) of the scores derived from the prediction model developed from the IPD to classify TB with 85% sensitivity. TB – tuberculosis, IPD – individual participant data, BD – Bangladesh, BR – Brazil, KE – Kenya, MM – Myanmar, Multi – Multi-country study (includes Burkina Faso, Cameroon, Vietnam, and Cambodia), MZ – Mozambique, PK – Pakistan, UG – Uganda, VN – Vietnam, ZA – South Africa.

These recommendations resulted in the development of the treatment-decision algorithm presented in **Figure 5**, in which children <10 years with presumptive pulmonary TB would be triaged by risk of mortality prior to entering the prediction model.

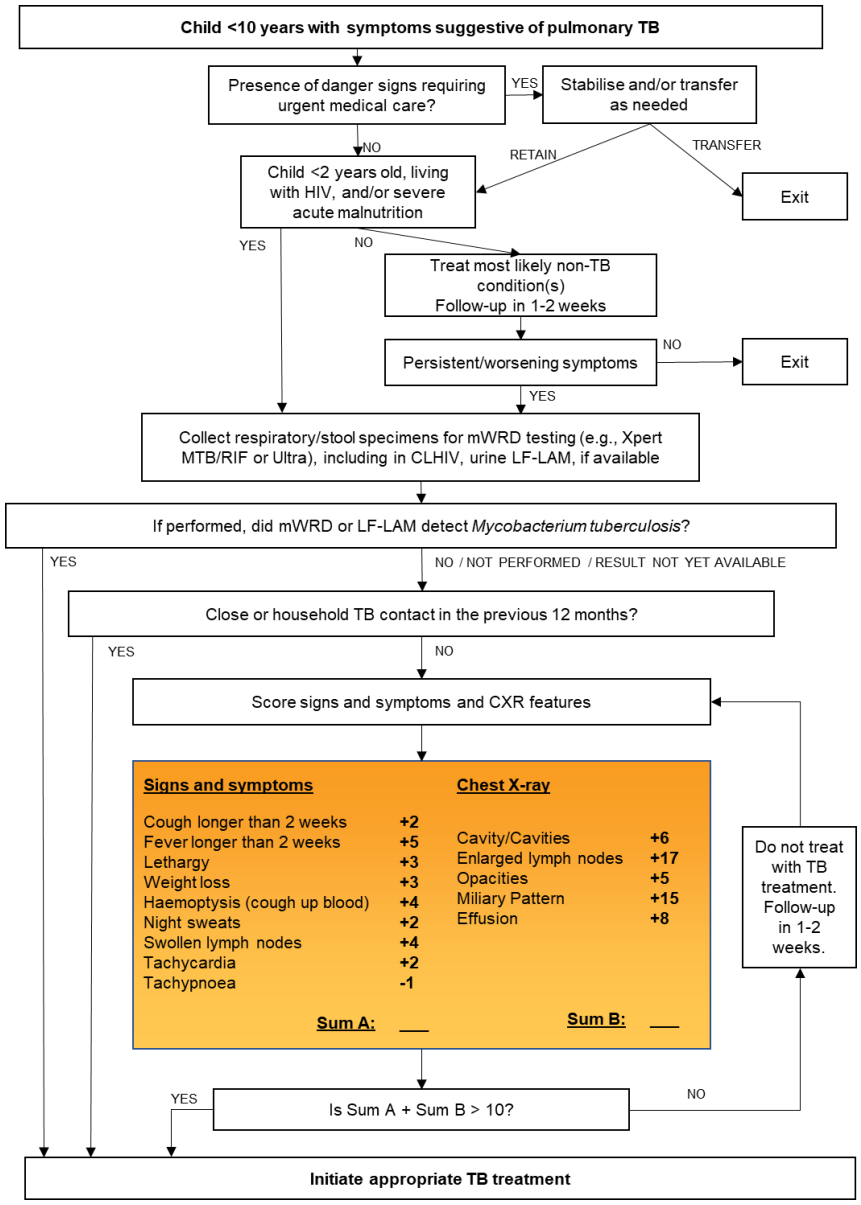

Figure 5. Treatment-decision algorithm derived from prediction model. Tuberculosis treatment-decision algorithm for use among children less than 10 years of age with symptoms suggestive of pulmonary tuberculosis, reproduced from the operational handbook accompanying the 2022 consolidated guidelines on the management of TB in children and adolescents.[18] Selection steps prior to entering scoring system reflect recommendations from the WHO expert panel to enrich the probability of TB among the population of children proceeding through the algorithm **to** the model such that the probability would more closely reflect the preselected population producing the data from which the prediction model was built while balancing the consequences of untreated TB among high-risk children. Scores associated with features from clinical history and physical exam and chest X-ray translate to risk of TB and are scaled from the prediction model developed from the IPD. WHO – World Health Organization, TB – tuberculosis, IPD – individual participant data, HIV – human immunodeficiency virus, mWRD – molecular WHO-recommended rapid diagnostic test, CLHIV – children living with HIV, LF-LAM – lateral flow urine lipoarabinomannan assay, CXR – chest X-ray.

The clinical and chest x-ray features included in the model were given a score corresponding to risk of TB such that a total score of >10 would result in classification of TB with a sensitivity of 85%. The same parameters were used to construct the treatment-decision algorithm from the model without chest x-ray features (supplemental Appendix S), for use in settings in which chest x-ray is not available.

DISCUSSION

This work describes the assembly of a large IPD cohort of children with presumptive pulmonary TB from geographically diverse, high-TB burden settings to evaluate existing algorithms and to develop a novel, prediction model for children being evaluated for pulmonary TB. We incorporated this prediction model into an algorithm to assist the evaluation of children with presumptive pulmonary TB for the 2022 WHO consolidated guidelines on the management of tuberculosis in children and adolescents. This model-based, algorithm-building approach represents an important advance to support uniform and rapid treatment decision-making for children being evaluated for pulmonary TB in high TB-burden settings.

Modeling diagnostic IPD from children with presumptive pulmonary TB provides quantitative evidence of which features from the clinical exam are sufficient to make sensitive TB-treatment decisions. Reviews of existing diagnostic algorithms reveal that many existing algorithms have been produced by expert opinion/consensus or from data sourced from small cohorts of children being investigated for pulmonary TB.[11,12] Few have been subject to any form of validation. Our modeling approach allows for validation and interrogation of model performance in various settings and selection of a sensitivity threshold to meet global TB treatment priorities. Notably, our approach is able to provide clear guidance as to which features from the clinical evaluation, if present, justify

treatment for TB, including suggesting when there is sufficient evidence to treat in the absence of chest x-ray.

Our development of two models, both with the same features from the clinical evaluation but one without features from baseline chest x-ray, is intended to acknowledge the reality that chest x-ray is not uniformly available in all settings. As demonstrated by the higher specificity (at a fixed sensitivity target) of the model that includes chest x-ray features as compared to the model without chest x-ray features, additional resources for testing/imaging would improve the specificity of treatment decisions. We did not include results from baseline Xpert MTB/RIF completed on respiratory specimens in our models to be consistent with the WHO recommendation to perform recommended rapid molecular testing on respiratory specimens in child presumptive TB cases whenever possible.

While it is true that inclusion of chest x-ray features still does not sufficiently raise the specificity of the algorithms to meet the targets in the WHO Target Product Profile for a triage test for TB, this provides pragmatic guidance driven by data to reduce the burden of childhood mortality associated with untreated TB.[44] Studies have yet to demonstrate evidence that any test for childhood pulmonary TB meets the performance targets outlined in the Target Product Profile. In the absence of such a test, a panel of experts convened by WHO identified that prioritizing the sensitivity of treatment decisions, at the expense of reduced specificity, is necessary to mitigate the public health crisis of untreated childhood TB. Antituberculosis treatment is relatively safe in children and poses a low concern for selection of drug resistance,[45] and many children may now be treated with a shorter fourth-month treatment regimen.[46] However, overtreatment of TB is not without consequence.[47] Decision-analytic modeling of the

relative weight of false positive and false negative classification of TB may provide insight to select an appropriate sensitivity threshold.

Our cross-validation analyses found study-level heterogeneity in discrimination and calibration. Though this IPD is the largest of its size compiled to date, there were not enough studies to investigate the features that drive this heterogeneity, which may include local prevalence of TB, heterogeneous population demographics, heterogeneities in variable and outcome definitions, and uncertainty introduced by the imputation. Given that the existing algorithms demonstrated similar heterogeneities in performance as compared to the one we developed, we suggest that this data-driven approach is superior as it offers the flexibility to further interrogate the sources of heterogeneity as additional data is accumulated into the IPD to inform model development.

Inclusion of children with unconfirmed pulmonary TB along with those that have bacteriologically-confirmed pulmonary TB as the definition of TB in the primary analyses is important, given the high burden of unconfirmed childhood TB presenting to healthcare. The underlying pathology associated with individuals in the unconfirmed TB group is unclear; it may represent either an early stage in TB disease, an alternative disease process or (most likely) a heterogenous group in which some children have TB and some have other causes for their symptoms.[48,49] Irrespective, current guidelines recommend treating children with unconfirmed TB. From an analytic perspective, exclusion of children without bacteriological confirmation may introduce bias, artificially inflating the estimates of the strength of the relationship for those features used by study clinicians to determine whether a child had pulmonary TB in the absence of bacteriological confirmation. A sensitivity analyses that restricted the definition of

pulmonary TB to bacteriologically-confirmed TB demonstrated generally improved sensitivity.

While there are many strengths to this data-driven algorithm-development approach, there are limitations due to missingness in the data and the absence of data from primary and peripheral health centers. The pre-test probability of TB (i.e., the prevalence) is likely substantially lower at peripheral settings and the disease presentation may be different as compared to tertiary and referral settings. We believe that the risk-stratification and delayed entry of lower-risk children is a practical attempt to raise the pre-test probability given that there is no perfect solution in the absence of relevant data. Studies evaluating the implementation of other algorithms are currently underway and are expected to provide important insight into how to support healthcare workers to adopt algorithmic approaches to antituberculosis treatment-decisions into clinical practice with high fidelity.[50] Additional work to externally validate our newly generated algorithm through a prospective, randomized investigation will be critical to evaluating efficacy. Finally, we acknowledge that children face a disproportionately high burden of extrapulmonary TB (EPTB). Given the highly varied presentation of EPTB, we restricted this analysis to provide guidance for pulmonary TB only. Developing tools to identify EPTB is an important area of future research.

A distinct advantage of the modeling approach to algorithm development is the ability to revise and improve the models as additional data become available. High-quality studies of new diagnostic tools, including biomarkers and those available at the point-of-care, may improve the specificity of such algorithms while maintaining strong sensitivity targets. Additionally, diagnostic studies that also stratify children with pulmonary TB by disease severity may inform the development of algorithms that determine first whether to treat a child for TB and then second, to stratify those with non-

severe disease who may be eligible for shorter treatment will be important pragmatic guidance to healthcare workers.

Treatment decision-algorithms represent an important pragmatic tool that could, in combination with improved health system investment, reduce the morbidity/mortality of this public health crisis. This work represents a pragmatic and transparent approach using advanced analytic methods to develop an algorithm based on the best available data that can be validated and further specified as additional becomes available.

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SUPPLEMENTARY INFORMATION

Abbreviations and shorthand

AUC – area under the receiver-operator curve
BCG - Bacille Calmette-Guérin vaccine
BD – Bangladesh
BR – Brazil
CI – confidence interval
CrI – credible interval
c-Statistic – concordance statistic
CXR – chest X-ray
EPTB – extrapulmonary tuberculosis
ES – expectorated sputum
GA – gastric aspirate
ART –Antiretroviral therapy
HIV – human immunodeficiency virus
IPD – individual participant data
IS – induced sputum
KE – Kenya
LF-LAM – lateral flow urine lipoarabinomannan assay
MICE – multiple imputation by chained equations
MM – Myanmar
MoH – Ministry of Health
Mtb – Mycobacterium tuberculosis
Multi – (PAANTHER) Multi-country study (includes Burkina Faso, Cameroon, Vietnam, and Cambodia)
mWRD – molecular WHO-recommended rapid diagnostic test
MZ – Mozambique
NTLP – National TB and Leprosy Program
O:E – observed: expected slope
OR – odds ratio
PAANTHER - Pediatric Asian African Network for Tuberculosis and HIV Research
PK – Pakistan
PPD – purified protein derivative
PTB – pulmonary tuberculosis
SAM – severely acutely malnourished
TB – tuberculosis
TST – tuberculin skin test
UG – Uganda
VN – Vietnam
WFAZ – weight-for-age Z-score
WHO – World Health Organization
Xpert – Xpert MTB/RIF
Xpert Ultra – Xpert MTB/RIF Ultra
ZA – South Africa

Appendix A: Data Requested

Table S1. Data requested from studies and suggested format

FIELD	VARIABLE	DESCRIPTION	FORMAT	CODE	LABEL
studyID	Study ID	Data source cohort	int	1	Brazil
				2	Kenya
				3	Mozambique ITACA
				4	Mozambique TOSSE
				5	Myanmar
				6	PAANTHER
				7	Pakistan
				8	South Africa DTTC
				9	Uganda 1
				10	Uganda 2
				11	Vietnam
				12	Bangladesh
				13	South Africa UCT
age	Age (months)	Age (months) at enrolment	num	###	NA = unknown
sex	Sex	Participant sex	int	0	Female
				1	Male
				NA	Unknown
weight	Weight (kg)	Weight (kg) at initial evaluation	num	###	NA = unknown
height	Height (cm)	Height/length (cm) at initial evaluation	num	###	NA = unknown
bcg_evidence	BCG evidence	Evidence of BGC vaccination (BCG scar or BCG recorded in immunization record) at initial evaluation	int	0	No evidence of BCG vaccination
				1	Evidence of BCG vaccination
				NA	Unknown
HIV_status_ba_pk_no	HIV-status	Participant HIV status	int	0	HIV-negative
				1	HIV-positive
				NA	Unknown
cough_less2wk_gr2wk_gr3wk_gr4wk	Cough duration	Duration of cough at initial evaluation	int	0	No cough
				1	Cough 0-13 days
				2	Cough 14-20 days
				3	Cough 21-27 days
				4	Cough ≥28 days
				NA	Unknown
cough_greater_2wk	Cough duration	Presence of cough ≥2 weeks at initial evaluation	int	0	Cough ≥2 weeks not present
				1	Cough ≥2 weeks present
				NA	Unknown
fever_less2wk_gr2wk_gr3wk_gr4wk	Fever duration	Duration of fever at initial evaluation	int	0	No fever
				1	Fever 0-13 days
				2	Fever 14-20 days
				3	Fever 21-27 days

				4	Fever ≥28 days
				NA	Unknown
fever_greater_1wk	Fever duration	Presence of fever ≥1 week at initial evaluation	int	0	Fever ≥1 week not present
				1	Fever ≥1 week present
				NA	Unknown
lethargy_any2wk	Lethargy	Presenting history of unusual lethargy or lack of playfulness at initial evaluation	int	0	No lethargy
				1	Lethargy
				NA	Unknown
weight_loss	Weight loss	Presenting history of poor growth over the preceding 3 months AND not responding to nutritional rehabilitation (or antiretroviral therapy if HIV infected)	int	0	No weight loss
				1	Weight loss
				NA	Unknown
significant_tbc	Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	int	0	No known TB exposure in previous 12 months
				1	Known TB exposure in previous 12 months
				NA	Unknown
night_sweats	Night sweats	Presenting history of night sweats at initial evaluation	int	0	No night sweats
				1	Night sweats
				NA	Unknown
hemoptysis	Hemoptysis	Presenting history of hemoptysis at initial evaluation	int	0	No hemoptysis
				1	Hemoptysis
				NA	Unknown
temp	Temperature (C)	Recorded temperature at initial evaluation	num	####	NA=unknown
heart_rate	Heart rate (per min)	Heart rate (per minute) at initial evaluation	num	###	NA=unknown
respiratory_rate	Respiratory rate (per min)	Respiratory rate (per minute) at initial evaluation	num	###	NA=unknown
peripheral_lad	Peripheral lymphadenopathy	Peripheral lymphadenopathy (at cervical, submandibular, and/or axillary nodes) at initial evaluation	int	0	No peripheral lymphadenopathy
				1	Peripheral lymphadenopathy
				NA	Unknown
first_xpertORculture_yn	First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	int	0	Xpert negative for MTB
				1	Xpert positive for MTB
				NA	Unknown/not performed

CXRcomb_TB_yn	CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	int	0	CXR not consistent with TB
				1	CXR consistent with TB
				NA	Unknown/not assessed
CXRindex_opacity	Opacities on CXR	Opacities (e.g., alveolar consolidation and/or bronchopneumonia) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	int	0	Opacities not present on CXR
				1	Opacities present on CXR
				NA	Unknown/not assessed
CXRindex_cavity	Cavities on CXR	Cavities on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	int	0	Cavities not present on CXR
				1	Cavities present on CXR
				NA	Unknown/not assessed
CXRindex_mili	Miliary infiltrate on CXR	Miliary infiltrate on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	int	0	Miliary infiltrate not present on CXR
				1	Miliary infiltrate present on CXR
				NA	Unknown/not assessed
CXRindex_nodes	Nodes on CXR	Nodes (e.g., perihilar nodes, paratracheal nodes, mediastinal nodes) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	int	0	Nodes not present on CXR
				1	Nodes present on CXR
				NA	Unknown/not assessed

CXRindex_effusion	Pleural effusion on CXR	Pleural effusion on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	int	0	Pleural effusion not present on CXR
				1	Pleural effusion present on CXR
				NA	Unknown/not assessed
TST_result	Tuberculin skin test	Tuberculin skin test positive at initial evaluation	num	0	TST negative
				1	TST positive
				NA	Unknown/not performed
TB_class	TB classification	Final classification of TB	int	0	Unlikely TB
				1	Bacteriologically-confirmed TB
				2	Unconfirmed TB
				NA	Unknown

Appendix B: Information about multiple imputation by chained equations

Imputation of missing data was carried out using the multiple imputation by chained equations (MICE) methods implemented in the *mice* package in R. MICE is a "fully conditionally specified" modeling approach that first imputes the mean for missing data in each variable then uses regression modeling to re-impute missing data in each variable by conditioning on the remaining variables, and iteratively updating imputations using the newly imputed data.

All IPD (specified in Table S1) were included in the imputation models. We included a cluster-specific random effects term in the imputation model for each variable whenever possible to allow for study-level heterogeneities in the baseline distribution for each imputed variable. For continuous variables and categorical variables, we used a two-level predictive mean matching model implemented using the "2l.pmm" function in the *miceadds* package in R; for binary variables, we used a two-level logistic model implemented using the "2l.bin" function. Few binary variables gave a singular fit warnings using two-level methods; for these variables, we reflexed to using a one-level logistic model implemented using the "logreg" function. MICE was run using the "mice" function with 20 iterations to generate 100 imputed datasets. The methods used to impute each variable are specified as follows:

> *2l.pmm*: cough_less2wk_gr2wk_gr3wk_gr4wk, fever_less2wk_gr2wk_gr3wk_gr4wk, weight, temp, heart_rate, respiratory_rate, height
>
> *2l.bin*: cough_greater_2wk, fever_greater_1wk, lethargy_any2wk, weight_loss, night_sweats, peripheral_lad, tbc_yn, bcg_evidence, HIV_status_ba_pk_no, CXRcomb_TB_yn, CXRindex_nodes, CXRindex_opacity, CXRindex_effusion, TST_result, CXRindex_cavity, first_xpertORculture_yn
>
> *logreg*: sex, hemoptysis, CXRindex_mili

Additional imputation specifications are as follows:

> *Cluster variable*: studyID
>
> *No imputation method specified (fully complete data)*: studyID, age

Successful imputation was assessed by visual assessment of convergence of the mean and standard deviation of each variable over the imputation iterations.

