External validation of a treatment decision algorithm for tuberculosis in children living with HIV: a diagnostic cohort study

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Summary

Background Tuberculosis is the leading cause of death in children living with HIV, and is challenging to diagnose owing to the limitations of microbiological approaches. The Pediatric Asian African Network for Tuberculosis and HIV Research (PAANTHER) treatment decision algorithm (TDA) was previously developed to improve the diagnosis of tuberculosis in children living with HIV, but has not yet been validated. We aimed to externally validate this TDA in a prospective cohort of children from four countries in Africa.

Methods The TB-Speed HIV study was a prospective diagnostic cohort study conducted in seven tertiary hospitals: two in Côte d'Ivoire, two in Mozambique, one in Uganda, and two in Zambia. Eligible participants were children living with HIV, aged 1 month to 14 years, with presumptive tuberculosis. Children who were currently receiving tuberculosis treatment, or who had received treatment within the past 3 months, were excluded. At enrolment, children were evaluated for suggestive tuberculosis symptoms (fever for >2 weeks, unremitting cough, haemoptysis and/or weight loss in the past 4 weeks, and tachycardia) and underwent Xpert MTB/RIF Ultra testing on respiratory and stool samples, chest radiography, and abdominal ultrasonography. Children were given a PAANTHER TDA score, with a score of less than 100 defined as negative and a score of 100 or higher defined as positive and prompting the initiation of treatment. At the end of the study, children were retrospectively classified by an endpoint review committee as having confirmed, unconfirmed, or unlikely tuberculosis, forming the composite reference standard against which diagnostic accuracy was assessed. The primary outcome was the proportion of children with missed tuberculosis (false negatives) among those who were not initiated on treatment as per the PAANTHER TDA. We assessed the diagnostic accuracy (sensitivity, specificity, and negative and positive predictive values) and feasibility (uptake and time to treatment initiation) of the PAANTHER TDA. The protocol-defined negative predictive value threshold for validation was 75%. This study is registered at ClinicalTrials.gov, NCT04121026, and is complete.

Findings From Oct 2, 2019, to Dec 31, 2021, 1706 children were prescreened for eligibility, of whom 713 children living with HIV were screened for tuberculosis symptoms; 423 were eligible for the study and 277 were enrolled. Of these 277 children, 272 (98%) had a complete TDA evaluation: 215 (79%) had a score of 100 or higher, including 24 (9%) with a positive Xpert MTB/RIF Ultra test. Treatment was initiated in 185 (86%) of 215 children with a positive score and 12 (20%) of 60 children with a negative score, at a median of 1 day [IQR 0–4] after inclusion. After assessment by the endpoint review committee, the proportion of children with tuberculosis in the classifiable study population (n=273) was 56·8% (95% CI 50·9–62·5), with 131 having unconfirmed tuberculosis and 24 having confirmed tuberculosis. Four (7%) of the 60 children with a negative score were subsequently classified as having tuberculosis by the endpoint review committee (missed tuberculosis). The TDA had a negative predictive value of 93·3% (95% CI 84·1–97·4), a positive predictive value of 70·9% (95% CI 64·5–76·6), a sensitivity of 97·4% (95% CI 93·6–99·0), and a specificity of 47·5% (95% CI 38·7–56·4).

Interpretation The PAANTHER TDA was externally validated in a cohort of children living with HIV as per the study protocol. The high sensitivity of this TDA and its potential to enable rapid treatment initiation could contribute to the reduction of mortality in children living with HIV.

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For the French translation of the abstract see Online for appendix 1

For the Portuguese translation of the abstract see Online for appendix 2

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Introduction

Tuberculosis is an important public health concern, particularly among children living with HIV, in whom it is the most common opportunistic infection and the leading cause of death. According to WHO, of the 1·25 million tuberculosis-related deaths estimated worldwide in 2024, 166 000 were in children aged 0–14 years and 25 000 were in children living with HIV,[1] most of whom are assumed to have never started antituberculosis treatment.