Appendix C: Estimation of algorithm performance accounting for multiply imputed data

For each algorithm, sensitivity and specificity estimates were computed at the study-level and pooled using a bivariate model as implemented in the “reitsma” function in the *mada* package in R. To account for the uncertainty associated with missing data, we created 100 imputed datasets as specified in supplemental Appendix C. Study-level and pooled estimates of sensitivity and specificity were computed for each of the 100 datasets. To obtain a point estimate for each study-level and pooled measure of sensitivity and specificity, we determined the median value over the 100 estimates; to obtain a 95% credible interval for each measure, we respectively determined the median value of the upper and lower bounds of each estimate provided by the “reitsma” function over the 100 estimates.

Appendix D: Develop a score from models produced on multiply imputed data

A general form of a multivariate logistic regression equation is given as follows:

$$\text{logit}(p) = \beta_0 + \beta_1 * x_1 + \beta_2 * x_2 + \cdots + \beta_n * x_n$$

Where p is the probability of tuberculosis, $x_{1\ldots n}$ refers to the predictors and $\beta_{1\ldots n}$ refers to the coefficients describing the relationship between the predictor and the logit-transformed probability. We fit the prediction model to the data, and we identified the probability corresponding to classification of tuberculosis with a given sensitivity compared to the reference standard. For example, let us specify an interest in classifying tuberculosis with a sensitivity of at least 85%. We obtained a threshold probability by subtracting the intercept from the logit-transformed probability corresponding to diagnosis with at least an 85% sensitivity. We scaled the threshold probability to 10 by multiplying by a scaling factor, and we multiplied the coefficients for each predictor by that scaling factor to obtain the score for that predictor. Thus, the score for each individual meeting entry criteria was obtained by summing the scaled coefficients for each factor present in the patient, and a total score of >10 constituted a diagnosis of tuberculosis with a sensitivity of 85% using this treatment-decision algorithm.

Given that we generated multiple imputed datasets, we had to take additional steps to determine the probability threshold and pooled coefficient estimates. We used the "metapred" function in package *metamisc* to fit a logistic regression model on each imputed dataset, resulting in 100 logistic regression models. Note that the model generated by "metapred" is a pooled model of models with the same specifications fit at the study-level. A pooled estimate of each parameter coefficient was obtained by taking the mean of each of the 100 coefficient estimates for each parameter. A pooled probability threshold was determined by taking the mean of the probability threshold corresponding to classification of tuberculosis with a given sensitivity compared to the reference standard of each model. The pooled probability threshold and pooled coefficient estimates were used to produce the scores as described above.

Appendix E: Composition of WHO expert panel to inform algorithm development

- Anna Mandalakas; Global TB Program, Baylor College of Medicine and Texas Children's Hospital, Houston, TX, USA
- Ben Marais; The Children's Hospital at Westmead Clinical School, Faculty of Medicine and Health, University of Sydney, Australia
- Farhana Amanullah; Indus Hospital & Health Network
- Moorine Sekkade; National Tuberculosis and Leprosy Program, Kampala, Uganda.
- Olivier Marcy; University of Bordeaux, Inserm, Institut de Recherche pour le Développement, Bordeaux, France
- Stephen Graham; Centre for International Child Health, University of Melbourne Department of Paediatrics and Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia and International Union Against Tuberculosis and Lung Disease (The Union), Paris, France

Appendix F: Study Information
Table S2. Study information for Kabir/2020/BD

Geographic setting	Dhaka, Bangladesh		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Dhaka Medical College and Hospital	Tertiary	Inpatient
	Sir Salimullah Medical College and Mitford Hospital	Tertiary	Inpatient
	Shaheed Suhrawardy Medical College and Hospital	Tertiary	Inpatient
	icddr,b Dhaka Hospital	Tertiary	Inpatient
Enrolment duration	22 January 2018 – 04 April 2019		
Purpose for data collection	Evaluate the performance of Xpert MTB/RIF Ultra assay on stool specimen for the diagnosis of childhood TB		
Study design	Cross-sectional study with follow-up of children diagnosed both bacteriologically and clinically at every month over phone started on antituberculosis therapy of 6 months		
Inclusion criteria	Children aged 0-15 years with symptoms suggestive of pulmonary TB based on any of the following: persistent non-remitting cough for >14 days weeks not responding to antibiotics, persistent documented fever for >14 days, document weight loss or failure to gain weight over the preceding 3 months, or fatigue/reduced playfulness/decreased activity		
Exclusion criteria	Children with serious co-morbid condition (e.g., in intensive care unit, co-morbid heart condition, etc.); physician unable to collect respiratory specimen; children started on anti-tuberculosis treatment; children suspected clinically to have intestinal TB		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	NO: local treating physicians evaluated CXR		
Standardized follow-up for all children?	NO: only children diagnosed w/ TB and initiated on anti-tuberculosis treatment were followed-up over phone to assess symptom resolution		
Reference classification of TB	Confirmed PTB – bacteriologically positive on culture/Xpert on induced sputum or stool specimens; Unconfirmed PTB – bacteriologically negative but diagnosed by managing clinical team based on symptoms, CXR, TST, and contact history; Unlikely PTB – not meeting criteria for confirmed TB or unconfirmed TB; Classifications made by study team (separate from managing clinical team) based on data from the initial evaluation		
No. screened/No. enrolled	454/447		
Ethics review	Protocol no.PR#17072, Approved from Institutional Review Board, icddr,b constitutes of two Committee Research Review Committee on RRC on 18 July 2017 and Ethical Review Committee on 28 August 2017		
References	Kabir S, Rahman SMM, Ahmed S, et al. Xpert Ultra assay on stool to diagnose pulmonary tuberculosis in children. *Clin Infect Dis* 2020.		

Table S3. Study information for Aurilio/2020/BR

Geographic setting	Rio de Janeiro, Brazil		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Instituto de Puericultura e Pediatria Martagao Gesteira	Tertiary	Inpatient/Outpatient
	Hospital Raphael de Paula Souza	Tertiary	Inpatient/Outpatient
	Hospital Universitário Antonio Pedro	Tertiary	Inpatient/Outpatient
Enrolment duration	17 April 2014 – 27 July 2020		
Purpose for data collection	Evaluate Xpert MTB/RIF as diagnostic test for PTB in children		
Study design	Prospective cohort study with baseline assessment and follow-up of all children at 60 days. Assessment of treatment outcome at 6 months or upon completion of treatment for those started on anti-TB treatment.		
Inclusion criteria	Children aged 0-19 years with symptoms of respiratory infection for ≥14 days and abnormal CR		
Exclusion criteria	Inappropriate samples for Xpert		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	YES		
Reference classification of TB	Graham 2015: Confirmed PTB, Unconfirmed PTB, Unlikely PTB; Retrospective classifications made by study team (separate from managing clinical team) at the 2-month follow-up visit		
No. screened/No. enrolled	50/50 (among those children <10 years old)		
Ethics review	Instituto de Puericultura e Pediatria Martagão Gesteira (24/02/2015, number 961.452 and 07/11/2017 number 2.369.814) and Hospital Universitário Antônio Pedro (28/07/2015 number 1.160.695)		
References	Aurilio RB, Luiz RR, Land MGP, Cardoso CAA, Kritski AL, Sant Anna CC. The clinical and molecular diagnosis of childhood and adolescent pulmonary tuberculosis in referral centers. *Rev Soc Bras Med Trop* 2020; **53**.		

Table S4. Study information for Song/2021/KE

Geographic setting	Kisumu County, Kenya		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Jaramogi Oginga Odinga Teaching and Referral Hospital	Tertiary	Inpatient/Outpatient
	*Additional patients from unspecified secondary inpatient/outpatient, and contact tracing		
Enrolment duration	October 2013 – August 2015		
Purpose for data collection	Determine the performance of a wide panel of specimen types and microbiological tests in children evaluated for TB		
Study design	Prospective cohort study with baseline assessment and follow-up of all children at 2 weeks, 2 months, and 6 months.		
Inclusion criteria	Children aged 0-5 years and >2.5 kg with either parenchymal abnormality on CXR or visible cervical lymph node mass persisting for >1 month despite antibiotics and either 1) persistent cough not resolving after treatment with antibiotics or 2) moderate or severe malnutrition		
Exclusion criteria	Currently on anti-tuberculosis treatment or isoniazid preventive therapy or history of anti-tuberculosis treatment or isoniazid preventive therapy in the 6 months prior to enrolment.		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	YES		
Reference classification of TB	Graham 2015: Confirmed PTB, Unconfirmed PTB, Unlikely PTB; Retrospective classifications made by study team (separate from managing clinical team) using information from all visits up to the 2-month follow-up		
No. screened/No. enrolled	2564/300		
Ethics review	US Centers for Disease Control and Prevention (#6334) Kenya Medical Research Institute (#2343) Jaramogi Oginga Odinga Teaching and Referral Hospital Children's Hospital Boston/Harvard Medical School (relied on the review and oversight of the Centers for Disease Control and Prevention institutional review board)		
References	Song R, Click ES, McCarthy KD, et al. Sensitive and feasible specimen collection and testing strategies for diagnosing tuberculosis in young children. *JAMA Pediatr* 2021: e206069-e.		

Table S5. Study information for LopezVarela/2015/MZ

Geographic setting	Manhiça District, Mozambique		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Manhiça District Hospital (and attached health centre)	Secondary	Inpatient/Outpatient
	*1483 patients from Manhiça District Hospital and Manhiça Health Research Centre Health and Demographic Surveillance System peripheral health centres (Palmeira, Maragra, Ilha, Josina, Taninga) and 180 contacts through contact tracing		
Enrolment duration	2011 - 2012		
Purpose for data collection	Estimate the annual minimum incidence of TB in children <3 in the Manhiça District		
Study design	Prospective cohort study with baseline assessment and follow-up of all children within 6 months of enrolment. Persistently symptomatic children had additional evaluation and testing.		
Inclusion criteria	Children aged 0-3 years with symptoms suggestive of PTB or EPTB or who are close contacts of notified TB cases. Symptoms suggestive of PTB included one or more of the following: cough ≥14 days not responding to appropriate antibiotics, fever ≥14 days after excluding malaria/pneumonia, chronic or acute malnutrition or failure to gain weight for more than 2 months, unexplained wheeze ≥14 months not responding to treatment, lower respiratory tract infection ≥14 days not responding to antibiotics after 72 hours, contact with TB case in previous 12 months)		
Exclusion criteria	Children aged >3 who reside outside the study area or with diagnosis of TB at pre-enrolment		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	NO		
Reference classification of TB	Graham 2012: Confirmed PTB, Probable PTB, Possible PTB, PTB Unlikely, MTB infection; Classification made by the managing clinical team using information from the baseline visit and all available follow-up visits		
No. screened/No. enrolled	1663/789		
Ethics review	The study protocol was approved by the Mozambican National Bioethics Committee and the Hospital Clinic of Barcelona Ethics Review Committee.		
References	López-Varela E, Augusto OJ, Gondo K, et al. Incidence of tuberculosis among young children in rural Mozambique. *Pediatr Infect Dis J* 2015; **34**(7): 686-92.		

Table S6. Study information for García/2020/MZ

Geographic setting	Manhiça District, Mozambique		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Manhiça District Hospital (and attached health centre)	Secondary	Inpatient/Outpatient
	*Manhiça Health Care Centre and Manhiça District Hospital and 9 peripheral health care centre (Maluana, Munguine, Taninga, Maragra, Malavela, Palmeiras, Chibututuine, Calanga, Chibucutzo)		
Enrolment duration	20 August 2013 – 20 August 2014		
Purpose for data collection	Improve the quality of TB surveillance indicators using newly introduced Xpert MTB/RIF		
Study design	Cross-sectional study with baseline assessment. Digital CXR only if clinician ordered. Two-week follow-up for children not initially started on TB treatment. Follow-up of all children started on TB treatment at months 2 and 6.		
Inclusion criteria	Children and adults with symptoms suggestive of PTB or EPTB or who are close contacts of notified TB cases. Symptoms suggestive of PTB include cough ≥2 weeks, night sweats, weight loss, fever, and/or hemoptysis.		
Exclusion criteria	Children diagnosed with TB prior to enrolment.		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	NO		
Reference classification of TB	Confirmed PTB – Bacteriologically positive on culture/Xpert on any respiratory specimen; Unconfirmed PTB - bacteriologically negative but diagnosed by managing clinical team based on symptoms, CXR, TST, and contact history; Unlikely PTB - not meeting criteria for confirmed TB or unconfirmed TB; Classification made by the managing clinical team using information from the initial visit and information gathered on follow-up at 2-weeks for those not started on TB treatment and after first few weeks of follow-up for those started on TB treatment		
No. screened/No. enrolled	UNKNOWN/142		
Ethics review	The study was approved by CISM local bioethics committee (CIBS) and the National Bioethics Committee (CNBS). Ref. 199/CNBS13		
References	García JI, Mambuque E, Nguenha D, et al. Mortality and risk of tuberculosis among people living with HIV in whom TB was initially ruled out. *Sci Rep* 2020; **10**(1): 15442-.		

Table S7. Study information for Myo/2018/MM

Geographic setting	Mandalay, Myanmar		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Children Hospital, Mandalay	Tertiary	Inpatient and Casualty/Emergency
Enrolment duration	01 January 2015 – 21 March 2017		
Purpose for data collection	Evaluate Xpert MTB/RIF as diagnostic test for PTB in children		
Study design	Prospective cohort study with baseline assessment and 8-week follow-up.		
Inclusion criteria	Children aged 0-12 years with cough ≥14 days and one of the following: fever >7 days, weight loss or failure to thrive, unexplained loss of appetite, or lethargy.		
Exclusion criteria	Receipt of anti-tuberculosis treatment for >72 hours before specimen collection.		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	YES		
Reference classification of TB	Graham 2015: Confirmed PTB, Unconfirmed PTB, Unlikely PTB; Retrospective classifications made by study team (separate from managing clinical team) at the 2-month follow-up visit		
No. screened/No. enrolled	259/255		
Ethics review	Research Ethics Committee, University of Medicine, Mandalay		
References	Myo K, Zaw M, Swe TL, et al. Evaluation of Xpert® MTB/RIF assay as a diagnostic test for pulmonary tuberculosis in children in Myanmar. *Int J Tuberc Lung Dis* 2018; **22**(9): 1051-5.		

Table S8. Study information for Marcy/2016/Multi

Geographic setting	Bobo Dioulasso, Burkina Faso Phnom Penh, Cambodia Siem Reap, Cambodia Yaounde, Cameroon Ho Chi Minh City, Vietnam		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Pediatric Department, Centre Hospitalier Universitaire Souro Sanou, (Bobo Dioulasso, Burkina Faso)	Tertiary	Inpatient/Outpatient
	National Pediatric Hospital (Phnom Penh, Cambodia)	Tertiary	Inpatient/Outpatient
	Angkor Hospital for Children (Siem Reap, Cambodia)	Tertiary	Inpatient/Outpatient
	Centre Hospitalier de la Caisse d'Essos (Yaounde, Cameroon)	N/A	Inpatient/Outpatient
	Centre Mère et Enfant de la Fondation Chantal Biya (Yaounde, Cameroon)	N/A	Inpatient/Outpatient
	Pediatric Department, Pham Ngoc Thach Hospital (Ho Chi Minh City, Vietnam)	Tertiary	Inpatient/Outpatient
	Infectious Diseases Department, Pediatric Hospital No. 1 (Nhi Dong 1) (Ho Chi Minh City, Vietnam)	Tertiary	Inpatient/Outpatient
	Infectious Diseases Department, Pediatric Hospital No. 2 (Nhi Dong 2) (Ho Chi Minh City, Vietnam)	Tertiary	Inpatient/Outpatient
Enrolment duration	April 2011 – December 2014		
Purpose for data collection	Evaluate Xpert MTB/RIF performed on stool for MTB and to assess response to antituberculosis treatment for children living with HIV		
Study design	Prospective cohort study with baseline assessment and follow-up of all children at months 1,2,3, and 6.		
Inclusion criteria	Children aged 0-12 years with HIV-1 infection (irrespective of HAART) and one or more of the following: cough >14 days, fever > 14 days, failure to thrive (deviation from previous growth trajectory in previous 3 months or weight-for-age Z-score <-2), failure to improve on broad spectrum antibiotics for pulmonary infection, or CXR suggestive of PTB		
Exclusion criteria	History of any anti-tuberculosis treatment in the 2 years prior to enrolment.		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	YES		
Reference classification of TB	Graham 2015: Confirmed PTB, Unconfirmed PTB, Unlikely PTB; Retrospective classifications made by an algorithm following the Graham 2015 classification using information from all visits up to the 6-month follow-up visit		
No. screened/No. enrolled	XXX/438		
Ethics review	Ethics Committee for Research in Health (Burkina Faso); National Ethics Comity for Health and Research (Phnom Penh, Cambodia); National Ethics Committee (Cameroon); Division of Health Operations Research Ministry of Public Health (Cameroon); Pham Ngoc Thach Hospital Institutional Review Board (Vietnam); Ho Chi Minh City Department of Health (Vietnam); Ho Chi Minh City People's Committee (Vietnam).		
References	Marcy O, Ung V, Goyet S, et al. Performance of Xpert MTB/RIF and alternative specimen collection methods for the diagnosis of tuberculosis in HIV-infected children. *Clin Infect Dis* 2016; **62**(9): 1161-8.		

Table S9. Study information for Hamid/2019/PK

Geographic setting	Karachi, Pakistan		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Indus Hospital Ghauri Clinic	Tertiary/Referral	Outpatient
	* Participants were referred from contact tracing program as well as from other general physicians in the community, and family physicians/pediatricians/ surgeons of the hospital.		
Enrolment duration	01 January 2019 – 06 April 2020		
Purpose for data collection	Identify gaps in childhood TB care delivery and improve Pediatric TB Program implementation		
Study design	Cross-sectional study with baseline assessment and 1-month follow-up		
Inclusion criteria	Children aged 0-10 years with any of the following: 2 symptoms of TB (cough ≥14 days, fever, weight loss, lethargy, loss of appetite, night sweats), a TB known TB exposure within the past 2 years with ≥1 symptom suggestive of TB, swollen lymph node for >14 days, previous history of TB and ≥1 symptom suggestive of TB		
Exclusion criteria	N/A		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	YES		
Reference classification of TB	Confirmed PTB – bacteriologically positive on culture/Xpert/ on any respiratory specimen (including stool); Unconfirmed PTB – bacteriologically negative but diagnosed by managing clinical team based on symptoms, CXR, TST, and contact history; Unlikely PTB – not meeting criteria for confirmed TB or unconfirmed TB; Retrospective classification made at the 1-month follow-up visit		
No. screened/No. enrolled	XXX/447		
Ethics review	N/A		
References	Hamid M, Brooks MB, Madhani F, et al. Risk factors for unsuccessful tuberculosis treatment outcomes in children. *PLoS One* 2019; **14**(9): e0222776.		