Undiagnosed and untreated tuberculosis increases the risk of death in children, especially in those living with HIV, who have a higher mortality than HIV-negative children even if diagnosed and treated.[2] Tuberculosis disease progresses more rapidly in children living with HIV, owing to impaired immunological containment of *Mycobacterium tuberculosis*, and can lead to more severe disease. Hospital-based studies report case-fatality rates of 14–41% in children living with HIV receiving tuberculosis treatment.[3–5] A retrospective study in Cape Town, South Africa found that children living with HIV who were treated for tuberculosis had higher mortality than HIV-negative children and twice the odds of an unfavourable outcome.[6]

Rapid and earlier diagnosis and treatment of tuberculosis in children is therefore essential, especially in those living with HIV, who typically have more severe clinical presentation than HIV-negative children and for whom drug–drug interactions are an important consideration.[7] However, despite access to molecular diagnosis and antigen-based point-of-care tests,[8] tuberculosis poses diagnostic challenges in this vulnerable population. These challenges arise in part from the low sensitivity of diagnostic tests, driven by the paucibacillary presentation of the disease, and in part from the poorly specific and atypical symptoms, signs, and radiological characteristics resulting from the underlying immunodeficiency,[7] meaning that symptom-based approaches that perform well in HIV-negative children might perform poorly in children living with HIV.[2] As such, alternative diagnostic approaches and novel tools are required.

The Pediatric Asian African Network for Tuberculosis and HIV Research (PAANTHER) treatment decision algorithm (TDA) was developed using data collected in Burkina Faso, Cambodia, Cameroon, and Viet Nam from children living with HIV who were evaluated for tuberculosis.[9] Data on clinical, microbiological, and radiological characteristics were evaluated for the ability to discriminate between children with tuberculosis and those with other diseases, and that discriminatory power was then scaled into a scoring system that could be used to make treatment decisions. When evaluated internally, the PAANTHER TDA scoring system had a sensitivity of 88·6% and a specificity of 61·2%.[9] However, external validation is crucial for evaluating the effectiveness and generalisability of TDAs. To our knowledge, no published studies have described the external evaluation of tuberculosis TDA performance in diverse clinical (ie, different levels of health care), geographical (ie, west, east, and southern Africa), and epidemiological (ie, different tuberculosis and HIV burdens and health system capabilities) settings, particularly in low-income and middle-income settings. A further challenge inherent to paediatric diagnostic research is the absence of a microbiological gold standard for the diagnosis of tuberculosis, which complicates the design and interpretation of external validation studies.

We aimed to externally validate the PAANTHER TDA in children living with HIV with presumptive tuberculosis by

Research in context

Evidence before this study

We searched PubMed from Jan 1, 2000, to Dec 31, 2025, with no restrictions on language or article type, using the terms "tuberculosis", "children", "HIV", "diagnosis", "treatment decision algorithm", and "external validation". Only one study reported the validation of treatment decision algorithms (TDAs) for tuberculosis in the general paediatric population and in children living with HIV, using retrospective data. We found no published studies reporting the prospective external validation of tuberculosis TDAs in children living with HIV with the aim of implementing the TDAs for diagnostic decision making; we also found no prospective evaluation of tuberculosis TDAs in the general paediatric population. This gap is recognised by WHO, which conditionally recommends the use of TDAs while emphasising the need for robust validation before widespread implementation.

Added value of this study

To our knowledge, this is the first prospective external validation diagnostic study of the Pediatric Asian African Network for Tuberculosis and HIV Research (PAANTHER) TDA in children living with HIV. Our study was conducted in real-world settings across seven tertiary hospitals in four African countries with a high burden of HIV and tuberculosis: Côte d'Ivoire, Mozambique, Uganda, and Zambia. Our findings support the high sensitivity and negative predictive value of the algorithm, meeting the prespecified validation criteria. The TDA also showed high feasibility and enabled a short turnaround time for the delivery of results and the initiation of treatment.

Implications of all the available evidence

Our findings suggest that the PAANTHER TDA could be a promising, feasible, and sensitive tool for the diagnosis of tuberculosis in children living with HIV. This TDA could support treatment decisions in high-burden, resource-limited settings in which diagnostic capacity is low. We provide evidence for the inclusion of such validated algorithms into the global guidelines for tuberculosis diagnosis and treatment.

assessing its diagnostic performance, feasibility, and effect on treatment decisions in diverse geographical and epidemiological settings.