Table S10. Study information for Nicol/2017/ZA

Geographic setting	Cape Town, South Africa Port Elizabeth, South Africa		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Red Cross War Memorial Children's Hospital	Tertiary/Referral	Inpatient/Outpatient and Emergency/Casualty
	Dora Nginza Provincial Hospital	Tertiary/Referral	Inpatient/Outpatient and Emergency/Casualty
Enrolment duration	01 February 2010 – 31 January 2017		
Purpose for data collection	Novel tuberculosis diagnostics in HIV-infected and HIV-uninfected children.		
Study design	Prospective cohort study with baseline assessment and follow-up of all children at months 1, 2, and 6.		
Inclusion criteria	Children aged 0-15 years with clinical suspicion of PTB based on cough and one of (household TB contact within preceding 3 months, weight loss of failure to gain weight for preceding 3 months, positive TST, or chest radiograph suggestive of PTB) or clinical suspicion of EPTB		
Exclusion criteria	Children who had received treatment for tuberculosis or TB prophylaxis for >72 hours prior to enrolment; patients living outside the catchment area; patients for whom adequate clinical samples could not be obtained; or patients for whom informed consent or permission for HIV testing could not be obtained		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	YES		
Reference classification of TB	Graham 2015: Confirmed PTB, Unconfirmed PTB, Unlikely PTB; Retrospective classifications made by study team (separate from managing clinical team) using data from all visits up to the 3-month follow-up visit		
No. screened/No. enrolled	4548/1346		
Ethics review	University of Cape Town Human Research Ethics Committee (HREC), 2008, Ref no. 045/2008.		
References	Nicol MP, Workman L, Prins M, et al. Accuracy of Xpert MTB/RIF ultra for the diagnosis of pulmonary tuberculosis in children. Pediatr Infect Dis J 2018**; 37(10).**		

Table S11. Study information for Walters/2017/ZA

Geographic setting	Cape Town, South Africa		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Tygerberg Hospital	Tertiary/Referral	Inpatient/Outpatient
	Karl Bremer Hospital	Secondary	Inpatient/Outpatient
Enrolment duration	March 2012 – November 2017		
Purpose for data collection	Evaluate feasible strategies to improve and promote microbiological testing of children with PTB and treatment response.		
Study design	Prospective cohort study with baseline assessment and follow-up of all children at months 1, 2, and 6.		
Inclusion criteria	Children 0-12 with any of the following: cough ≥2 weeks, unexplained fever ≥1 week, poor growth/weight loss over the preceding 3 months, or cough <1 week with a known TB exposure in the previous 12 months, a positive TST, or a CXR suggestive of PTB		
Exclusion criteria	Children who had received treatment for tuberculosis for >1 day or were being evaluated for EPTB without being evaluated for PTB.		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	YES		
Reference classification of TB	Graham 2015: Confirmed PTB, Unconfirmed PTB, Unlikely PTB; Retrospective classifications made by study team (separate from managing clinical team) using information from all visits up to the 6-month follow-up visit		
No. screened/No. enrolled	XXX/620		
Ethics review	Health Research Ethics Committee of Stellenbosch University Faculty of Health Sciences No. N11/09/282		
References	Walters E, Demers AM, van der Zalm MM, et al. Stool culture for diagnosis of pulmonary tuberculosis in children. *J Clin Microbiol* 2017; **55**(12): 3355-65. Walters E, Scott L, Nabeta P, et al. Molecular detection of Mycobacterium tuberculosis from stools in young children by use of a novel centrifugation-free processing method. *J Clin Microbiol* 2018; **56**(9). Walters E, van der Zalm MM, Palmer M, et al. Xpert MTB/RIF on stool is useful for the rapid diagnosis of tuberculosis in young children with severe pulmonary disease. *Pediatr Infect Dis J* 2017; **36**(9): 837-43.		

Table S12. Study information for Orikiriza/2018/UG

Geographic setting	Mbarara, Uganda		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Mbarara Regional Referral Hospital	Tertiary/Referral	Inpatient/Outpatient (includes children referred from TB contact screening)
Enrolment duration	12 April 2012 – 14 January 2014		
Purpose for data collection	Evaluate the performance of Xpert MTB/RIF on induced sputum and to assess treatment outcome and safety of pediatric TB drug dosages.		
Study design	Prospective cohort study with baseline assessment and follow-up at 3 months for children not started on TB treatment and follow-up at 12 months for children started on TB treatment.		
Inclusion criteria	Children aged 0-14 with any of: weight loss/failure to thrive/growth faltering over preceding 3 months, non-remittent cough or wheeze >14 days, night sweats in preceding 14 days, unexplained fever for ≥7 days, chest pain within the preceding 2 weeks, unexplained fatigue/weakness/apathy/lethargy in previous 2 weeks, or abnormal CXR suggestive of TB		
Exclusion criteria	Children who had received >3 days of treatment for tuberculosis or had completed treatment within the past 6 months or with poor access to follow-up evaluation.		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	YES		
No. screened/No. enrolled	467/392		
Reference classification of TB	Graham 2012: Confirmed PTB, Probable PTB, Possible PTB, PTB Unlikely; Retrospective classification made by blinded, independent endpoint review committee at 3-month visit for children not started on TB treatment and 6-month visit for children started on TB treatment		
Ethics review	MUST Research Ethics Committee (MUST-REC), Uganda National Council for Science and Technology (UNCST), Comité de Protection des Personnes (CPP), Iles de France XI France.		
References	Orikiriza P, Nansumba M, Nyehangane D, et al. Xpert MTB/RIF diagnosis of childhood tuberculosis from sputum and stool samples in a high TB-HIV-prevalent setting. *Eur J Clin Microbiol Infect Dis* 2018; **37**(8): 1465-73.		

Table S13. Study information for Bonnet/**/UG

Geographic setting	Mbarara, Uganda		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Mbarara Regional Referral Hospital	Tertiary/Referral	Inpatient
Enrolment duration	September 2015 – March 2018		
Purpose for data collection	Evaluate the performance of Xpert MTB/RIF on stool and urine AlereLAM among children with increased risk of disseminated or severe TB.		
Study design	Prospective cohort study with baseline assessment and follow-up at weeks 1, 2, 8, and 24 for all children.		
Inclusion criteria	Children aged 0-1 year or HIV-infected or with severe malnutrition and either 1) at least two of the following: cough >2 weeks, fever >1 week, severe malnutrition, >2 lethargy >2 weeks, known exposure to TB within preceding 2 years, or 2) any sign suggestive of TB meningitis or disseminated/miliary TB		
Exclusion criteria	Children who received anti-tuberculosis treatment		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	YES		
Standardized follow-up for all children?	YES		
Reference classification of TB	Graham 2015: Confirmed PTB, Unconfirmed PTB, Unlikely PTB; Automated diagnostic algorithm for retrospective classification using information from all visits up to the 6-month follow-up visit, review by independent endpoint committee for cases not classified by the algorithm		
No. screened/No. enrolled	238/219		
Ethics review	MUST Research Ethics Committee (MUST-REC), Uganda National Council for Science and Technology (UNCST), Comité de Protection des Personnes (CPP), Iles de France XI France.		
References	N/A		

Table S14. Study information for Giang/2015/VN

Geographic setting	Ho Chi Minh City, Vietnam		
Healthcare setting	**Name**	**Healthcare level**	**Recruitment setting**
	Pham Ngoc Thach Hospital	Tertiary/Referral	Inpatient
Enrolment duration	01 April 2013 – 01 October 2013		
Purpose for data collection	Evaluate the performance of Xpert MTB/RIF for the diagnosis of TB in HIV-uninfected children.		
Study design	Prospective cohort study with baseline assessment and unspecified minimum follow-up (consistent with routine clinical practice).		
Inclusion criteria	HIV-uninfected children aged 0-15 years with 1 or more of: persistent unexplained fever, cough >2 weeks, night sweats, weight loss, failure to thrive, reduced playfulness/lethargy, and/or any of the following for infants <60 days: neonatal pneumonia, unexplained hepatomegaly, or sepsis-like illness		
Exclusion criteria	Children who received anti-tuberculosis treatment prior to specimen collection for MTB confirmation or children living with HIV.		
Standardized form to guide evaluation?	YES		
Standardized form to guide CXR evaluation?	NO		
Standardized follow-up for all children?	YES		
Reference classification of TB	Graham 2012: Confirmed PTB, Probable PTB, Possible PTB, PTB Unlikely; Retrospective classification made by the managing clinical team at 2-month visit		
No. screened/No. enrolled	154/150		
Ethics review	Pham Ngoc Thach Hospital Institutional review Board (IRB), the Oxford Tropical Ethics Committee (OxTREC) and the Health services of Ho Chi Minh City.		
References	Giang do C, Duong TN, Ha DT, et al. Prospective evaluation of GeneXpert for the diagnosis of HIV- negative pediatric TB cases. *BMC Infect Dis* 2015; **15**: 70.		

Appendix H: Modifications to IPD received

Table S15. Modifications to IPD from Kabir/2020/BD

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
HIV-status	Participant HIV status	0	HIV-negative	HIV status was not collected as a part of this study. In consultation with study authors, we assumed that all children in this study were HIV-negative.
		1	HIV-positive	
		NA	Unknown	
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	An exposure was defined as having a family member living with the child who was diagnosed with and received treatment for TB in the previous 12 months.
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert performed on induced sputum specimens.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	CXR assessment made by managing clinical team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above.
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S16. Modifications to IPD from Aurilio/2020/BR

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	An exposure was defined as a mother, household member, or someone spending ~4 hours a day with the child having documented or reported positive Xpert or TB culture [or receiving treatment for TB] in the previous 12 months).
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert: mostly GA/ES/IS, some pleural effusion, bronchalveolar lavage, and tracheal aspirate.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	All CXR assessments made by the study team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
Opacities on CXR	Opacities (e.g., alveolar consolidation and/or bronchopneumonia) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Opacities not present on CXR	Received data corresponding to presence of alveolar opacification and bronchopneumonia; if either of these were positive, then the CXR was said to demonstrate opacities.
		1	Opacities present on CXR	
		NA	Unknown/not assessed	
Nodes on CXR	Nodes (e.g., perihilar nodes, paratracheal nodes, mediastinal nodes) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Nodes not present on CXR	Received data corresponding to presence of perihilar lymphadenopathy, paratracheal lymphadenopathy, and calcified nodes; if any of these were positive, then the CXR was said to demonstrate nodes.
		1	Nodes present on CXR	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above.
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S17. Modifications to IPD from Song/2021/KE

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	Tuberculosis exposure was defined as caregiver-reported household contact with someone with TB within 24 months prior to enrollment.
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert: all GA specimens.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	CXR assessment made by the study team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above.
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S18. Modifications to IPD from LopezVarela/2015/MZ

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Weight loss	Presenting history of poor growth over the preceding 3 months AND not responding to nutritional rehabilitation (or antiretroviral therapy if HIV infected)	0	No weight loss	Used WAZ/HAZ for this definition.
		1	Weight loss	
		NA	Unknown	
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	Exposure to TB was defined as contact with someone diagnosed as or being treated for TB. No time-limit, but given that all kids were under the age of 3, this would have included any exposure during lifetime. For those children identified through active case finding, the definition was contact with a smear-positive adult with PTB registered at the district National TB Program (NTP) in the previous 24 months.
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
Peripheral lymphadenopathy	Peripheral lymphadenopathy (at cervical, submandibular, and/or axillary nodes) at initial evaluation	0	No peripheral lymphadenopathy	Received data corresponding to presence of cervical lymphadenopathy and axillary lymphadenopathy; if either of these were positive, then the child was said to have peripheral lymphadenopathy. Not all children were assessed for this feature.
		1	Peripheral lymphadenopathy	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Xpert was not performed as a part of this study. We assumed that a positive culture was equivalent to a positive Xpert result. Preferentially used the result from liquid culture or solid culture of the first GA specimen. If GA was not available, then we took the result of either liquid culture or solid culture from the first ES specimen.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	All CXR assessments made by the study team, which was the same as the managing clinical team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
Opacities on CXR	Opacities (e.g., alveolar consolidation and/or bronchopneumonia) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Opacities not present on CXR	Received data corresponding to presence of alveolar opacification; if this was positive, then the CXR was said to demonstrate opacities.
		1	Opacities present on CXR	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above. 'Probable TB' and 'possible TB' were coded as 'unconfirmed TB,' 'MTB infection' was coded as 'unlikely TB.'
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S19. Modifications to IPD from Garcia/2020/MZ

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	An exposure was defined as a mother, household member, or someone spending ~4 hours a day with the child receiving treatment for TB in the previous 12 months.
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
Peripheral lymphadenopathy	Peripheral lymphadenopathy (at cervical, submandibular, and/or axillary nodes) at initial evaluation	0	No peripheral lymphadenopathy	Received data corresponding to presence of cervical lymphadenopathy; if if this was positive, then the child was said to have peripheral lymphadenopathy.
		1	Peripheral lymphadenopathy	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert: all either ES or IS specimens.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	All CXR assessments made by the managing clinical team. CXR was only performed for children for whom the managing clinical team determined that CXR was necessary; thus, not all children had CXR performed.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
Opacities on CXR	Opacities (e.g., alveolar consolidation and/or bronchopneumonia) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Opacities not present on CXR	Received data corresponding to presence of alveolar opacification and bronchopneumonia; if either of these were positive, then the CXR was said to demonstrate opacities.
		1	Opacities present on CXR	
		NA	Unknown/not assessed	
Nodes on CXR	Nodes (e.g., perihilar nodes, paratracheal nodes, mediastinal nodes) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Nodes not present on CXR	Received data corresponding to presence of perihilar lymphadenopathy, paratracheal lymphadenopathy, and calcified nodes; if any of these were positive, then the CXR was said to demonstrate nodes.
		1	Nodes present on CXR	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above.
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S20. Modifications to IPD from Myo/2018/MM

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	Defined as a documented or reported exposure to a case of tuberculosis (household or close contact) within the preceding 12 months
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert: all GA specimens.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	CXR assessment made by the study team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above.
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S21. Modifications to IPD from Marcy/2016/Multi

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Fever duration	Presence of fever 1 week at initial evaluation	0	Fever 1 week not present	Fever duration was not provided in granular enough detail to identify those with fever for greater than or equal to one week.
		1	Fever 1 week present	
		NA	Unknown	
Lethargy	Presenting history of unusual lethargy or lack of playfulness at initial evaluation	0	No lethargy	Positive if the patient experienced lethargy in the previous 4 weeks.
		1	Lethargy	
		NA	Unknown	
Weight loss	Presenting history of poor growth over the preceding 3 months AND not responding to nutritional rehabilitation (or antiretroviral therapy if HIV infected)	0	No weight loss	Positive if the patient experienced weight loss in the previous 4 weeks.
		1	Weight loss	
		NA	Unknown	
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	Exposure defined as having a household contact with smear + TB in the previous 12 months.
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
Night sweats	Presenting history of night sweats at initial evaluation	0	No night sweats	Positive if the patient experienced night sweats in the previous 4 weeks.
		1	Night sweats	
		NA	Unknown	
Hemoptysis	Presenting history of hemoptysis at initial evaluation	0	No hemoptysis	Positive if the patient experienced hemoptysis in the previous 4 weeks.
		1	Hemoptysis	
		NA	Unknown	
Peripheral lymphadenopathy	Peripheral lymphadenopathy (at cervical, submandibular, and/or axillary nodes) at initial evaluation	0	No peripheral lymphadenopathy	Received data corresponding to presence of cervical lymphadenopathy, submandibular lymphadenopathy, and axillary lymphadenopathy; if any of these were positive, then the child was said to have peripheral lymphadenopathy.
		1	Peripheral lymphadenopathy	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert: mostly ES, with some IS and GA specimens.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	All CXR assessments made by the managing clinical team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
Opacities on CXR	Opacities (e.g., alveolar consolidation and/or bronchopneumonia) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Opacities not present on CXR	Received data corresponding to presence of alveolar opacification; if this was positive, then the CXR was said to demonstrate opacities.
		1	Opacities present on CXR	
		NA	Unknown/not assessed	
Nodes on CXR	Nodes (e.g., perihilar nodes, paratracheal nodes, mediastinal nodes) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Nodes not present on CXR	Received data corresponding to presence of perihilar lymphadenopathy and paratracheal lymphadenopathy; if either of these were positive, then the CXR was said to demonstrate nodes.
		1	Nodes present on CXR	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above.
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S22. Modifications to IPD from Hamid/2019/PK

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Age (months)	Age (months) at enrolment	###	NA = unknown	Age was reported as years old; assumed to be at midpoint of year and converted to months.
HIV-status	Participant HIV status	0	HIV-negative	HIV status was not collected as a part of this study. In consultation with study authors, we assumed that all children in this study were HIV-negative.
		1	HIV-positive	
		NA	Unknown	
Weight loss	Presenting history of poor growth over the preceding 3 months AND not responding to nutritional rehabilitation (or antiretroviral therapy if HIV infected)	0	No weight loss	Defined as subjective weight loss reported by parents/guardians.
		1	Weight loss	
		NA	Unknown	
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	An exposure was defined as a mother, household member, or someone spending ~4 hours a day with the child having documented or reported positive Xpert or TB culture (or receiving treatment for TB) in the previous 24 months.
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert: performed only on stool specimens. Not all children received Xpert testing.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	All CXR assessments made by the managing clinical team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	Eighteen children were given a diagnosis of EPTB; these children were classified as unlikely PTB given different presentation. Otherwise, see note on reference classification in study description table above.
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S23. Modifications to IPD from Nicol/2017/ZA

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	An exposure was defined as a mother, household member, or someone spending ~4 hours a day with the child having documented or reported positive Xpert or TB culture (or receiving treatment for TB) in the previous 24 months.
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert: performed only on IS specimens.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	All CXR assessments made by the study team; many were determined to be inconclusive for PTB.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
Opacities on CXR	Opacities (e.g., alveolar consolidation and/or bronchopneumonia) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Opacities not present on CXR	Received data corresponding to presence of alveolar opacification; if positive, then the CXR was said to demonstrate opacities.
		1	Opacities present on CXR	
		NA	Unknown/not assessed	
Nodes on CXR	Nodes (e.g., perihilar nodes, paratracheal nodes, mediastinal nodes) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Nodes not present on CXR	Received data corresponding to presence of perihilar lymphadenopathy and paratracheal lymphadenopathy; if either of these were positive, then the CXR was said to demonstrate nodes.
		1	Nodes present on CXR	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	Removed data from 37 individuals with EPTB as not relevant to the analysis population. Otherwise, see note on reference classification in study description table above.
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S24. Modifications to IPD from Walters/2017/ZA

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Weight loss	Presenting history of poor growth over the preceding 3 months AND not responding to nutritional rehabilitation (or antiretroviral therapy if HIV infected)	0	No weight loss	Weight loss was specifically defined as follows: Poor growth documented over the preceding 3 months (clear deviation from the child's previous growth trajectory and/or static growth or weight loss in the preceding 3 months; alternatively, weight-for-age Z-score (WFAZ) ≤2 in children with no previous weight measurements).
		1	Weight loss	
		NA	Unknown	
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	Exposure to any identified adult TB source case in the preceding 12 months, where exposure was either within the household; or involved the child's primary caregiver; or occurred for >4 hours per day during the period of exposure.
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
Peripheral lymphadenopathy	Peripheral lymphadenopathy (at cervical, submandibular, and/or axillary nodes) at initial evaluation	0	No peripheral lymphadenopathy	Received data corresponding to presence of cervical lymphadenopathy, submandibular lymphadenopathy, and axillary lymphadenopathy; if any of these were positive, then the child was said to have peripheral lymphadenopathy.
		1	Peripheral lymphadenopathy	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert performed.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	All CXR assessments made by the study team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
Opacities on CXR	Opacities (e.g., alveolar consolidation and/or bronchopneumonia) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Opacities not present on CXR	Received data corresponding to presence of alveolar opacification and bronchopneumonia; if either of these were positive, then the CXR was said to demonstrate opacities.
		1	Opacities present on CXR	
		NA	Unknown/not assessed	
Nodes on CXR	Nodes (e.g., perihilar nodes, paratracheal nodes, mediastinal nodes) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Nodes not present on CXR	Received data corresponding to presence of perihilar lymphadenopathy, paratracheal lymphadenopathy, and calcified nodes; if any of these were positive, then the CXR was said to demonstrate nodes.
		1	Nodes present on CXR	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above.
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S25. Modifications to IPD from Orikiriza/2018/UG