Methods

Study design and participants

The TB-Speed HIV study was a prospective diagnostic cohort study conducted in seven tertiary hospitals: two in Côte d'Ivoire, two in Mozambique, one in Uganda, and two in Zambia. These four countries have a high incidence of tuberculosis and a high HIV prevalence: the estimated tuberculosis incidence per 100 000 population in 2024 was approximately 361 cases in Mozambique and 100–299 cases in Zambia, Uganda, and Côte d'Ivoire.[1] Children younger than 15 years with HIV comprised 0·52% of the total population in Mozambique, 0·28% in Zambia, 0·14% in Uganda, and 0·07% in Côte d'Ivoire.[10] Mozambique, Zambia, and Uganda are among the 30 countries designated by WHO as having a high dual burden of HIV and tuberculosis.

We assessed the overall diagnostic performance and feasibility of the PAANTHER TDA in children with HIV and presumptive tuberculosis and the safety of withholding tuberculosis treatment in those with a negative PAANTHER tuberculosis score. The key validation criteria were based on the occurrence of failures of the algorithm to identify children with tuberculosis (ie, false negatives).

From Oct 2, 2019, to Dec 31, 2021, children with presumptive tuberculosis were identified by routine clinicians using WHO symptom-based screening at outpatient clinics and inpatient wards of the participating hospitals and evaluated by study nurses. We enrolled children aged 1 month to 14 years with documented HIV infection who had presumptive tuberculosis based on at least one of the following five criteria: a persistent cough for more than 2 weeks, persistent fever for more than 2 weeks, failure to thrive in the past 3 months, failure of broad-spectrum antibiotics for the treatment of pneumonia, and chest x-ray features suggestive of tuberculosis.[11] Also included were children who had a history of exposure to tuberculosis, regardless of symptom presentation, and children who had any of the symptoms listed for a shorter duration (ie, <2 weeks).[11] We excluded children who were receiving tuberculosis treatment at the time of screening or who had received tuberculosis treatment in the preceding 3 months, except for those on tuberculosis preventive treatment (appendix 3 pp 26–27). Written informed consent was obtained from parents or guardians and assent was obtained from children aged 7 years or older, in compliance with local regulations.

The study is registered at ClinicalTrials.gov (NCT04121026) and was approved by the sponsor's ethics evaluation committee (Comité d'Evaluation Ethique de l'Inserm; CD/EB 19-001) and the WHO Ethics Review Committee (ERC.0003154) as well as by the following national ethics committees and institutional review boards: Comité National d'Ethique des Sciences de la vie et de la Santé (105-19/MSHP/CNEVS-kp) in Côte d'Ivoire, Comité Nacional de Bioética para Saúde (611/CNBS/19) in Mozambique, the Uganda National Council for Science and Technology (HS 2647) in Uganda, and the Zambia National Health Research Authority (008-11-18) in Zambia (appendix 3 pp 2–3).

See Online for appendix 3

Procedures

Data on sex were reported by parents or guardians. Race and ethnicity data were not collected in this study. The study was conducted across four sub-Saharan African countries (Côte d'Ivoire, Mozambique, Uganda, and Zambia), and participants were recruited from public health facilities serving predominantly Black African populations.

At enrolment, children underwent the following assessments: clinical evaluation for a history of close exposure to a person with bacteriologically confirmed tuberculosis and assessment for suggestive tuberculosis symptoms (ie, protracted fever for more than 2 weeks, unremitting cough, haemoptysis and/or weight loss in the past 4 weeks, and tachycardia); microbiological testing using the molecular Xpert MTB/RIF Ultra (hereafter Xpert; Cepheid, Sunnyvale, CA, USA) assay on one nasopharyngeal aspirate and one stool sample and either two expectorated sputum samples or two gastric aspirates; a chest radiograph to assess pulmonary and intrathoracic disease; and abdominal ultrasonography to assess for the presence of intra-abdominal lymphadenopathy. We used the PAANTHER TDA as developed initially in the ANRS 12229 PAANTHER 01 study.[9]

In addition, for the purpose of this study, additional clinical signs and symptoms and ultrasonography features were recorded. Mycobacterial culture testing was conducted on two expectorated sputum samples or gastric aspirates, and blood samples were obtained from children for additional laboratory tests (appendix 3 p 44). All data were collected using an electronic case report form (CRF), developed in Research Electronic Data Capture (REDCap), which was accessible on remote devices. This CRF also had a score-calculation module. The algorithm and score-calculation study standard operating procedures were also provided in paper form alongside the electronic CRF module.

For more on **REDCap** see https://project-redcap.org/

The diagnostic process was expected to last 1–2 days. Attending routine care clinicians were encouraged, where indicated, to initiate tuberculosis treatment without delay on the basis of the PAANTHER TDA score (figure 1). Treatment was promptly initiated in children with a score of 100 or higher (defined as a positive score), and followed the standard 6-month regimen recommended by WHO. Flexibility to start tuberculosis treatment in children with a score of less than 100 (defined as a negative score) was allowed in the case of a severe or life-threatening condition at the clinician's discretion.

All children had a diagnostic visit at the hospital 1–2 days after enrolment and were seen at the hospital on day 15 and

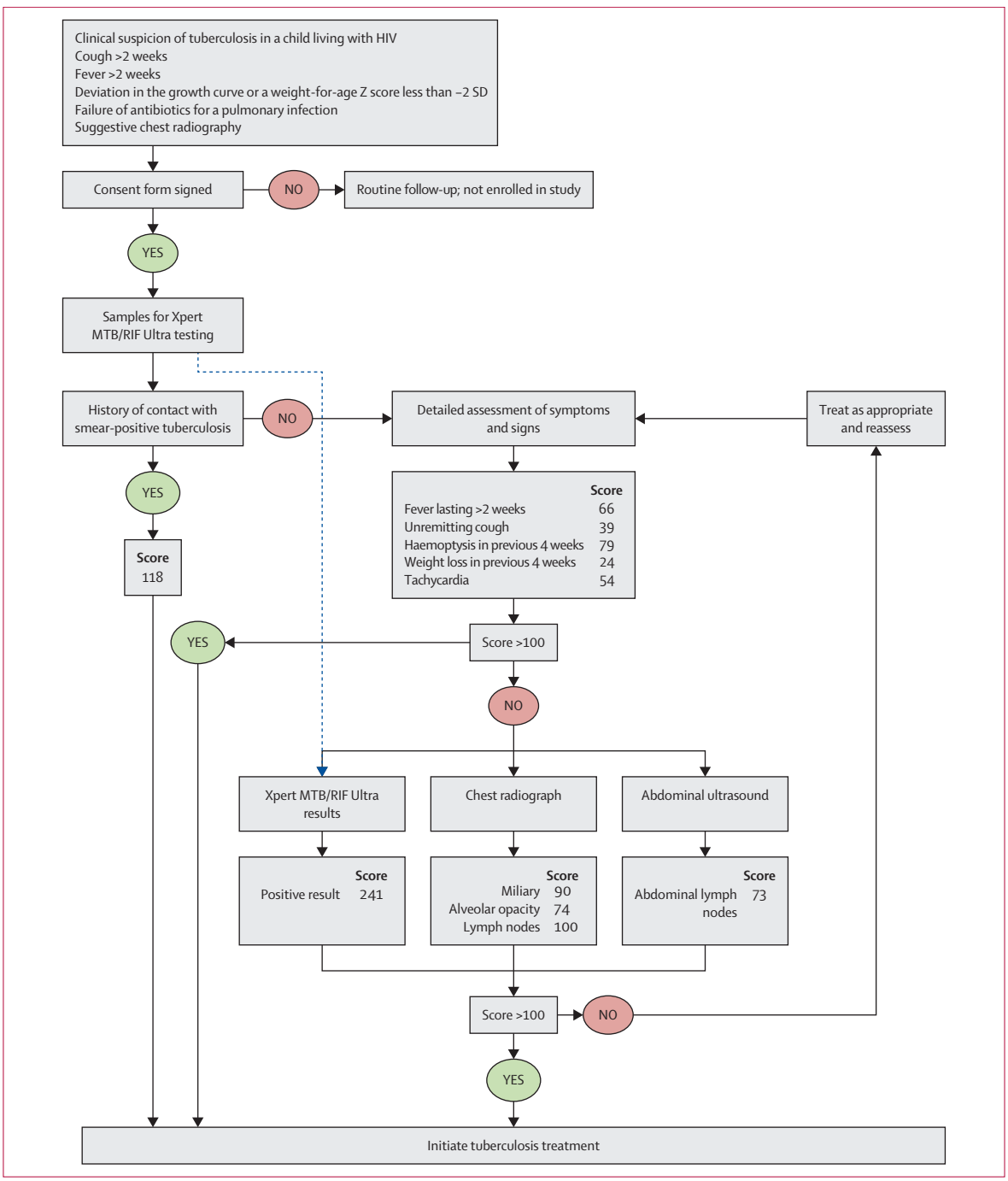

Figure 1: **PAANTHER treatment decision algorithm**
Reproduced with permission from *Pediatrics*, **144:** e20182065, Copyright © 2019 by the AAP.[9] The algorithm specifies that antituberculosis treatment is initiated when the cumulative score exceeds 100. In the present TB-Speed HIV validation study, treatment was initiated in children with a score of 100 or higher, consistent with the per-protocol cutoff used for all diagnostic-accuracy analyses. PAANTHER=Pediatric Asian African Network for Tuberculosis and HIV Research.