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Cough duration	Duration of cough at initial evaluation	0	No cough	Duration of cough was only provided a greater than or equal to 2 weeks or less than 2 weeks/no cough.
		1	Cough 0-13 days	
		2	Cough 14-20 days	
		3	Cough 21-27 days	
		4	Cough 28 days	
		NA	Unknown	
Fever duration	Duration of fever at initial evaluation	0	No fever	Duration of fever was only provided as greater than or equal to 1 week or less than 1 week/no cough.
		1	Fever 0-13 days	
		2	Fever 14-20 days	
		3	Fever 21-27 days	
		4	Fever 28 days	
		NA	Unknown	
Lethargy	Presenting history of unusual lethargy or lack of playfulness at initial evaluation	0	No lethargy	Lethargy was positive if present for greater than or equal to 2 weeks; negative if no lethargy or for less than 2 weeks.
		1	Lethargy	
		NA	Unknown	
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	For children referred from another contact study (any child who has lived in the same household with the index case continuously for at least 2 weeks within the 3-month period immediately preceding the diagnosis of smear-positive or culture-positive TB in the index case. For other children, documented as reported contact with a bacteriologically-positive case within the preceding 12 months.
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
Night sweats	Presenting history of night sweats at initial evaluation	0	No night sweats	Night sweats coded using the following scale: absent, mild, moderate, severe, or life threatening. Recoded absent = 0, and others = 1.
		1	Night sweats	
		NA	Unknown	
Peripheral lymphadenopathy	Peripheral lymphadenopathy (at cervical, submandibular, and/or axillary nodes) at initial evaluation	0	No peripheral lymphadenopathy	Location of peripheral lymphadenopathy not specified.
		1	Peripheral lymphadenopathy	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert: performed on two pooled IS specimens.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	All CXR assessments made by the managing clinical team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
Opacities on CXR	Opacities (e.g., alveolar consolidation and/or bronchopneumonia) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Opacities not present on CXR	Received data corresponding to presence of alveolar opacification and bronchopneumonia; if either of these were positive, then the CXR was said to demonstrate opacities.
		1	Opacities present on CXR	
		NA	Unknown/not assessed	
Nodes on CXR	Nodes (e.g., perihilar nodes, paratracheal nodes, mediastinal nodes) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Nodes not present on CXR	Positive if mediastinal lymphadenopathy was present.
		1	Nodes present on CXR	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above. 'Probable TB' and 'possible TB' were coded as 'unconfirmed TB.'
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S26. Modifications to IPD from Bonnet/**/UG

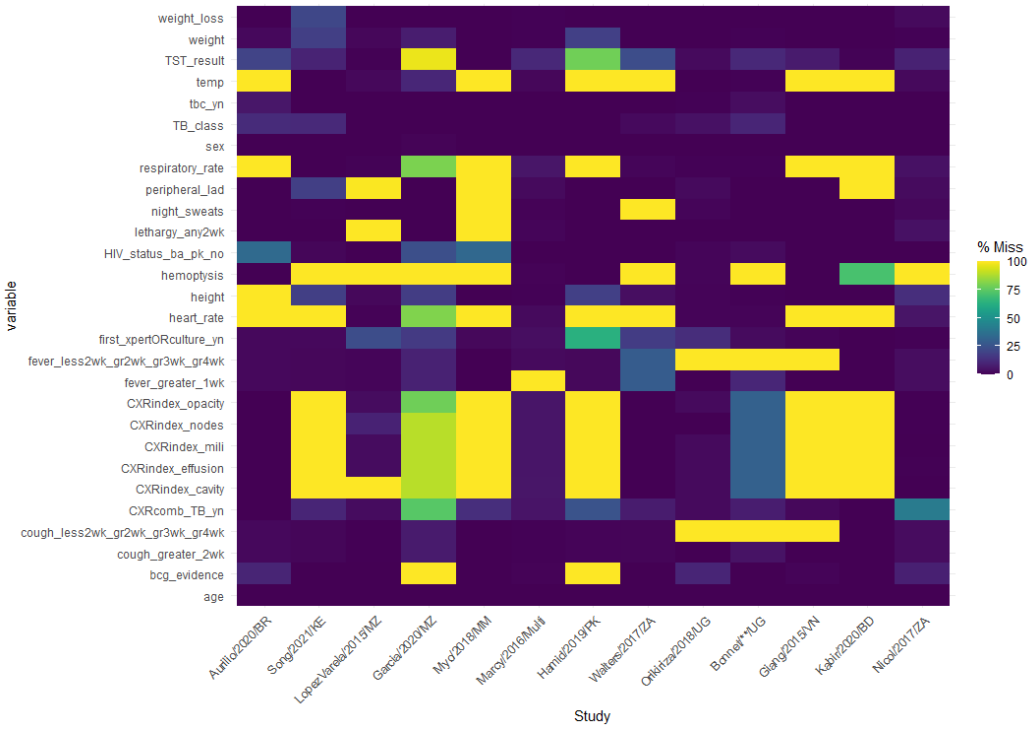
VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
BCG evidence	Evidence of BGC vaccination (BCG scar or BCG recorded in immunization record) at initial evaluation	0	No evidence of BCG vaccination	If had a BCG-scar or a positive immunization card/verbal response, then determined to have evidence of BCG vaccination.
		1	Evidence of BCG vaccination	
		NA	Unknown	
Cough duration	Duration of cough at initial evaluation	0	No cough	Duration of cough was only provided a greater than or equal to 2 weeks or less than 2 weeks/no cough.
		1	Cough 0-13 days	
		2	Cough 14-20 days	
		3	Cough 21-27 days	
		4	Cough 28 days	
		NA	Unknown	
Fever duration	Duration of fever at initial evaluation	0	No fever	Duration of fever was only provided as greater than or equal to 1 week or less than 1 week/no cough.
		1	Fever 0-13 days	
		2	Fever 14-20 days	
		3	Fever 21-27 days	
		4	Fever 28 days	
		NA	Unknown	
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	Contact of a household member with positive Xpert or TB culture in the previous 12 months
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
Peripheral lymphadenopathy	Peripheral lymphadenopathy (at cervical, submandibular, and/or axillary nodes) at initial evaluation	0	No peripheral lymphadenopathy	Significant peripheral lymphadenopathy on screening (location unspecified).
		1	Peripheral lymphadenopathy	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert: performed on GA specimens.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	All CXR assessments made by the managing clinical team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
Opacities on CXR	Opacities (e.g., alveolar consolidation and/or bronchopneumonia) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Opacities not present on CXR	Received data corresponding to presence of alveolar opacification and bronchopneumonia; if either of these were positive, then the CXR was said to demonstrate opacities.
		1	Opacities present on CXR	
		NA	Unknown/not assessed	
Nodes on CXR	Nodes (e.g., perihilar nodes, paratracheal nodes, mediastinal nodes) on CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	Nodes not present on CXR	Received data corresponding to presence of Gohn focus and hilar lymphadenopathy (grouped together) and mediastinal nodes; if either of these were positive, then the CXR was said to demonstrate nodes.
		1	Nodes present on CXR	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above.
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Table S27. Modifications to IPD from Giang/2015/VN

VARIABLE	DESCRIPTION	CODE	LABEL	MODIFICATION
Cough duration	Duration of cough at initial evaluation	0	No cough	Duration of cough was only provided a greater than or equal to 2 weeks or less than 2 weeks/no cough.
		1	Cough 0-13 days	
		2	Cough 14-20 days	
		3	Cough 21-27 days	
		4	Cough 28 days	
		NA	Unknown	
Fever duration	Duration of fever at initial evaluation	0	No fever	Duration of fever was only provided as greater than or equal to 1 week or less than 1 week/no cough.
		1	Fever 0-13 days	
		2	Fever 14-20 days	
		3	Fever 21-27 days	
		4	Fever 28 days	
		NA	Unknown	
Weight loss	Presenting history of poor growth over the preceding 3 months AND not responding to nutritional rehabilitation (or antiretroviral therapy if HIV infected)	0	No weight loss	Subjective weight loss and/or failure to thrive.
		1	Weight loss	
		NA	Unknown	
Known TB exposure	Known exposure to MTB at initial evaluation in previous 12 months	0	No known TB exposure in previous 12 months	Exposure was defined as a household or close contact with a TB case (unspecified).
		1	Known TB exposure in previous 12 months	
		NA	Unknown	
Peripheral lymphadenopathy	Peripheral lymphadenopathy (at cervical, submandibular, and/or axillary nodes) at initial evaluation	0	No peripheral lymphadenopathy	Received data corresponding to presence of cervical lymphadenopathy and submandibular lymphadenopathy; if either of these were positive, then the child was said to have peripheral lymphadenopathy.
		1	Peripheral lymphadenopathy	
		NA	Unknown	
First Xpert MTB/RIF	Result from first Xpert MTB/RIF (not Ultra) performed on ES/IS (or GA for young children) collected at initial evaluation	0	Xpert negative for Mtb	Result from first Xpert: performed on mostly GA specimens.
		1	Xpert positive for Mtb	
		NA	Unknown/not performed	
CXR consistent with TB	Result of CXR performed at initial evaluation as assessed by reader performing clinical evaluation/making TB-treatment decision or by reader to inform research classification of TB if former not available	0	CXR not consistent with TB	Unclear whether this data corresponds to result as assessed by the study team or the managing clinical team.
		1	CXR consistent with TB	
		NA	Unknown/not assessed	
TB classification	Final classification of TB	0	Unlikely TB	See note on reference classification in study description table above. 'Probable TB' and 'possible TB' were coded as 'unconfirmed TB.' One child unable to classify as 'probable TB' or 'possible TB' in original data was coded as 'unconfirmed TB' for the purposes of this analysis
		1	Bacteriologically-confirmed TB	
		2	Unconfirmed TB	
		NA	Unknown	

Appendix I: Missingness in IPD received

Figure S1. Missingness in IPD received (note variables names per Table S1)



Appendix J: Generate additional variables

After imputation, additional variables were computed from requested variables as follows:

- **Temperature >38°C**
  - Objective temperature recorded as greater than 38°C
- **Tachycardia**
  - Children <2 months old, heart rate >160
  - Children 2-12 months old, heart rate >150
  - Children 12 months – 5 years old, heart rate >140
  - Children >5 years old, heart rate >120
- **Tachypnea**
  - Children <2 months old, respiratory rate >60
  - Children 2-12 months old, respiratory rate >50
  - Children 12 months – 5 years old, respiratory rate >40
  - Children >5 years old, respiratory rate >30
- **Weight-for-age Z-score**
  - Determined from sex, age, and weight as per WHO Child Growth Standards
  - Implemented in function “addWGSR” in package *zscorer*
- **Weight-for-height Z-score**
  - Determined from sex, weight, and height as per WHO Child Growth Standards
  - Implemented in function “addWGSR” in package *zscorer*
- **Body-mass-index-for-height Z-score**
  - Determined from sex, weight, height, and age as per WHO Child Growth Standards
  - Implemented in function “addWGSR” in package *zscorer*
- **Severely acutely malnourished**
  - Children <5 years old, weight-for-height Z-score <-3
  - Children ≥5 years old, body-mass-index-for-height Z-score <-3

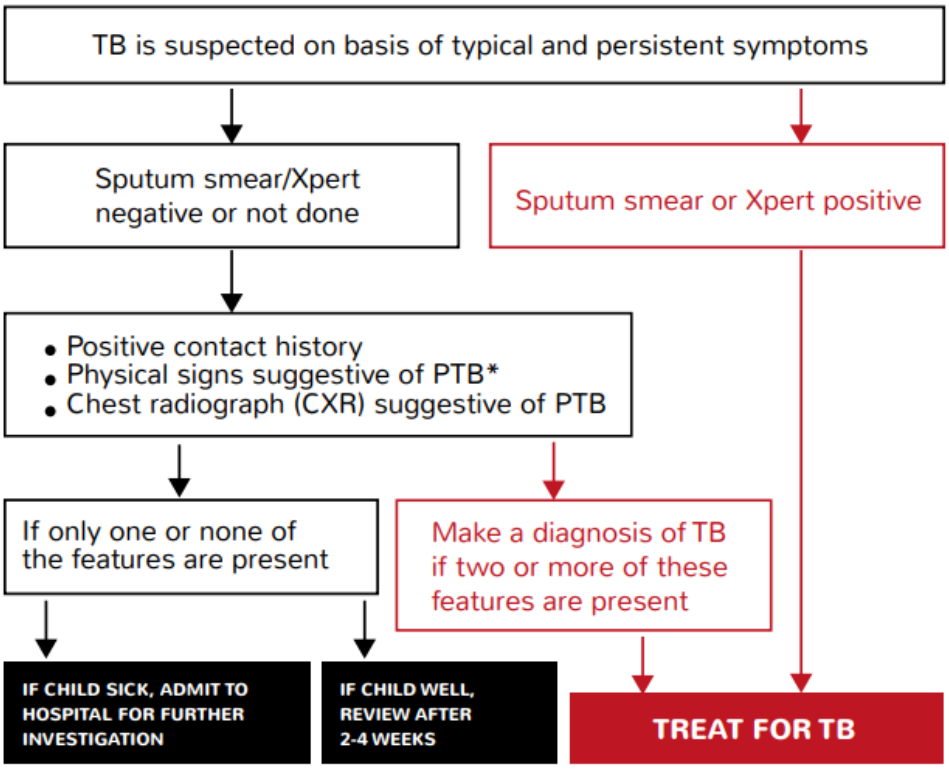
Appendix K: Existing algorithms and modifications to make maximal use of IPD

Table S28. Modifications to Marais et al. Criteria

Algorithm	Variable in data	Differences
Persistent, nonremitting cough > 2 weeks	Cough duration	Cannot specify cough characteristic (persistent and nonremitting)
Objective weight loss (documented failure to thrive) during the preceding 3 months	Weight loss	Definition of weight loss was not specific to failure to thrive
Reported fatigue	Lethargy	

Marais BJ, Gie RP, Hesseling AC, Schaaf HS, Lombard C, Enarson DA, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. Pediatrics. 2006;118(5):e1350-9.

Figure S2. The Union's Desk Guide



Graham S. The Union's desk guide for diagnosis and management of TB in children. 3 ed. Paris, France: International Union Against Tuberculosis and Lung Disease; 2016.

Table S29. Modifications to The Union's Desk Guide

Algorithm	Variables in data	Differences
Strict Symptom Criteria		
Persistent, non-remitting cough or wheeze for more than 2 weeks not responding to standard therapy	Cough duration	Cannot specify cough characteristic (persistent and nonremitting)
Documented loss of weight or failure to thrive during past 3 months especially if not responding to food and/or micronutrient supplementation, or severe malnutrition	Weight loss Weight/Height/Age	Definition of weight loss was not specific to failure to thrive Use weight/height/age to determine if severely acutely malnourished
Fatigue/reduced playfulness	Lethargy	
Persistent fever >10 days	Fever duration	Evaluated as fever >7 days
TB contact in the preceding year	Known TB exposure	Some studies defined known TB exposure as within the previous 24 months
HIV	HIV-status	
Physical signs		
Weight loss or poor weight gain, evidence of growth faltering	Weight loss	Definition of weight loss was not specific to failure to thrive
Fever	Temperature (C)	
Increased respiratory rate	Respiratory rate (per min)	
Signs of respiratory distress	N/A	N/A
Auscultation and percussion	N/A	N/A
CXR		
Enlarged hilar lymph nodes	Nodes on CXR	
Opacification in lung tissue	Opacities on CXR	
Miliary mottling	Miliary infiltrate on CXR	
Cavitation	Cavities on CXR	
Pleural or pericardial effusion	Pleural effusion on CXR	Did not evaluate pericardial effusion
Marked abnormality on CXR in child with no signs of respiratory distress (no fast breathing or chest indrawing) is supportive of TB	N/A	N/A
Sputum Xpert	First Xpert MTB/RIF	
Sputum smear	N/A	N/A

Figure S3. Stegen-Toledo Score

Finding	Score
Positive culture result	7
Tuberculous granuloma	4
Positive PPD test result[a]	3
Known contact with a person with TB during past 2 years	2
Radiographic results suggestive of TB	2
Clinical presentation suggestive of TB[b]	2

NOTE. Highly probable tuberculosis was denoted by a Stegen-Toledo score of ≥7; probable tuberculosis, by a score of 5–6; suspected tuberculosis, by a score of 3–4; and unlikely tuberculosis, by a score of 0–2. PPD, tuberculin purified protein derivative.

[a] Induration >10 mm.

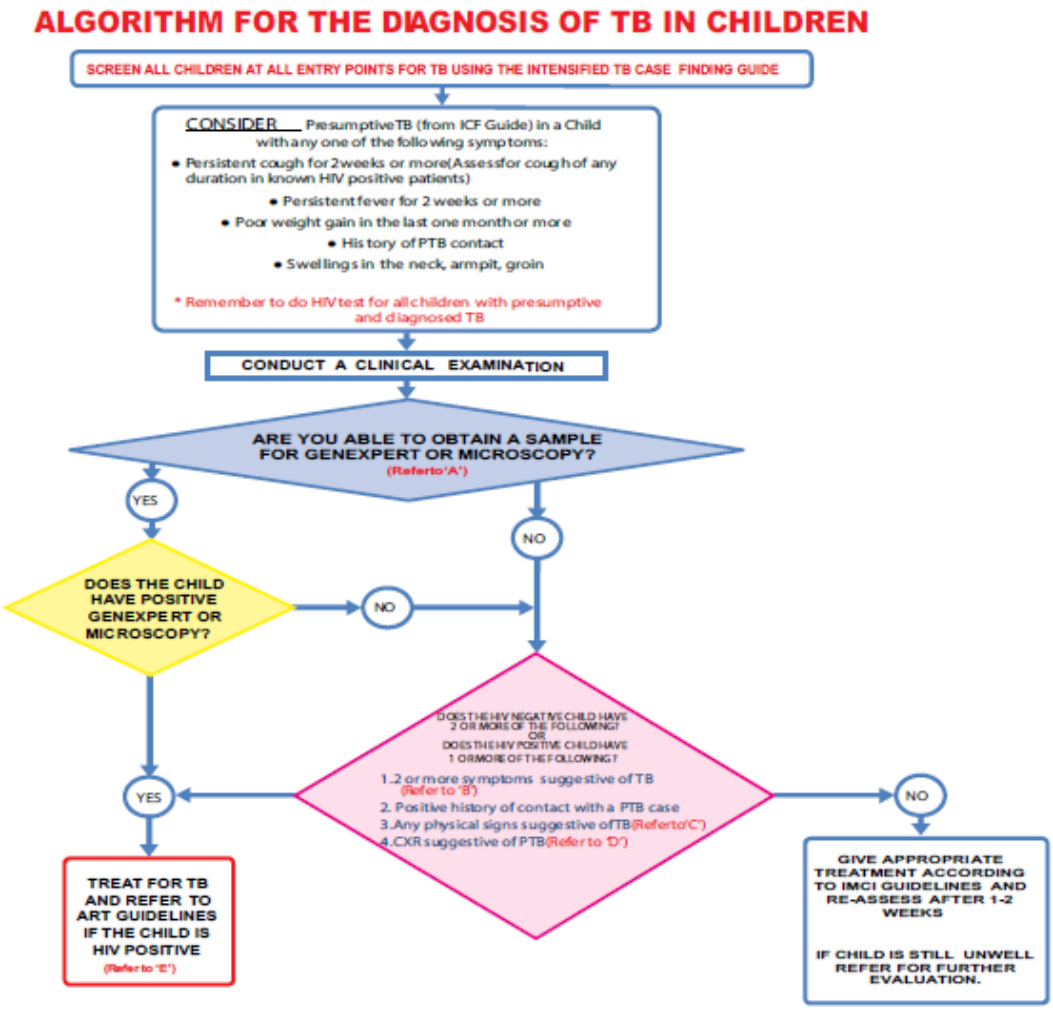
[b] Duration of cough >2 weeks.

Montenegro SH, Gilman RH, Sheen P, Cama R, Caviedes L, Hopper T, et al. Improved Detection of Mycobacterium tuberculosis in Peruvian Children by Use of a Heminested IS6110 Polymerase Chain Reaction Assay. Clin Infect Dis. 2003;36(1):16-23.

Table S30. Modifications to Stegen-Toledo Score (using cutoff of 5 points to classify TB)

Algorithm	Variables in data	Differences
Positive culture result	First Xpert MTB/RIF	Used Xpert MTB/RIF rather than culture given practical advantage of Xpert
Tuberculosis granuloma	N/A	N/A
Positive PPD test result	TST result	
Known contact with a person with TB during past 2 years	Known TB exposure	Some studies defined known TB exposure as within the previous 12 months
Radiological results suggestive of TB	CXR consistent with TB	
Clinical presentation suggestive of TB (defined as duration of cough >2 weeks)	Cough duration	

Figure S4. Uganda NTLP Algorithm



Uganda Ministry of Health, Uganda National Tuberculosis and Leprosy Control Programme. *Manual for management and control of tuberculosis and leprosy in Uganda*. Kampala, Uganda: MoH, 2017.