at months 1, 2, 3, and 6. For children not initiated on tuberculosis treatment at baseline, a visit was planned on day 7 to identify those with possible missed tuberculosis. At each visit, children had a medical history taken, underwent a clinical evaluation for any new symptoms or signs of tuberculosis, and were evaluated for adverse events, adherence to tuberculosis medications, nutritional recovery, and symptom resolution. At month 2 and month 6, a

chest radiograph was obtained and blood samples were taken for laboratory tests. At any time during the study, Xpert testing and chest radiography could be repeated if a child without a tuberculosis diagnosis showed no clinical improvement or presented with new symptoms or signs of tuberculosis (appendix 3 p 6). Tuberculosis treatment outcomes were assessed at 6 months.

At the end of the study, children were retrospectively classified by an endpoint review committee (ERC) as having confirmed, unconfirmed, or unlikely tuberculosis. This ERC classification served as the composite reference standard against which the diagnostic accuracy of the PAANTHER TDA was assessed. An ERC was established in each country, and a centralised international ERC comprised independent experts who were not involved in the management of the study. Each country's ERC reviewed the following: children with clinically diagnosed tuberculosis who had a negative PAANTHER TDA score (ie, potential false negatives), differential diagnoses in children who were not clinically improving at month 2, and all deaths and ongoing disease at the time of death for causality. The classification process differed between children with negative PAANTHER TDA scores and those with positive scores: children with microbiologically confirmed tuberculosis (via Xpert testing), and children with negative scores who had subsequently been initiated on tuberculosis treatment, were classified according to the updated National Institutes of Health Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children[12] by the relevant country's ERC. Children who were identified as potential false-negative cases by national ERCs were reviewed and the final classification was made by the centralised international ERC. Children with positive PAANTHER TDA scores and without microbiological confirmation of tuberculosis were classified as having either unconfirmed or unlikely tuberculosis, on the basis of expert opinion, by the centralised international ERC. For these children, the updated Clinical Case Definitions for Classification of Intrathoracic Tuberculosis in Children could not be used to assess the reference standard, as the treatment decision in the study was guided by an algorithm rather than being based on clinician judgement.

During the COVID-19 pandemic lockdowns in the study countries (April–October, 2020), follow-up was conducted by telephone when physical visits were not possible. The safety of staff and of children and their families were ensured at the study visits and at times of sample collection and processing in the laboratory.

An independent data monitoring committee monitored the safety of the study through regular safety reports.

Outcomes

The primary outcome was the proportion of children with missed tuberculosis (false negatives) among those who were not initiated on treatment as per the PAANTHER TDA. Secondary outcomes were the time to final tuberculosis treatment decision, the proportion of children with presumptive tuberculosis with a complete PAANTHER TDA (ie, either receiving a positive score or having tuberculosis ruled out on the basis of the score), the proportion of children classified as having unlikely tuberculosis by the ERC among those who were initiated on treatment as per the PAANTHER TDA (false positives), and the diagnostic accuracy (measured by negative and positive predictive values and corresponding sensitivity and specificity) of the PAANTHER TDA overall and in subgroups of participants according to age, severity of immunosuppression, nutritional status, and antiretroviral therapy (ART) status.

Statistical analysis

On the basis of a hypothesised tuberculosis prevalence of 50% and an estimated TDA sensitivity of 89% and specificity of 61%,[9] we estimated the proportion of missed cases of tuberculosis among children who were not started on treatment based on the PAANTHER TDA (assessed by the number of tuberculosis incident cases in the 6-month period after applying the algorithm) to be 15%. This proportion corresponds to a negative predictive value of 85%. For sample size calculations, we used an unacceptable negative predictive value of 75% (minimal acceptable lower limit of the 95% CI), a one-sided test of level 5%, and a probability β of 5% (power 95%), which resulted in a sample of 176 children not initiated on treatment based on the PAANTHER TDA and a total sample of 550 children, accounting for an expected proportion of missing data of 10%.[13] After discussions with the scientific advisory board on feasibility and budgetary issues, study recruitment was concluded on Dec 31, 2021, when 277 participants had been enrolled. This decision was not based on the review of accumulated efficacy data, during which those conducting the review were masked to the interim estimate of negative predictive value.

We evaluated the proportion of missed tuberculosis cases in children living with HIV with presumptive tuberculosis who were not initiated on treatment (ie, false negatives) and estimated the negative predictive value of the PAANTHER TDA and its 95% CI. We compared the lower limit of the 95% CI to the minimal acceptable lower limit to assess whether the algorithm was validated. We assessed the proportion of overdiagnosed tuberculosis cases among children with a positive PAANTHER TDA score (ie, false positives), and estimated the positive predictive value of the PAANTHER TDA, the prevalence of tuberculosis in the study, and the sensitivity and specificity of the TDA, all with 95% CIs. We assessed and compared the diagnostic accuracy of the TDA between subgroups using two-sample, three-sample, or four-sample tests for equality of proportions without continuity correction, depending on the number of subgroups. Given the asymmetric ERC classification process, negative predictive value and positive predictive value are the primary accuracy metrics for interpreting the performance of the TDA, whereas sensitivity and specificity are prespecified analyses to ensure comparability with other TDAs.

As a post-hoc analysis, we assessed the concordance between clinician-calculated scores and CRF-derived recalculated scores using Cohen's κ statistic. First, we compared the score obtained in real time by a clinician using the PAANTHER TDA during routine care (the clinician-calculated score) with the score recalculated retrospectively from clinical, imaging, and microbiological data entered in the CRF, independent of the clinician's live scoring (the CRF recalculated score). Then, we conducted a sensitivity analysis comparing the diagnostic performance, in terms of sensitivity and specificity, of the PAANTHER TDA based on clinician-calculated scores versus CRF-recalculated scores using McNemar's test and type I error rate at 0·05.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From Oct 2, 2019, to Dec 31, 2021, 1706 children were prescreened for eligibility, of whom 713 children living with HIV were screened for tuberculosis symptoms. Of these 713 children, 423 were eligible for the study and 277 were enrolled (figure 2). 275 (99%) of the 277 children received a clinician-calculated score; the baseline and disease characteristics of these children are shown in table 1. The median age of participants was 5·0 years (IQR 2·0–10·0), 142 (52%) were female and 133 (48%) were male, 175 (70%) of 250 children for whom data were available were on ART at recruitment, the median CD4 count was 737 cells per μL (IQR 322–1305), the median CD4 percentage was 21·0 (IQR 10·1–30·0), and 84 (42%) of 201 children for whom data were available had severe immunosuppression. Of the 274 children for whom data were available, 172 (63%) had a persistent cough for more than 2 weeks, 90 (33%) had a persistent fever for more than 2 weeks, 177 (65%) had weight loss in the previous 4 weeks, 61 (22%) had been treated unsuccessfully with broad-spectrum antibiotics for pneumonia, 189 (72%) had features on chest radiography suggestive of tuberculosis, and 18 (7%) had a history of exposure to an adult with bacteriologically confirmed tuberculosis, together with symptoms of a shorter duration.

Of the 275 children who had a clinician-calculated score, scoring was considered complete for 272 (99%)—defined as a total PAANTHER score of at least 100 or, if less than 100, as the assessment of all score items. Around 90% of children had Xpert testing of microbiological samples, 94% had abdominal ultrasonography, and 97% had chest radiography (table 2). All tests were completed within a median time of 1 day. 215 (78%) children were scored positive by the clinicians, including 24 (9%) with microbiological confirmation, and 60 (22%) were scored negative (figure 2). The clinician scoring and the supporting data in the study CRF were concordant in 248 (90%) of 275 cases overall in terms of the total score (Cohen's κ=0·73 [95% CI 0·63–0·83]), with higher discrepancies for tuberculosis exposure history, unremitting cough, and tachycardia (appendix 3 p 11).