Table S31. Modifications to Uganda NTLP Algorithm

Algorithm	Variables in data	Differences
Xpert or microscopy	First Xpert MTB/RIF	Did not evaluate microscopy
Symptoms suggestive of TB (*≥2* of the following)		
Persistent cough ≥2 wks	Cough duration	
Persistent fever for ≥2 wks	Fever duration	
Poor weight gain in the last ≥1 month	Weight loss	
CXR findings suggestive of PTB		
Miliary picture	Miliary infiltrate on CXR	
Hilar adenopathy	Nodes on CXR	
Cavitation	Cavities on CXR	
Physical signs suggestive of TB		
Severe malnutrition	Weight/Height/Age	Use weight/height/age to determine if severely acutely malnourished
Enlarged lymph nodes around neck or arm pit	Peripheral lymphadenopathy	
Acute pneumonia not responding to complete course of appropriate antibiotics	N/A	N/A
Recurrent pneumonias	N/A	N/A
Persistent wheeze not responding to bronchodilators	N/A	N/A
Persistence of swelling on the back (Gibbus)	N/A	N/A
Signs of meningitis in child with symptoms suggestive of TB	N/A	N/A

Figure S5. Brazilian Ministry of Health Score

Diagnosis of pulmonary tuberculosis in children and adolescents with negative smear microscopy or undetected RMT 2 .

Clinical condition	**Radiological patterns**	Contact with adult with TB*	TST*	**Nutritional status**
Fever or symptoms such as cough, adynamia, expectoration, slimming, sweating > 2 weeks **15 points**	Hilar adenomegaly or miliary pattern and/or condensation or infiltrate (with or without cavitation) unchanged by ≥ 2 weeks and/or condensation or infiltrate (with or without excavation) for ≥ 2 weeks, progressing with worsening or without improvement with antibiotics for common germs **15 points**	Close contact in he last 2 years **10 points**	TST between 5 and 9 mm **5 points** TST ≥10 mm **10 points**	Serious malnutrition **5 points**
Asymptomatic or with symptoms < 2 weeks **0 points**	Condensation or infiltrate of any type for less than 2 weeks **5 points**	Occasional or negative **0 points**	TST < 5 mm **0 points**	Weight ≥ 10 th percentile **0 points**
Respiratory infection that improved after using antibiotics for common germs or without antibiotics **(– 10 points)**	Normal radiography **(–5 points)**			

RMT = rapid molecular test; TB = tuberculosis; TST = tuberculin skin test. At least 40 points (very likely diagnosis) = it is recommended to start TB treatment; 30- 35 points (possible diagnosis) = indicative of TB; it is advised to initiate treatment, at medical discretion; Less than 25 points (diagnosis is unlikely) = investigation of the child should be continued.

Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância das Doenças Transmissíveis. Manual de recomendações para o controle da tuberculose no Brasil. 2 ª ed. atual. Brasília: Ministério da Saúde; 2019.

Table S32. Modifications to Brazilian Ministry of Health Score (using cutoff of 30 points to classify TB)

Algorithm	Variables in data	Differences
Fever *≥2 wks*	Fever duration	
Cough *≥2 wks*	Cough duration	
Adynamia *≥2 wks*	Lethargy	Duration not specified in data
Expectoration *≥2 wks*	N/A	N/A
Slimming *≥2 wks*	Weight loss	Duration not specified in data
Sweating *≥2 wks*	Night sweats	Duration not specified in data
Respiratory infection that improved after using antibiotics for common germs or without antibiotics	N/A	
Hilar adenomegaly or miliary pattern and/or condensation or infiltrate (with or without cavitation) unchanged by ≥ 2 weeks and/or condensation or infiltrate (with or without excavation) for ≥ 2 weeks, progressing with worsening or without improvement with antibiotics for common germs	Nodes on CXR Miliary infiltrate on CXR Opacities on CXR Cavities on CXR	CXR abnormalities consistent with TB of unknown duration
Condensation or infiltrate of any type for less than 2 weeks	N/A	No data on duration of CXR abnormalities consistent with TB
Normal radiography	N/A	No data to indicate CXR
Close contact in the last 2 years (with adult with TB)	Known TB exposure	Some studies defined known TB exposure as within the previous 12 months
TST diameter	TST result	TST diameter not specified in data, only whether result was positive or not
Serious malnutrition (weight <10th percentile)	Weight/age	Weight and age used to compute weight-for-age z-score

Figure S6. Keith-Edwards Score

TABLE 1. Keith Edwards Score for Diagnosis of Tuberculosis in Children

Feature	Score		
	0	1	3
Duration of illness (weeks)	< 2	2-4	> 4
Nutrition (% of weight for age)	> 80	60-80	< 60
Family history of tuberculosis	None	Reported by family	Proven sputum positive

Score for Other Features if Present

Feature	Score
Unexplained fever, night sweats, no response to malaria treatment	2
Positive tuberculin test	3
Lymph nodes: large, painless, firm, soft sinus in neck/axilla	3
Malnutrition, not improving after 4 weeks	3
Central nervous system : change in temperament, fits with or without abnormal cerebrospinal fluid findings	3
Joint swelling, bone swelling, sinuses	3
Unexplained abdominal mass, ascites	3
Angle deformity of spine	4

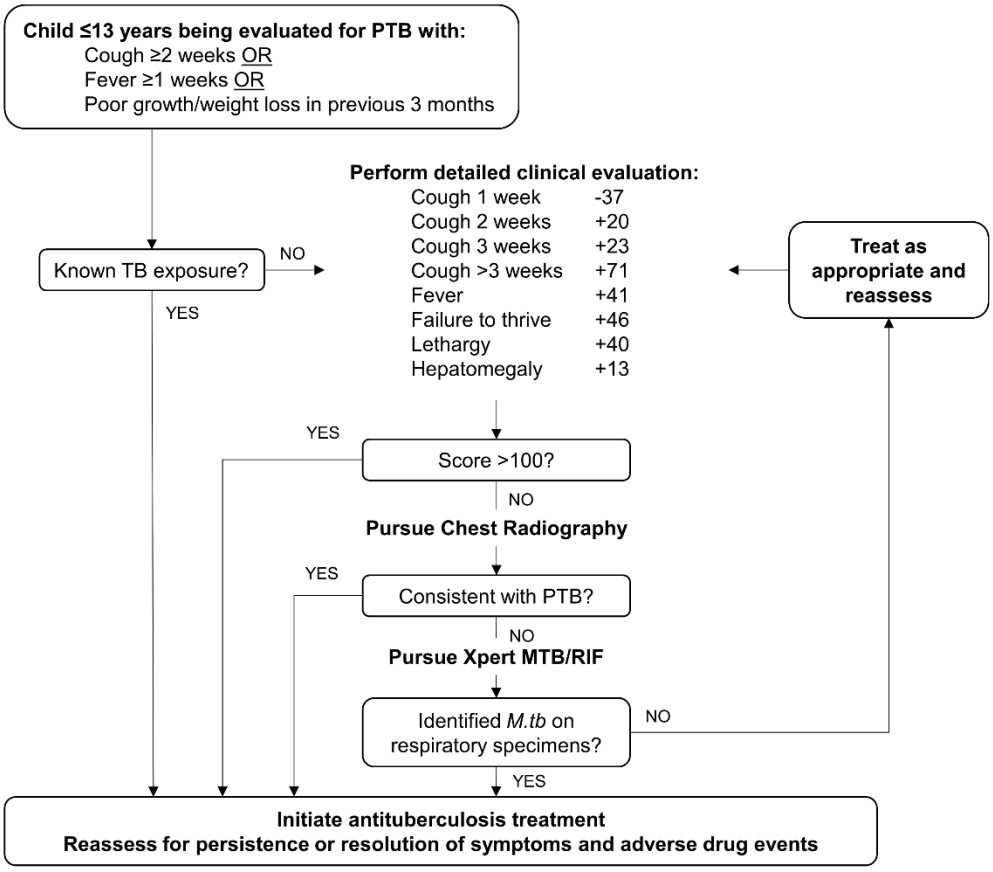
A score of 7 or more is indicative of tuberculosis

Edwards K. The diagnosis of childhood tuberculosis. P N G Med J. 1987;30(2):169-78.

Table S33. Modifications to Keith-Edwards Score

Algorithm	Variables in Data	Differences
Duration of illness	Cough duration Fever duration	Used the max of cough or fever duration to represent duration of illness
Nutrition (% of weight for age)	Weight/age	Weight and age used to compute weight-for-age z-score
Family history of tuberculosis	Known TB exposure	Data unavailable on whether TB exposure was bacteriologically-confirmed
Fever	Temperature (C)	
Night sweats	Night sweats	
No response to malaria treatment	N/A	N/A
Lymph nodes: large, painless, firm, soft sinus in neck/axilla	Peripheral lymphadenopathy	
Malnutrition, not improving after 4 weeks	Weight loss	Cannot specify whether malnutrition did not improve after 4 weeks
Central nervous system: change in temperament, fits with or without abnormal cerebrospinal fluid findings	Lethargy	Unable to evaluate fits or abnormal cerebrospinal fluid findings
Joint swelling, bone swelling, sinuses	N/A	N/A
Unexplained abdominal mass, ascites	N/A	N/A
Angle deformity of spine	N/A	N/A

Figure S7. Gunasekera et al. Algorithm

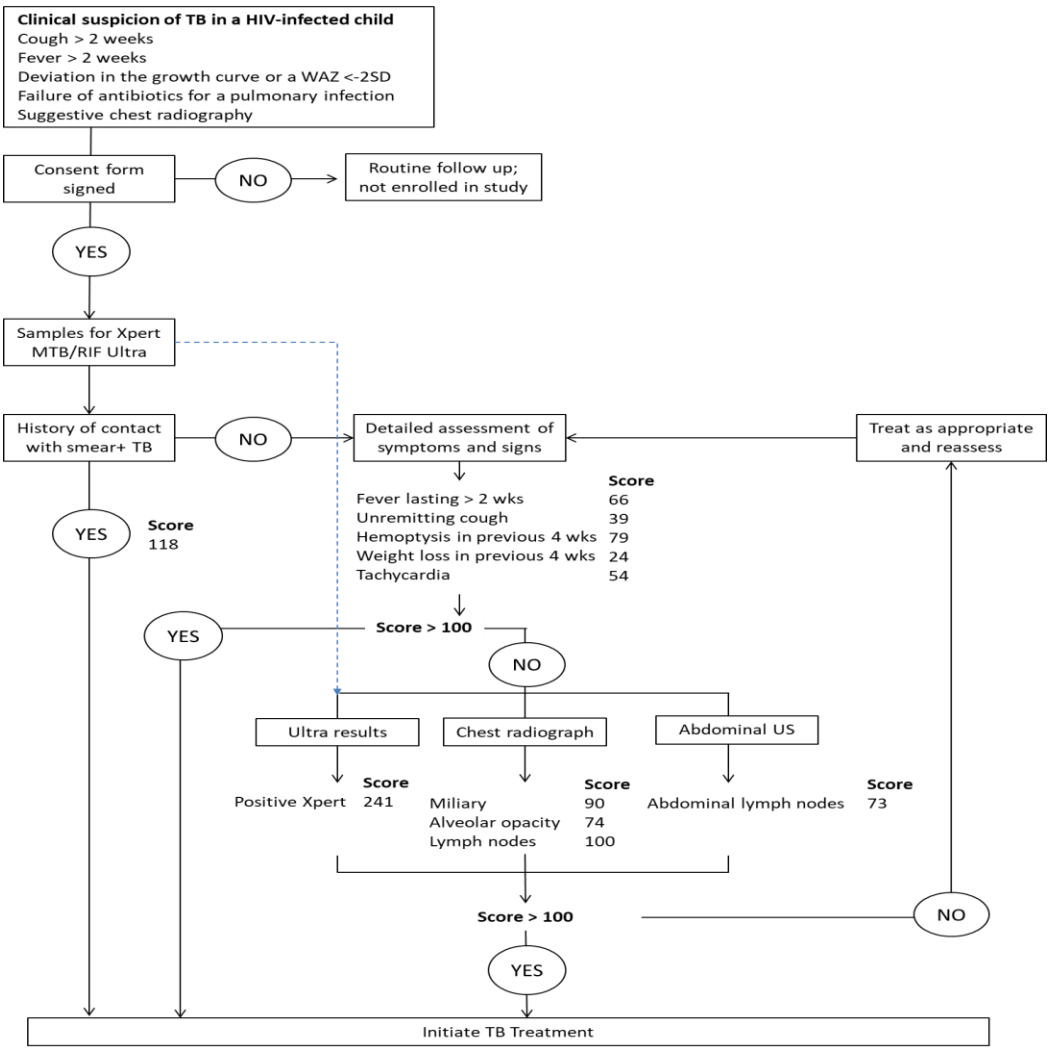


Gunasekera KS, Walters E, van der Zalm MM, Palmer M, Warren JL, Hesseling AC, et al. Development of a treatment-decision algorithm for human immunodeficiency virus–uninfected children evaluated for pulmonary tuberculosis. Clin Infect Dis. 2021.

Table S34. Modifications to Gunasekera et al. Algorithm. Given that we had access to the Walters/2017/ZA data from HIV-negative children used to develop this algorithm, we refit the logistic regression model using a complete case analysis of variables available in the IPD before any imputation; thus, this algorithm is modified from the originally stated algorithm (we do not include hepatomegaly and fever is defined as ≥1 week). This model had an AUC of 0.85. The model parameter coefficients were scaled to produce a score such that a sum of the scores resulted in classification of TB with a sensitivity of 90% -- this resulted in an algorithm with a sensitivity of 91% and a specificity of 49%.

	OR	2.50 %	97.5 %	p-value	Scaled score
(Intercept)	0.10	0.04	0.21	0.00	--
No cough	--				--
Cough < 2 weeks	0.81	0.37	1.78	0.60	-22
Cough 2 weeks	1.14	0.40	3.18	0.81	13
Cough 3 weeks	1.56	0.46	5.25	0.47	46
Cough >3 weeks	3.60	1.49	9.01	0.01	132
No fever or fever <1 week	--				--
Fever ≥1 week	2.12	0.87	5.33	0.10	78
No weight loss	--				--
Weight loss	1.98	1.06	3.76	0.03	71
No lethargy	--				--
Lethargy	1.43	0.71	2.88	0.32	37
No history of known TB contact	--				--
History of known TB contact	6.64	3.53	12.99	0.00	195
CXR not consistent with TB	--				--
CXR consistent with TB	11.02	5.39	23.90	0.00	248
Xpert negative for MTB	--				--
Xpert positive for MTB	13927274.15	0.00	Inf	0.98	1698

Figure S8. Marcy et al. Algorithm



Marcy O, Borand L, Ung V, Msellati P, Tejiokem M, Huu KT, et al. A treatment-decision score for HIV-infected children with suspected tuberculosis. Pediatrics. 2019;144(3):e20182065.

Table S35. Modifications to Marcy et al. Algorithm. Given that we had access to the Marcy/2016/Multi data from HIV-positive children used to develop this algorithm, we refit the logistic regression model using a complete case analysis of variables available in the IPD before any imputation; thus, this algorithm is modified from the originally stated algorithm (we use cough ≥2 weeks rather than remitting cough, and we do not include abdominal ultrasound results). This model had an AUC of 0.80. The model parameter coefficients were scaled to produce a score such that a sum of the scores resulted in classification of TB with a sensitivity of 90% -- this resulted in an algorithm with a sensitivity of 91% and a specificity of 40%.

	odds-ratio	2.50 %	97.50 %	p-value	scaled_coeff
(Intercept)	0.19	0.07	0.44	0.00	--
No cough or cough <2 weeks	--				--
Cough ≥2 weeks	1.11	0.52	2.37	0.78	9
No fever or fever <1 week	--				--
Fever ≥1 week	2.94	1.72	5.39	0.00	95
No weight loss	--				--
Weight loss	1.79	1.01	3.37	0.05	52
No hemoptysis	--				--
Hemoptysis	3.29	0.62	93.23	0.23	105
No tachycardia	--				--
Tachycardia	2.03	0.91	5.12	0.09	62
No history of known TB contact	--				--
History of known TB contact	1.71	0.60	5.59	0.33	47
Miliary infiltrate not present on CXR	--				--
Miliary infiltrate present on CXR	2.56	0.77	10.36	0.14	83
Opacities not present on CXR	--				--
Opacities present on CXR	2.36	1.32	4.53	0.00	76
Nodes not present on CXR	--				--
Nodes present on CXR	5.41	2.84	11.83	0.00	149
Xpert negative for MTB	--				--
Xpert positive for MTB	29.18	3.40	Inf	0.03	298

Appendix L: Performance of existing algorithms against reference classification of all TB

Figure S9. Performance of Marais et al. Criteria. Study-level and pooled estimates of the **(a)** sensitivity and **(b)** specificity of classifying TB (reference standard: bacteriologically-confirmed pulmonary TB and unconfirmed pulmonary TB).

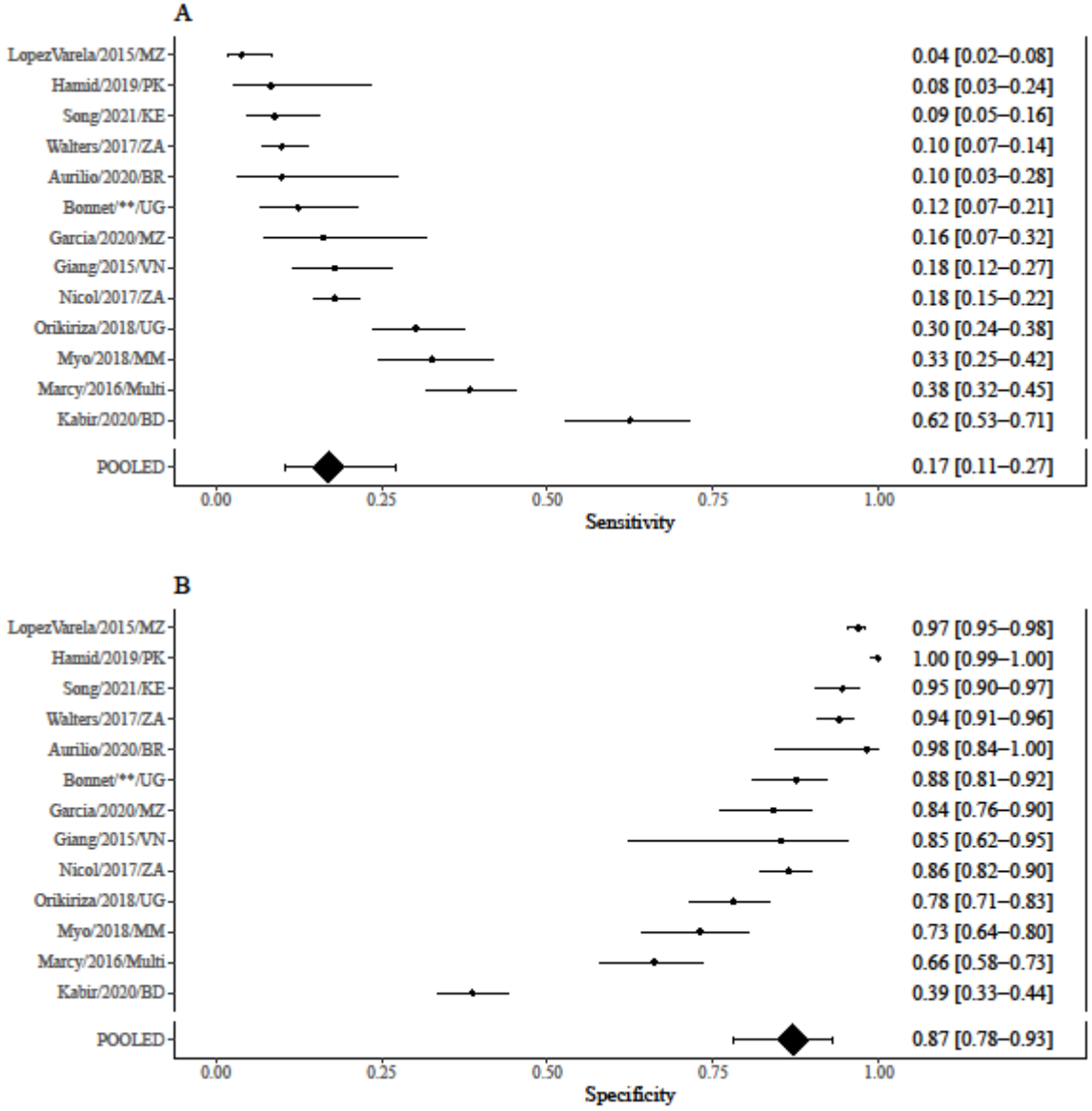


Figure S10. Performance of Stegen-Toledo Score (using cutoff of 5 points to classify TB). Study-level and pooled estimates of the (a) sensitivity and (b) specificity of classifying TB (reference standard: bacteriologically-confirmed pulmonary TB and unconfirmed pulmonary TB).