Tuberculosis treatment was initiated in 197 (71%) of 277 children at a median time of 1 day (IQR 0–4) after inclusion: 185 (86%) of 215 children with a positive score, who initiated treatment within a median of 1 day (0–3), and 12 (20%) of 60 children with a negative score, who initiated treatment at a median time of 27 days (8–64) after inclusion. Overall, 47 (17%) of 275 children died during the study: 37 (17%) of 215 children with a positive score and ten (17%) of 60 children with a negative score. Of the 30 children with a positive score who were not initiated on tuberculosis treatment, five (17%) died: one on the day of enrolment and one on each of days 31, 36, 76, and 102 after enrolment.

After ERC review, 62 (29%) of 215 children with a positive score were classified as having unlikely tuberculosis, with two as unevaluable. Four (33%) of 12 children who had a negative score but who had been started on tuberculosis treatment were classified as having unconfirmed tuberculosis (figure 2). The resulting proportion of tuberculosis in the classifiable study population (N=273) was 56·8% (95% CI 50·9–62·5), with 131 children having unconfirmed tuberculosis and 24 children having confirmed tuberculosis.

Four (7%) of the 60 children with a negative score were subsequently classified as having tuberculosis by the ERC (missed tuberculosis). The clinician-calculated score had a negative predictive value of 93·3% (95% CI 84·1–97·4), thereby reaching the per-protocol validation criteria. This score had a sensitivity of 97·4% (95% CI 93·6–99·0) and a specificity of 47·5% (95% CI 38·7–56·4) for the detection of tuberculosis (table 3). The subgroup analyses showed significant differences in the positive predictive value (p=0·031) between children with or without severe immunosuppression. Notably, the specificity was significantly lower in Uganda (24·2% [12·8–41·0]) than in the other three countries (p=0·0099; table 3).

The diagnostic performance of the CRF-recalculated score differed significantly from that of the clinician calculated score in terms of sensitivity (McNemar p=0·027, appendix 3 p 15) but not in terms of specificity (McNemar p=1·0).

Discussion

We validated the PAANTHER TDA for the diagnosis of tuberculosis in children living with HIV. The study corroborated the high sensitivity and high negative predictive value of the algorithm, meeting the prespecified validation criteria. The TDA showed high feasibility and enabled a short turnaround time to results and treatment initiation. This external validation step is key to supporting the implementation of this diagnostic tool in children living with HIV in settings with high burdens of tuberculosis and HIV.