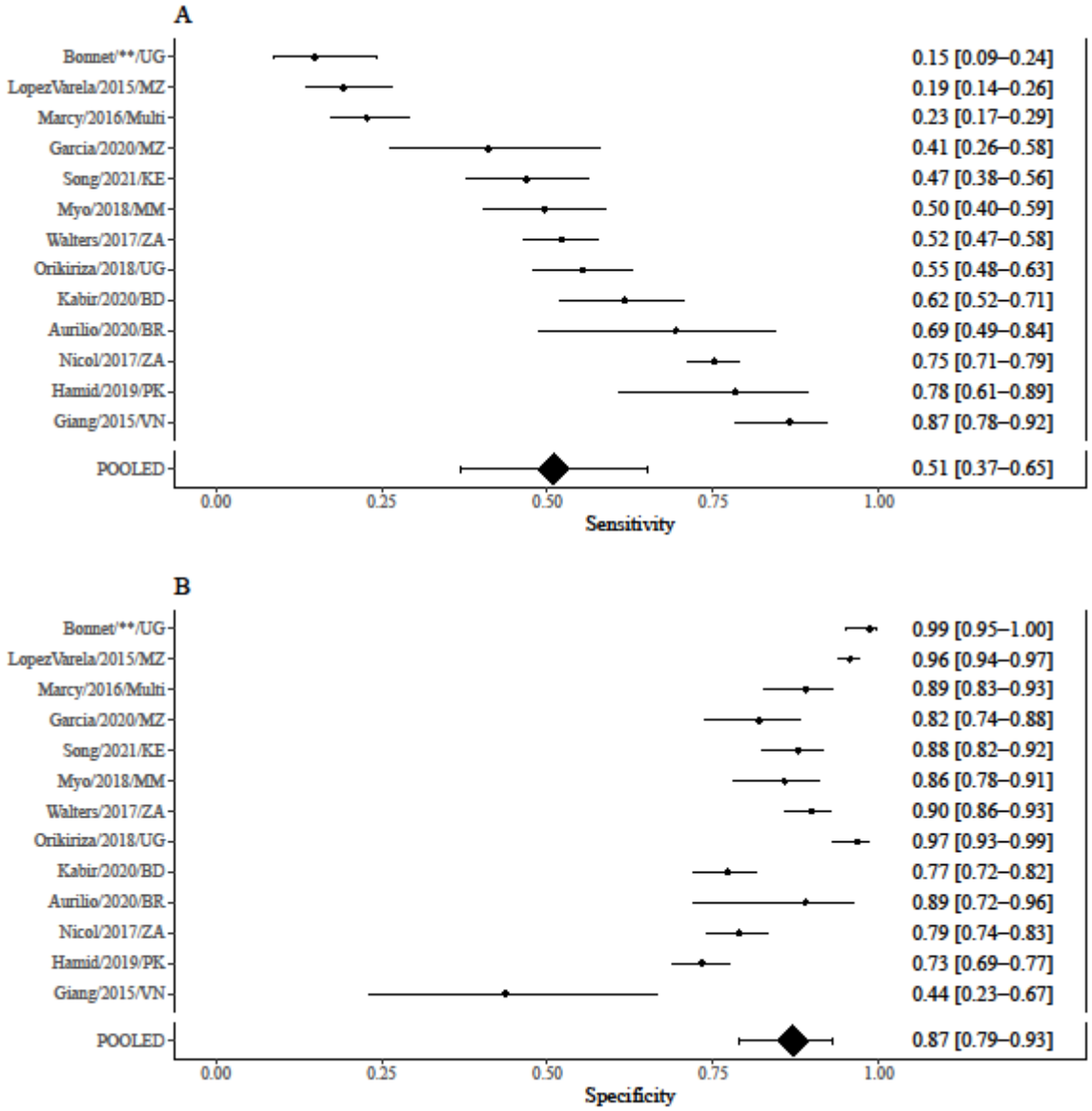


Figure S11. Performance of Uganda NTLP Algorithm. Study-level and pooled estimates of the **(a)** sensitivity and **(b)** specificity of classifying TB (reference standard: bacteriologically-confirmed pulmonary TB and unconfirmed pulmonary TB).

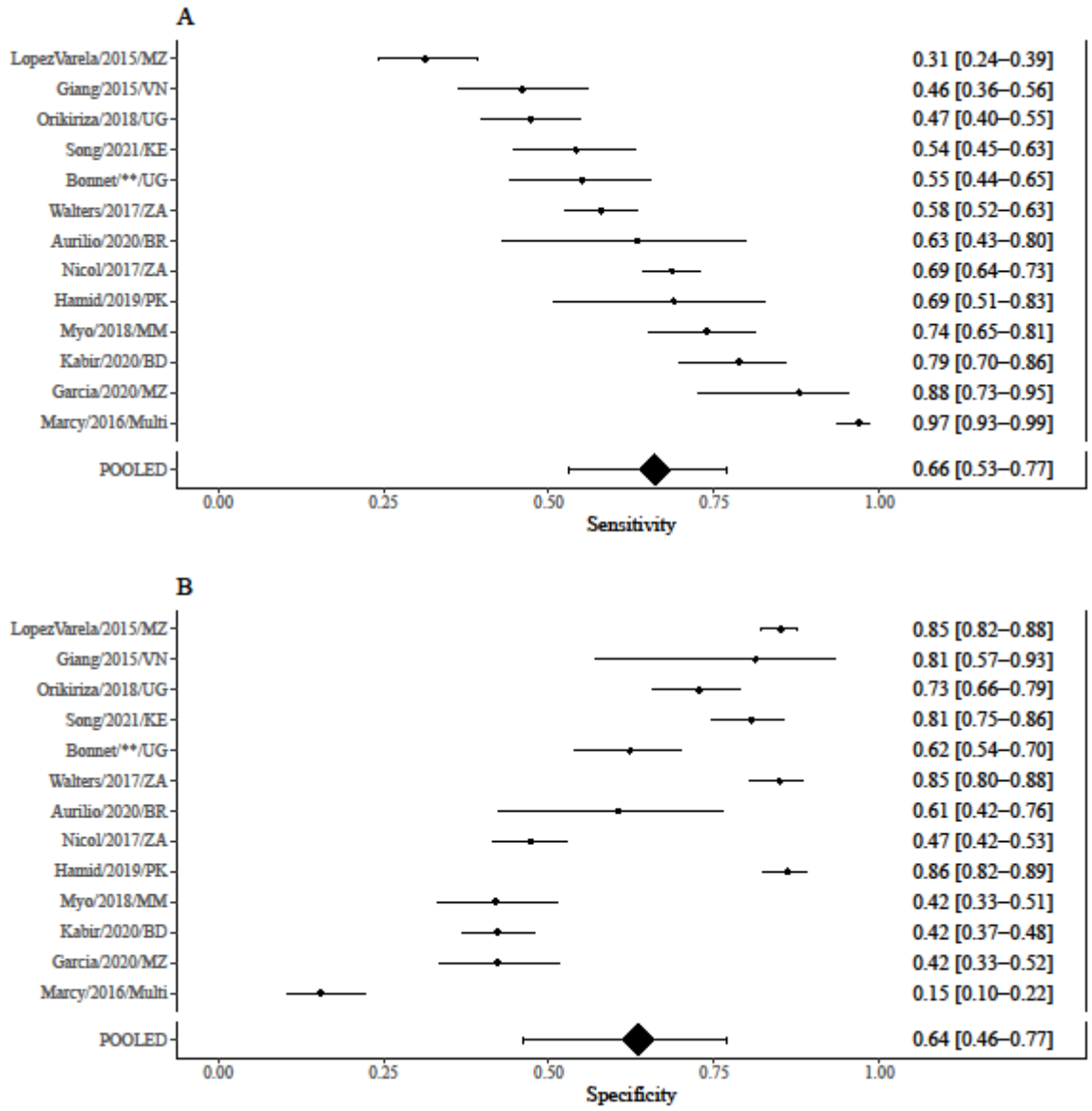


Figure S12. Performance of The Union's Desk Guide. Study-level and pooled estimates of the **(a)** sensitivity and **(b)** specificity of classifying TB (reference standard: bacteriologically-confirmed pulmonary TB and unconfirmed pulmonary TB).

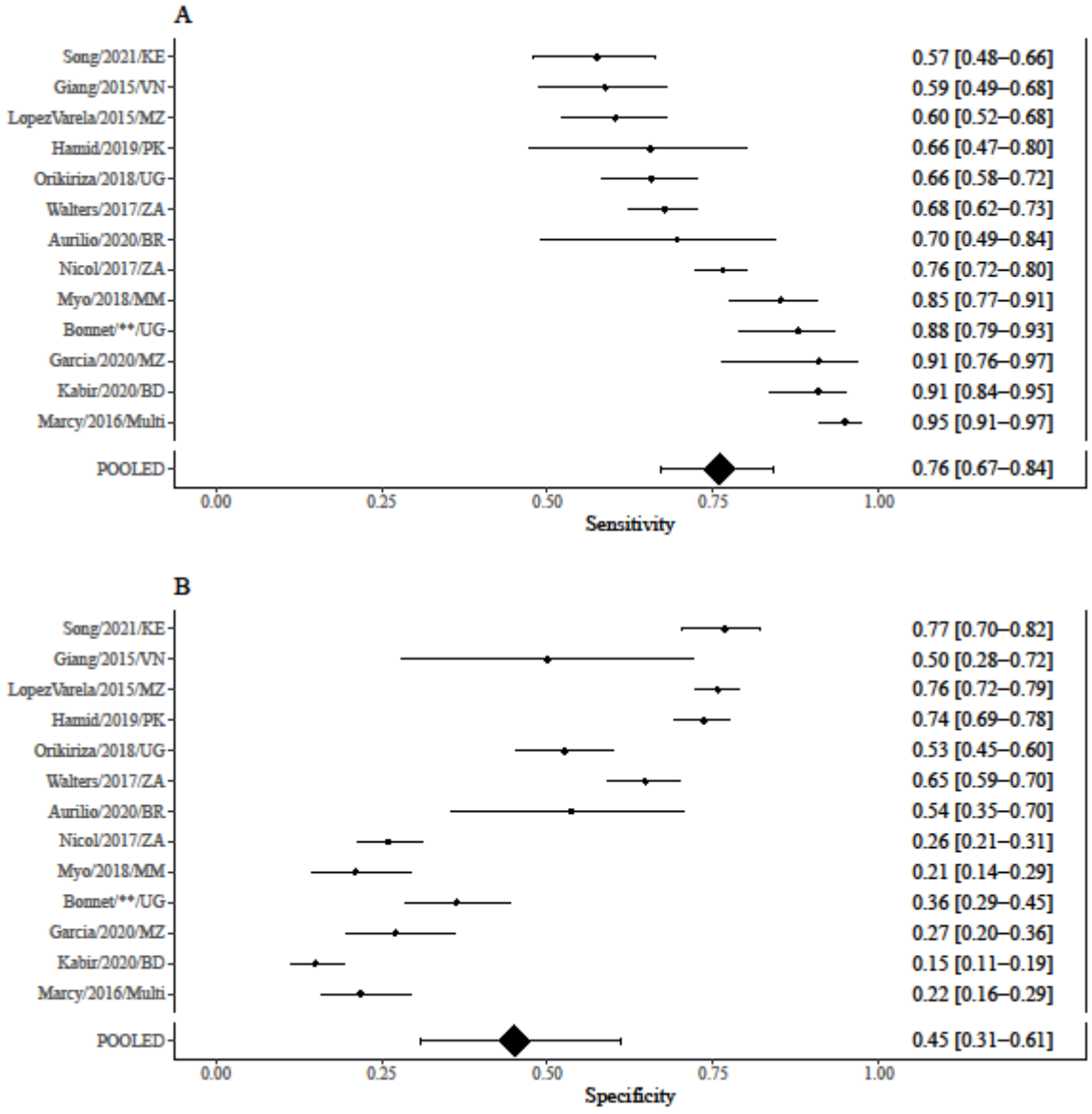


Figure S13. Performance of Brazilian Ministry of Health Score (using cutoff of 30 points to classify TB) Study-level and pooled estimates of the **(a)** sensitivity and **(b)** specificity of classifying TB (reference standard: bacteriologically-confirmed pulmonary TB and unconfirmed pulmonary TB).

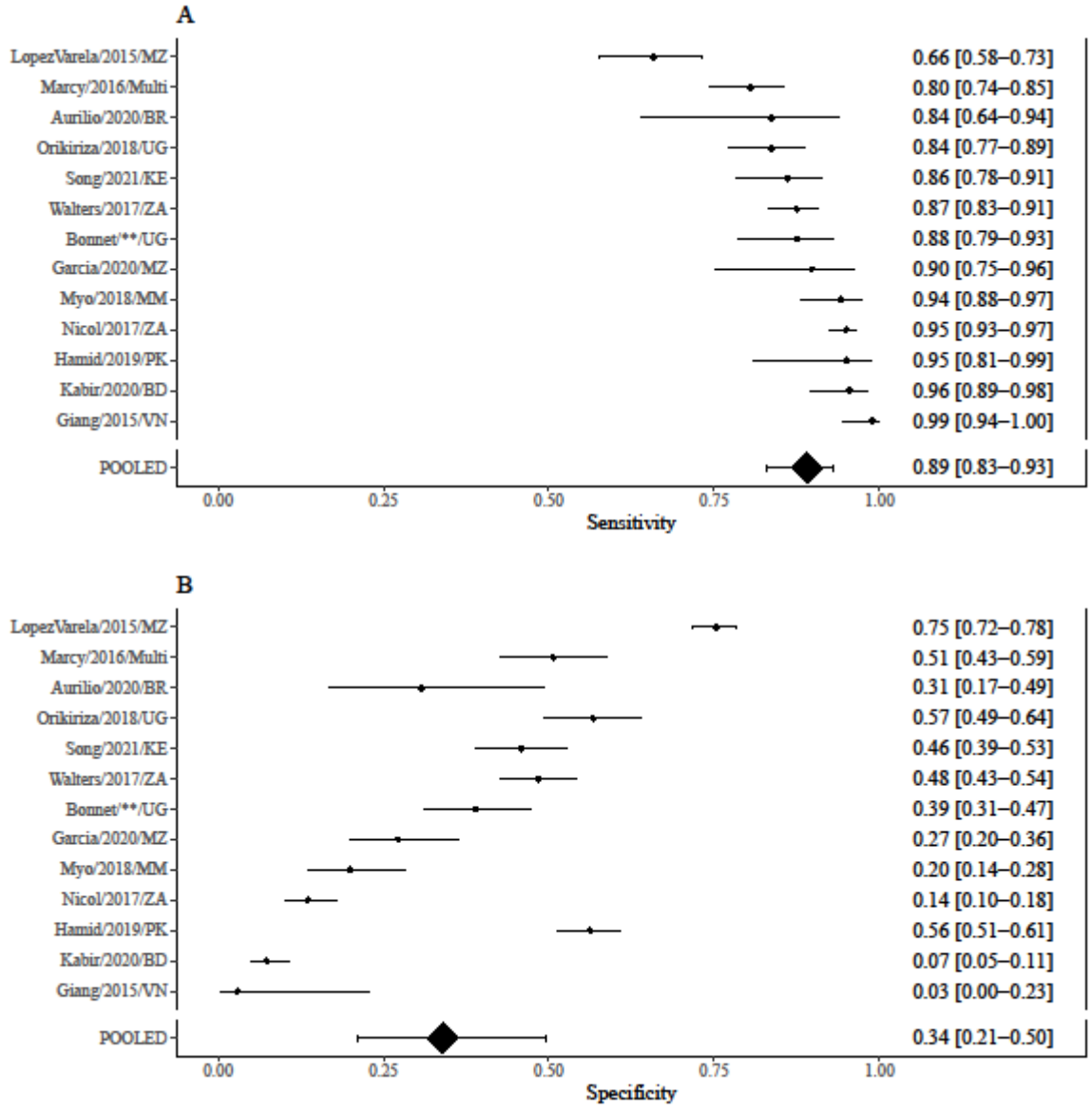


Figure S14. Performance of Keith-Edwards Score. Study-level and pooled estimates of the **(a)** sensitivity and **(b)** specificity of classifying TB (reference standard: bacteriologically-confirmed pulmonary TB and unconfirmed pulmonary TB).

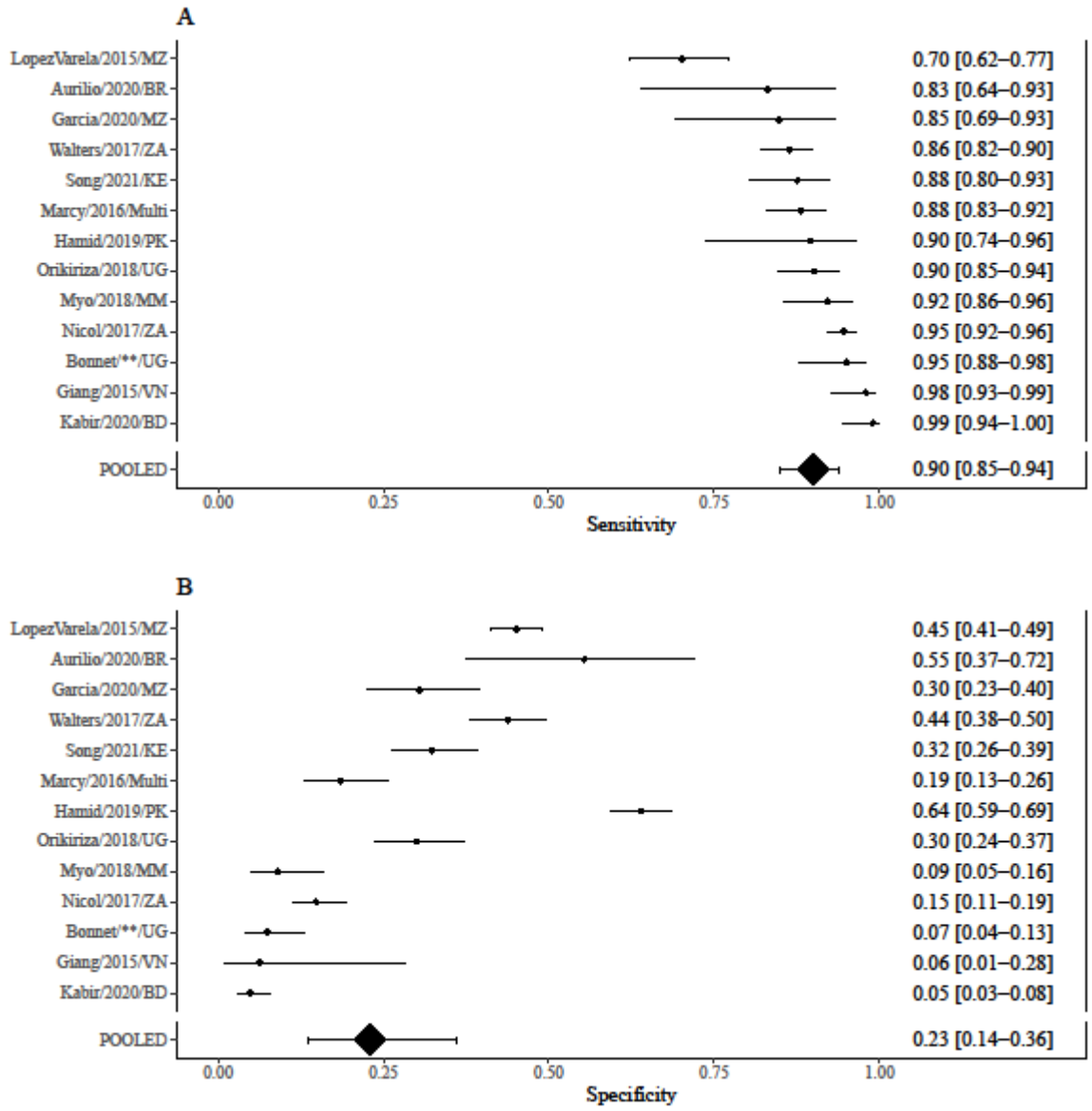


Figure S15. Performance of Marcy et al. Algorithm. Performance estimates of the Marcy et al. Algorithm were derived from only HIV-positive children in the IPD that excludes data form the Marcy/2016/Multi cohort (from which the algorithm was developed). Study-level and pooled estimates of the **(a)** sensitivity and **(b)** specificity of classifying TB (reference standard: bacteriologically-confirmed pulmonary TB and unconfirmed pulmonary TB).

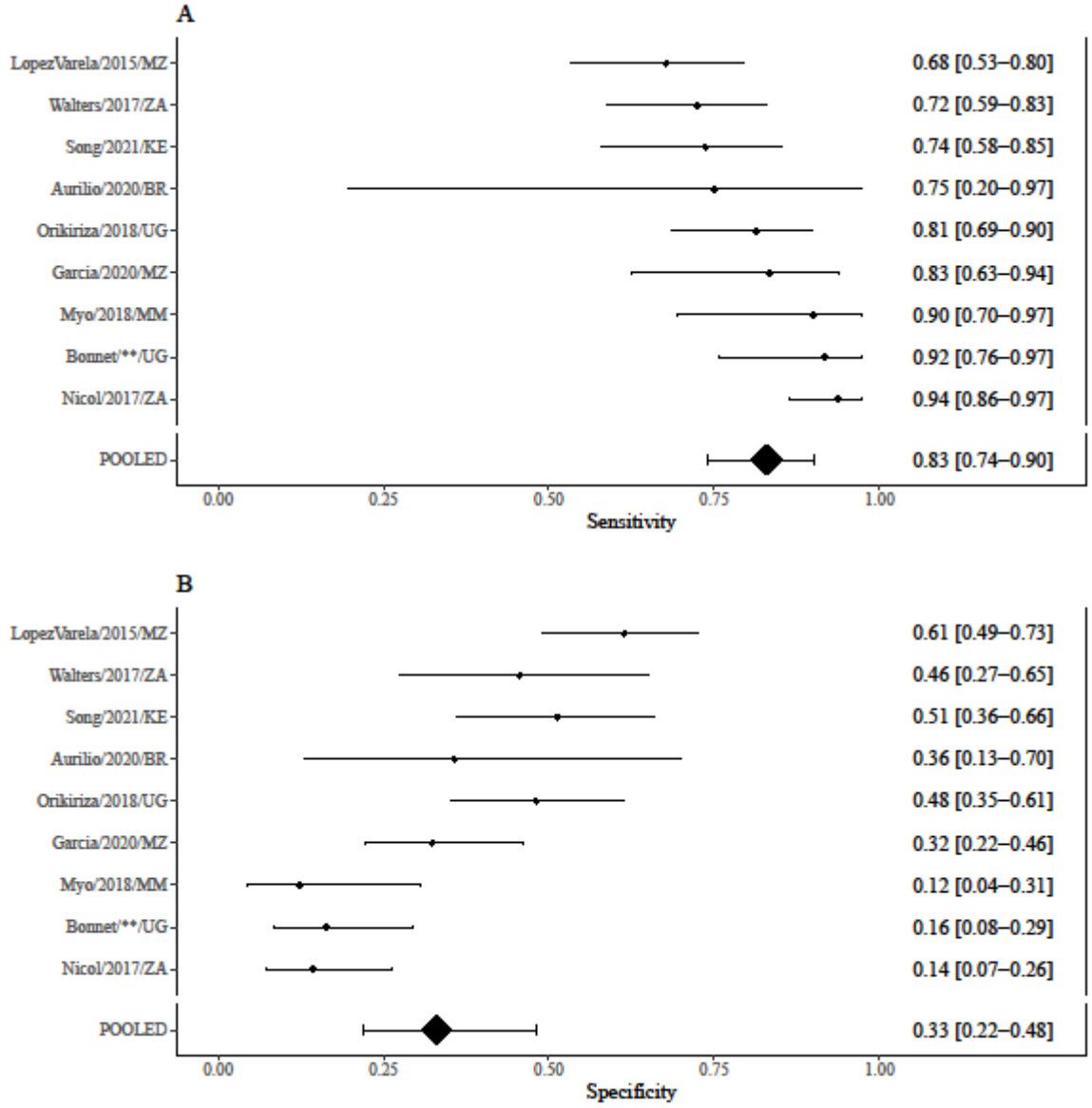
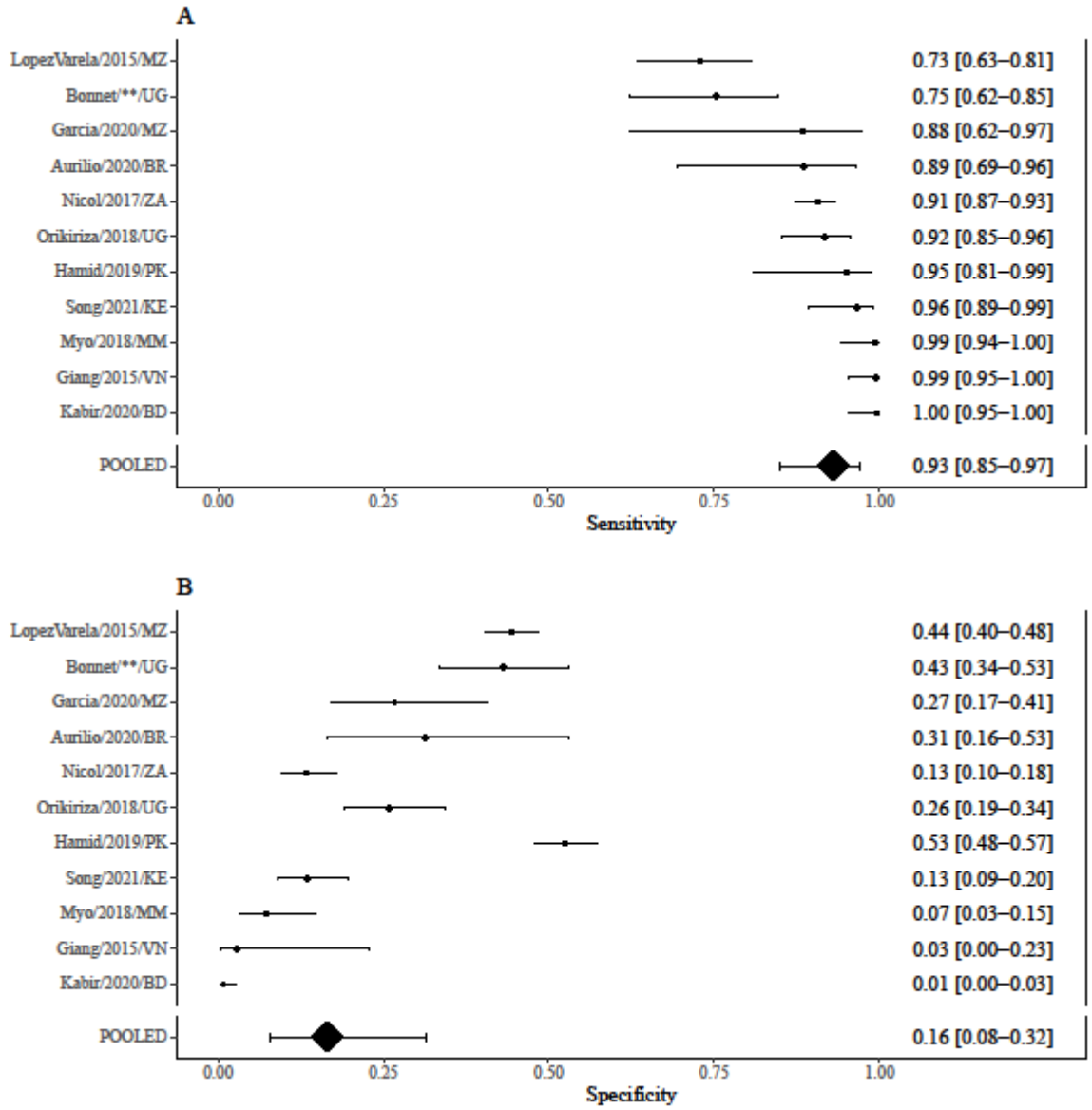
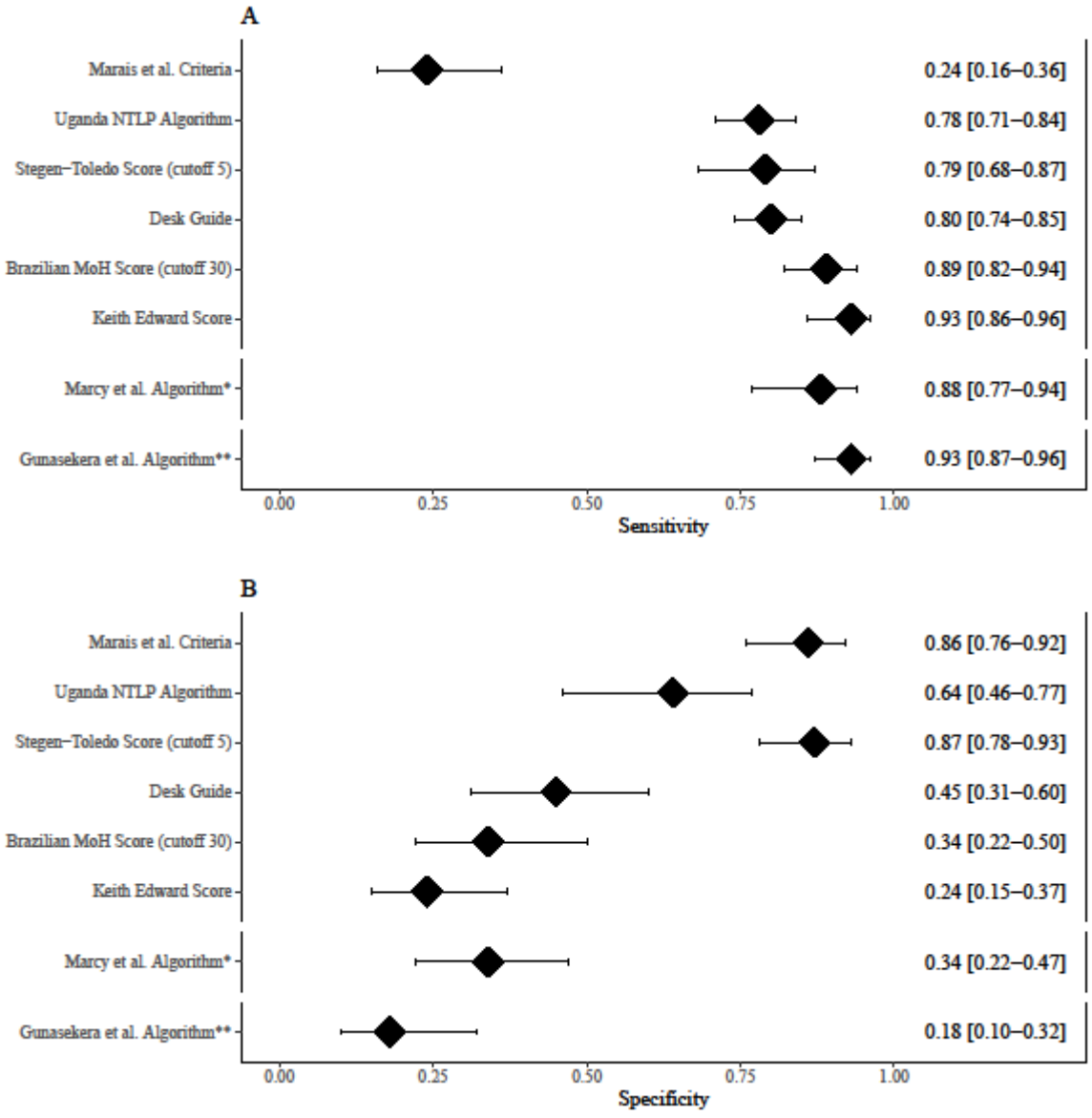


Figure S16. Performance of Gunasekera et al. Algorithm. Performance estimates of the Gunasekera et al. Algorithm were derived from only HIV-negative children in the IPD that excludes data from the Walter/2017/ZA population (from which the algorithm was developed). Study-level and pooled estimates of the **(a)** sensitivity and **(b)** specificity of classifying TB (reference standard: bacteriologically-confirmed pulmonary TB and unconfirmed pulmonary TB).



Appendix M: Performance of existing algorithms against reference classification of bacteriologically-confirmed TB

Figure S17. Performance of existing algorithms at classifying confirmed TB (excluding data from children with unconfirmed TB). Retrospective estimates of the pooled **(a)** sensitivity and **(b)** specificity of eight algorithms to guide treatment decision-making for children with presumptive pulmonary TB, had they been used to evaluate the children for whom we have IPD records. The reference classification of pulmonary TB included bacteriologically-confirmed pulmonary TB only (children with unconfirmed TB are excluded from this analysis).



Appendix N: Logistic regression model developed form IPD without CXR features

Table S36. Estimates of logistic regression prediction model developed from IPD without CXR features. Odds ratio with 95% confidence interval and p-value estimates for each parameter included in the logistic regression prediction model that does not include CXR features. The model parameter estimates account for potential clustering at the study-level as well as uncertainty introduced by missing data. IPD – individual participant data, OR – odds ratio.

		OR	2.5%ile	97.5%ile	P-value
	(Intercept)	0.257	0.144	0.458	0.000
Cough duration ≥ 2 weeks (Absence is no cough or <2 weeks)	Absent	--	--	--	--
	Present	1.248	0.972	1.600	0.747
Fever duration ≥ 2 weeks (Absence is no fever or <2 weeks)	Absent	--	--	--	--
	Present	1.576	1.203	2.066	0.207
Lethargy	Absent	--	--	--	--
	Present	1.223	0.989	1.513	0.753
Weight loss	Absent	--	--	--	--
	Present	1.276	1.007	1.618	0.680
History of known TB exposure	Absent	--	--	--	--
	Present	3.763	2.243	6.311	0.000
Hemoptysis	Absent	--	--	--	--
	Present	1.486	0.765	2.887	0.696
Night sweats	Absent	--	--	--	--
	Present	1.329	1.123	1.571	0.428
Peripheral lymphadenopathy	Absent	--	--	--	--
	Present	1.379	1.128	1.685	0.395
Temperature >38	Absent	--	--	--	--
	Present	1.006	0.801	1.264	1.000
Tachycardia	Absent	--	--	--	--
	Present	1.212	0.919	1.600	0.825
Tachypnea	Absent	--	--	--	--
	Present	1.077	0.836	1.387	0.971

Appendix O: Prediction model fit and scaled scores at different sensitivity thresholds

Table S37. OR and 95% CI of prediction model developed from IPD and corresponding scaled scores.

		OR	2.5%ile	97.5%ile	P-value	Score at 90% sens.	Score at 85% sens.	Score at 80% sens.	Score at 75% sens.	Score at 75% sens.
	(Intercept)	0.147	0.075	0.285	0.000	--	--	--	--	--
Cough duration ≥ 2 weeks	Absent	--	--	--	--	--	--	--	--	--
(Absence is no cough or <2 weeks)	Present	1.185	0.913	1.537	0.856	3	2	2	1	1
Fever duration ≥ 2 weeks	Absent	--	--	--	--	--	--	--	--	--
(Absence is no fever or <2 weeks)	Present	1.568	1.178	2.087	0.245	7	5	4	4	3
Lethargy	Absent	--	--	--	--	--	--	--	--	--
	Present	1.282	1.016	1.618	0.663	4	3	2	2	2
Weight loss	Absent	--	--	--	--	--	--	--	--	--
	Present	1.251	0.970	1.615	0.746	3	3	2	2	2
History of known TB exposure	Absent	--	--	--	--	--	--	--	--	--
	Present	4.195	2.385	7.377	0.000	22	17	14	12	10
Hemoptysis	Absent	--	--	--	--	--	--	--	--	--
	Present	1.404	0.690	2.857	0.788	5	4	3	3	2
Night sweats	Absent	--	--	--	--	--	--	--	--	--
	Present	1.224	1.022	1.465	0.709	3	2	2	2	1
Peripheral lymphadenopathy	Absent	--	--	--	--	--	--	--	--	--
	Present	1.422	1.141	1.772	0.353	5	4	3	3	2
Temperature >38	Absent	--	--	--	--	--	--	--	--	--
	Present	1.004	0.776	1.299	1.000	0	0	0	0	0
Tachycardia	Absent	--	--	--	--	--	--	--	--	--
	Present	1.159	0.879	1.529	0.896	2	2	1	1	1
Tachypnea	Absent	--	--	--	--	--	--	--	--	--
	Present	0.949	0.766	1.176	0.983	-1	-1	-1	0	0
Cavities on baseline CXR	Absent	--	--	--	--	--	--	--	--	--
	Present	1.600	0.898	2.849	0.527	7	6	5	4	3
Intrathoracic lymphadenopathy on baseline CXR	Absent	--	--	--	--	--	--	--	--	--
	Present	4.323	2.727	6.854	0.000	23	17	14	12	10
Opacities on baseline CXR	Absent	--	--	--	--	--	--	--	--	--
	Present	1.540	1.022	2.320	0.452	7	5	4	4	3
Miliary infiltrate on baseline CXR	Absent	--	--	--	--	--	--	--	--	--
	Present	3.558	1.761	7.191	0.000	20	15	12	10	9
Pleural effusion on baseline CXR	Absent	--	--	--	--	--	--	--	--	--
	Present	1.899	1.217	2.964	0.128	10	8	6	5	4

Table S38. OR and 95% CI of prediction model without chest x-ray features developed from IPD and corresponding scaled scores.

		OR	2.5%ile	97.5%ile	P-value	Score at 90% sens.	Score at 85% sens.	Score at 80% sens.	Score at 75% sens.	Score at 75% sens.
	(Intercept)	0.257	0.144	0.458	0.000	--	--	--	--	--
Cough duration ≥ 2 weeks (Absence is no cough or <2 weeks)	Absent	--	--	--	--	--	--	--	--	--
	Present	1.248	0.972	1.600	0.747	6	5	4	3	3
Fever duration ≥ 2 weeks (Absence is no fever or <2 weeks)	Absent	--	--	--	--	--	--	--	--	--
	Present	1.576	1.203	2.066	0.207	13	10	8	7	6
Lethargy	Absent	--	--	--	--	--	--	--	--	--
	Present	1.223	0.989	1.513	0.753	6	4	4	3	3
Weight loss	Absent	--	--	--	--	--	--	--	--	--
	Present	1.276	1.007	1.618	0.680	7	5	4	4	3
History of known TB exposure	Absent	--	--	--	--	--	--	--	--	--
	Present	3.763	2.243	6.311	0.000	39	29	24	20	17
Hemoptysis	Absent	--	--	--	--	--	--	--	--	--
	Present	1.486	0.765	2.887	0.696	12	9	7	6	5
Night sweats	Absent	--	--	--	--	--	--	--	--	--
	Present	1.329	1.123	1.571	0.428	8	6	5	4	4
Peripheral lymphadenopathy	Absent	--	--	--	--	--	--	--	--	--
	Present	1.379	1.128	1.685	0.395	9	7	6	5	4
Temperature >38	Absent	--	--	--	--	--	--	--	--	--
	Present	1.006	0.801	1.264	1.000	0	0	0	0	0
Tachycardia	Absent	--	--	--	--	--	--	--	--	--
	Present	1.212	0.919	1.600	0.825	6	4	3	3	2
Tachypnea	Absent	--	--	--	--	--	--	--	--	--
	Present	1.077	0.836	1.387	0.971	2	2	1	1	1

Appendix P: Performance of scores from prediction model at different sensitivity thresholds

Figure S18. (a) sensitivity and (b) specificity of score developed from prediction model to classify TB with 90% sensitivity.

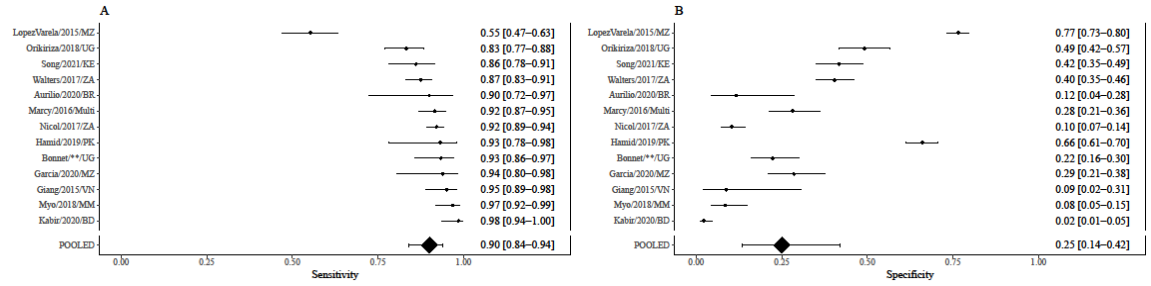


Figure S19. (a) sensitivity and (b) specificity of score developed from prediction model to classify TB with 85% sensitivity. Presented in the main text.

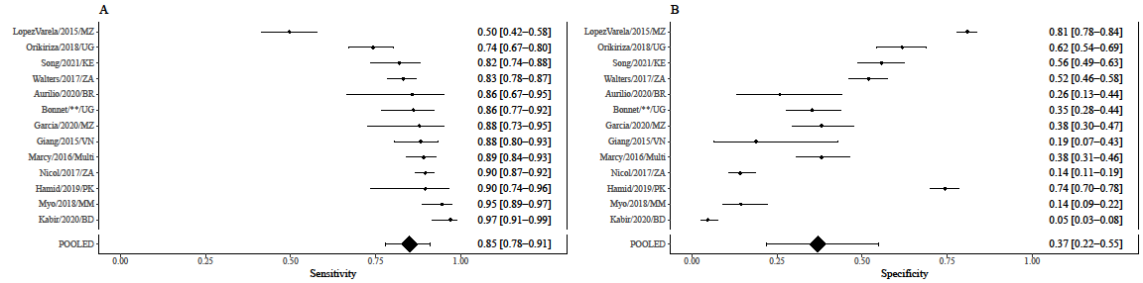


Figure S20. (a) sensitivity and (b) specificity of score developed from prediction model to classify TB with 80% sensitivity.

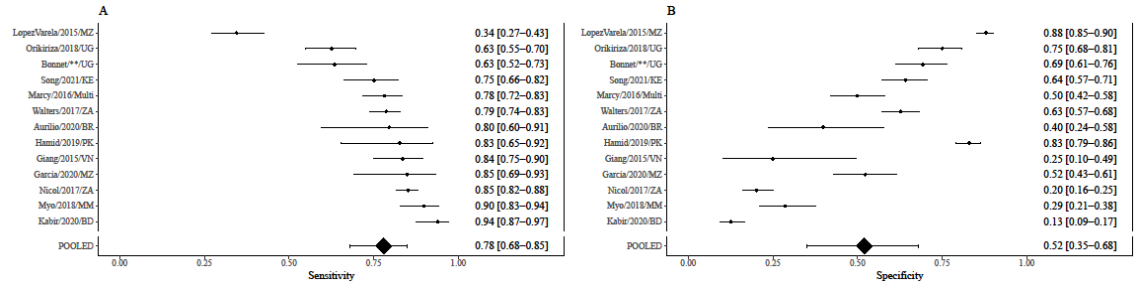


Figure S21. (a) sensitivity and (b) specificity of score developed from prediction model to classify TB with 75% sensitivity.

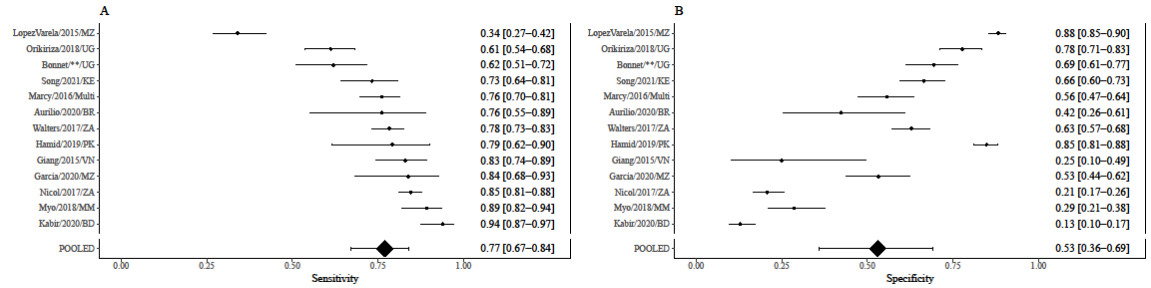
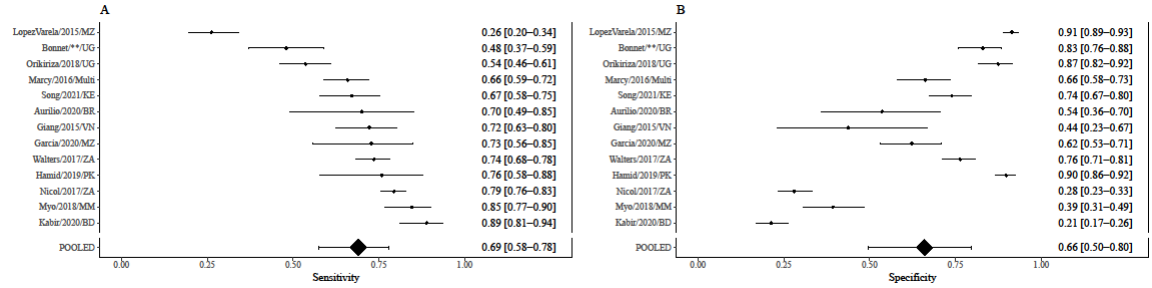


Figure S22. (a) sensitivity and (b) specificity of score developed from prediction model to classify TB with 70% sensitivity.



Appendix Q: Performance of scores from prediction model to classify TB with 85% sensitivity

Figure S23. Performance of scaled scores from prediction model to classify TB with 85% sensitivity. Presented in the main text.

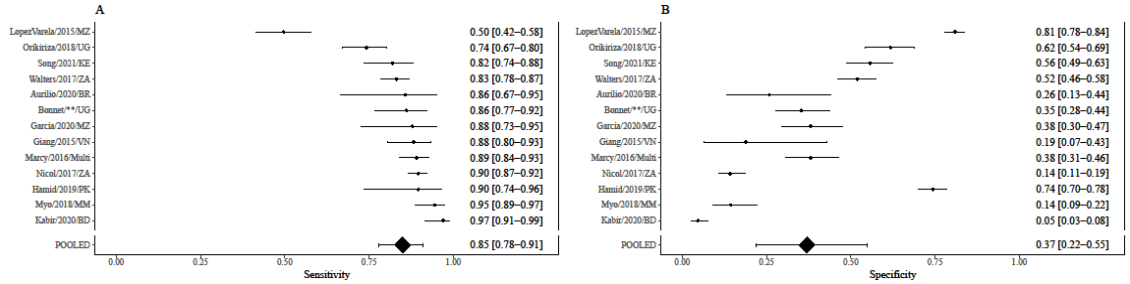
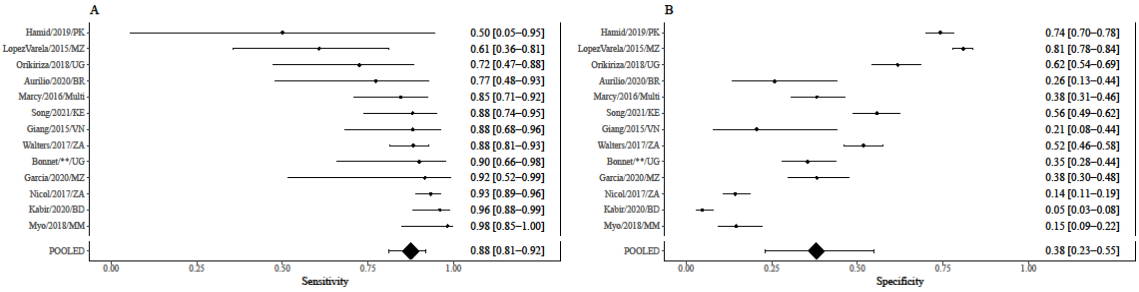


Figure S24. Performance of scaled scores from prediction model to classify confirmed TB with 85% sensitivity. Analysis excludes data from children with unconfirmed TB.



Appendix R: Performance of scores from prediction model without chest X-ray features to classify TB with 85% sensitivity

Figure S25. Performance of scaled scores from prediction model without chest x-ray to classify TB with 85% sensitivity.

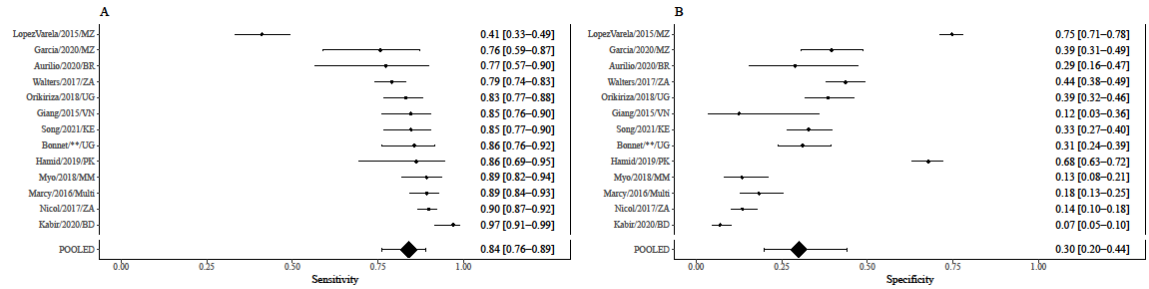
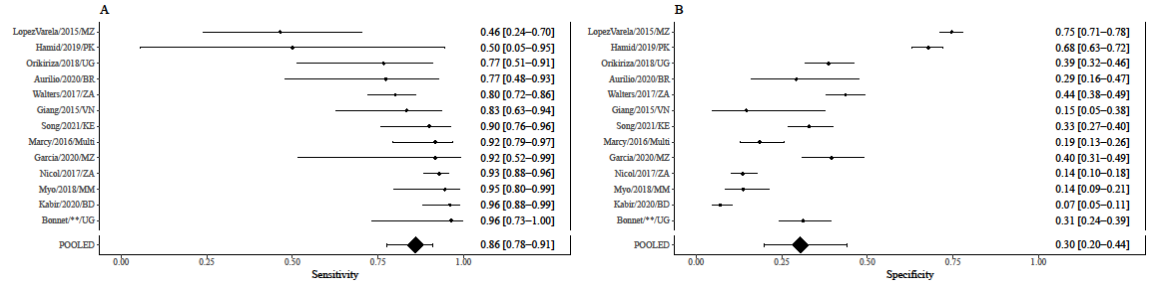
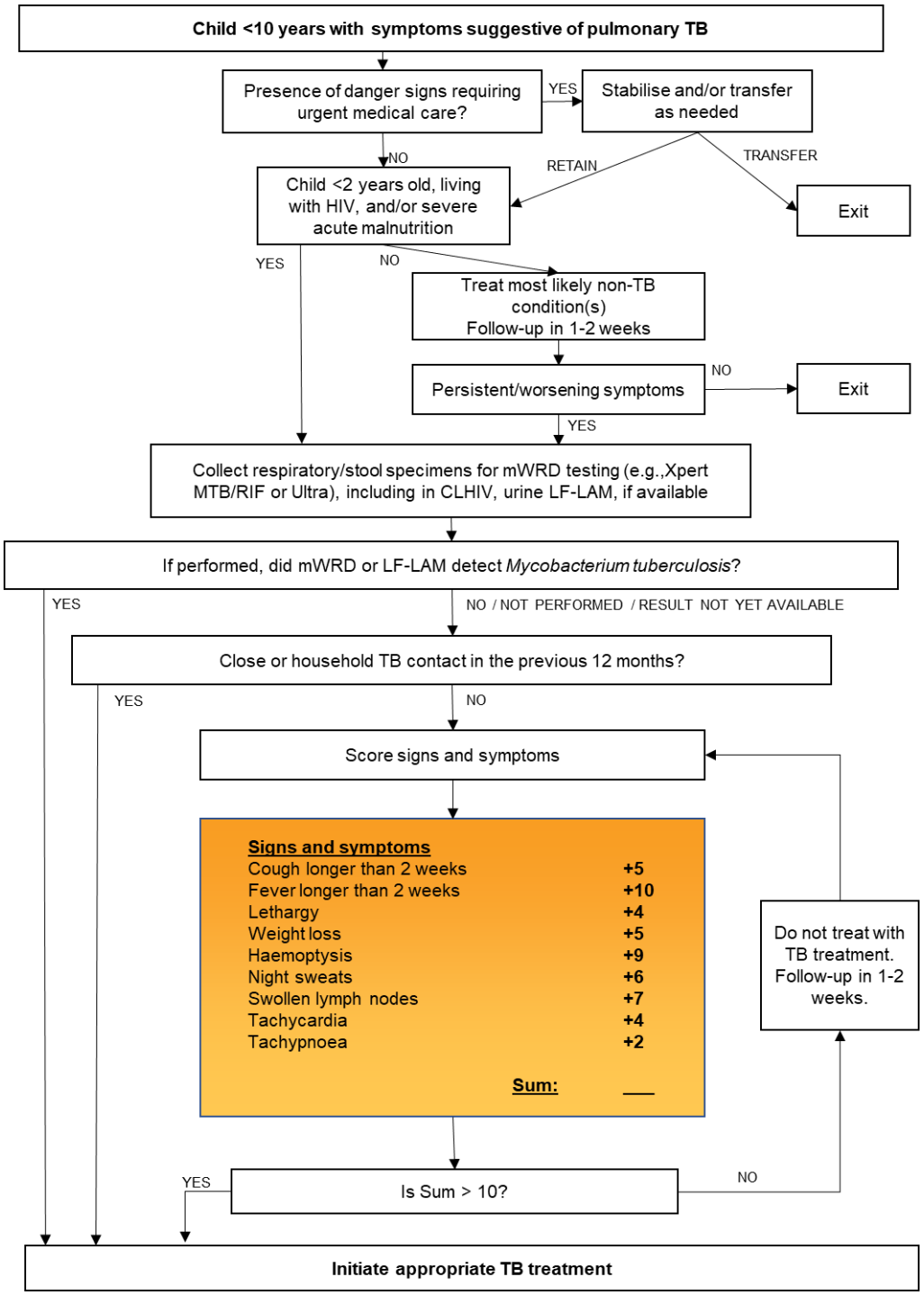


Figure S26. Performance of scaled scores from prediction model without chest x-ray to classify confirmed TB with 85% sensitivity. Analysis excludes data from children with unconfirmed TB.



Appendix S: Inspire algorithm without CXR features

Figure S27. Treatment-decision algorithm derived from prediction model without CXR features.



Conclusions

Childhood tuberculosis is a public health crisis that contributes substantially to the global burden of child mortality. This body of work describes analyses to address two major priorities in childhood tuberculosis: 1) preventing tuberculosis transmission to children and 2) improving case detection for children with tuberculosis.

The work in Chapter 1 described the application of a Bayesian spatial model to use accessible, age-disaggregated tuberculosis notification data to identify potential hotspots of tuberculosis transmission. A unique strength of this study was its ability to compare inference from the proposed application of disease mapping methodology on routinely-available notification data against conclusive molecular evidence of transmission from a prospective cohort study in the same setting. The concordance of transmission inference obtained using different methods and datasets provided compelling evidence in support of the concept that children are sentinels for community-transmission of tuberculosis. This finding suggests that the use of models that leverage widely available notification data should be explored as tools for targeting case-finding and treatment efforts in high-transmission locations, in the hope of maximizing the direct and indirect protective benefits of active screening approaches.

The work in Chapter 2 investigated subclinical tuberculosis, a poorly understood form of tuberculosis that may frustrate symptom-based active screening approaches to limit tuberculosis transmission. This study contributed to the growing body of evidence that has revealed that subclinical tuberculosis is more common than previously appreciated. The findings that subclinical tuberculosis was more common among active cigarette smokers and individuals living with HIV may inform the design of more effective

case-finding interventions. This work also suggests that efforts to screen individuals based on self-reported symptoms may not be sufficient to rule out tuberculosis, especially among individuals who smoke and/or who are living with HIV. While this study provided additional support for claims of the potential importance of subclinical disease, the epidemiological significance of subclinical disease remains unclear. Future studies are required to investigate the natural history and transmission potential of subclinically-infected individuals.

The work in Chapter 3 and Chapter 4 aimed to improve case detection for children with pulmonary tuberculosis by leveraging diagnostic evaluations data to build prediction models that may guide treatment decision-making among children with presumptive pulmonary tuberculosis. These works demonstrated that for symptomatic children being investigated for tuberculosis disease in resource-limited settings, an algorithmic approach may be sufficient to guide tuberculosis treatment initiation, even in the absence of chest x-ray or confirmatory testing.

The work in Chapter 3 outlined an approach to interpret clinical data to inform treatment-initiation decisions for children being evaluated for pulmonary tuberculosis. Diagnostic evaluations data from children in Cape Town, South Africa were used as the substrate to develop a prediction model that was operationalized as a treatment-decision algorithm to support decision-making for children with presumptive pulmonary tuberculosis. This work demonstrated that algorithms that incorporate evidence from a detailed clinical history and physical examination could play an important role in guiding sensitive treatment-initiation decisions for most children being evaluated for pulmonary tuberculosis. Additionally, this demonstrated that sensitive treatment-decisions for children with tuberculosis could be made based on clinical evidence alone.

The work in Chapter 4 arose from the desire to formally validate and investigate the generalizability of models to predict tuberculosis from diagnostic evaluations data. Thus, this work established the largest known cohort of individual participant diagnostic evaluations data from children being investigated for childhood pulmonary tuberculosis. These data were used to evaluate existing algorithms for pulmonary tuberculosis and to develop a model to predict pulmonary tuberculosis. This work, carried out in conjunction with the World Health Organization, described how this model was operationalized as a new treatment-decision algorithm to include in upcoming guidelines on the management of tuberculosis in children.

Treatment decision-algorithms represent an important pragmatic tool that could, in combination with improved health system investment, reduce the morbidity/mortality of this public health crisis. These works represent a pragmatic and transparent approach, using advanced analytic methods, to develop an algorithm based on the best available data that can be validated and further specified as additional becomes available.

Though the causes of the childhood tuberculosis public crisis are multifactorial, major challenges arise from the paucibacillary nature of childhood tuberculosis and from limited public health resources available to curtail this epidemic. In spite of these limitations, this body of work describes pragmatic attempts to address critical challenges that may have an impact on reducing the burden of child morbidity and mortality associated with tuberculosis.