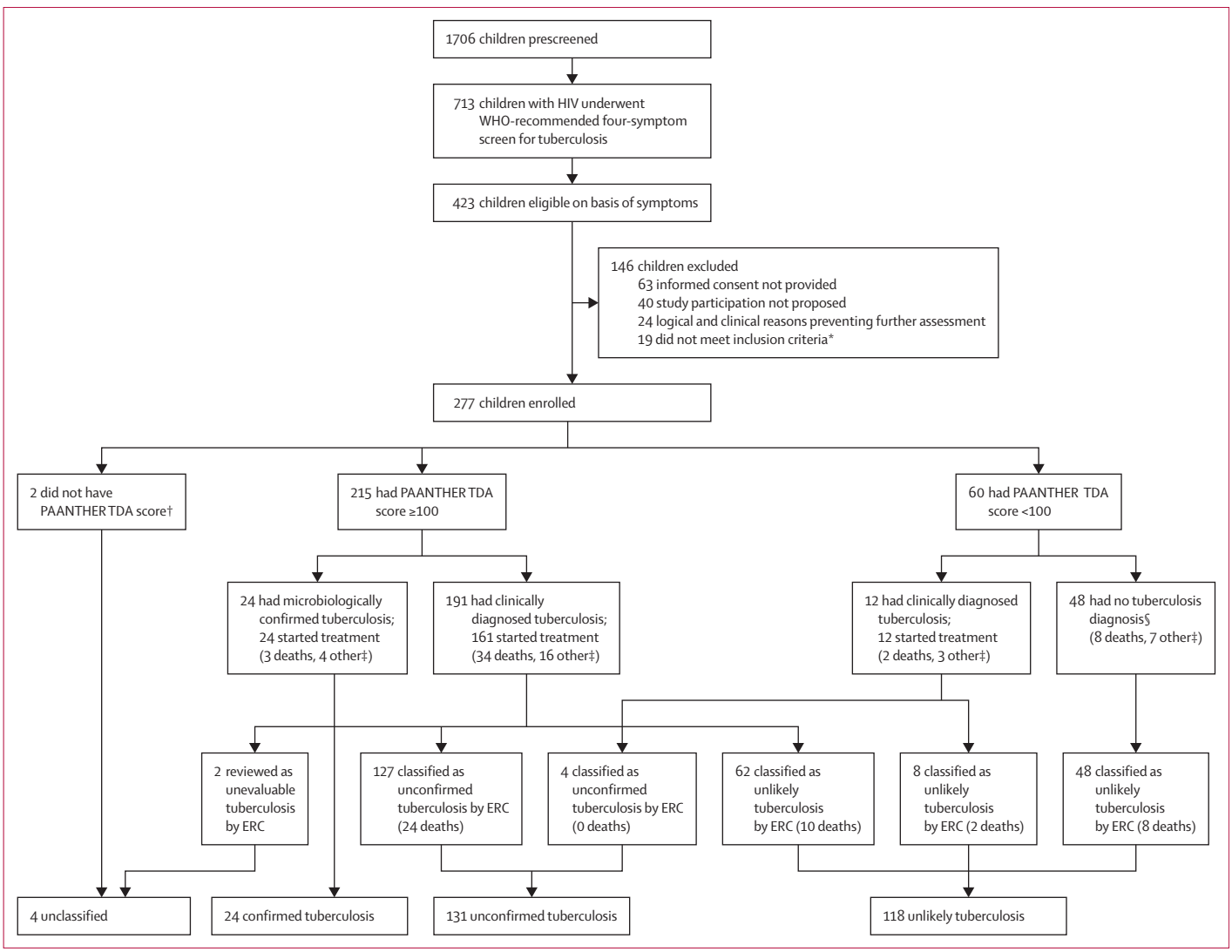

Figure 2: **Study flowchart**

ERC=endpoint review committee. PAANTHER=Pediatric Asian African Network for Tuberculosis and HIV Research. TDA=treatment decision algorithm. *Reasons were already being on tuberculosis treatment, being outside the eligible age range, or having an HIV-negative test result. †Owing to a data synchronisation failure in the electronic case report form. ‡Other comprises children who were lost to follow-up, transferred out of the study, or withdrew from the study. §One child, with a PAANTHER TDA score of less than 100, had a trace positive Xpert MTB/RIF Ultra result from nasopharyngeal aspirate, had no tuberculosis diagnosis or treatment, and was alive at the end of the study.

Overall, very few tuberculosis diagnoses were missed by the PAANTHER TDA, showing that sensitivity is maintained when this algorithm is implemented in settings other than those under which it was developed. These findings are in accordance with the development strategy for this TDA, which favoured sensitivity, aiming to reduce mortality in this vulnerable group.[14] A short time to treatment initiation is also essential to reduce mortality.[15] Clinicians using the TDA made a treatment decision in a median time of 1 day, which, as hypothesised during TDA development,[9] represents a substantial reduction compared with the development study, in which the median time to tuberculosis diagnosis was 7 days. There were no deaths in children with negative scores who were classified as having unconfirmed tuberculosis. The specificity was lower than estimated previously,[9] which could have several explanations. First, the unremitting cough criterion was assessed using a graphic method,[16] which was reported by clinicians to be challenging to use; this could have contributed to the overdiagnosis of a cough lasting more than 2 weeks as an unremitting cough, therefore contributing to a decreased specificity and increased sensitivity. Second, the reference classification in children with a positive score could not rely on a positive response to treatment, as the treatment decision was forced by the TDA; this could have led to biased estimates of the tuberculosis prevalence and the diagnostic accuracy. Finally, specificity was much lower in one study country than in the other three, which could be explained by

	All children (n=275)*	Positive score (n=215)	Negative score (n=60)	p value
Age, years	5 (2 to 10)	5 (2 to 10)	5 (2 to 10)	0·98
Sex				
Female	142 (52%)	110 (51%)	32 (53%)	..
Male	133 (48%)	105 (49%)	28 (47%)	0·77
Country				
Côte d'Ivoire	26 (9%)	20 (9%)	6 (10%)	..
Mozambique	40 (15%)	28 (13%)	12 (20%)	..
Uganda	83 (30%)	74 (34%)	9 (15%)	..
Zambia	126 (46%)	93 (43%)	33 (55%)	0·031
On ART at inclusion	175/250 (70%)	132/198 (67%)	43/52 (83%)	0·025
CD4 count (cells per mm^3)	737 (322 to 1305); n=208	730 (330 to 1283); n=165	870 (218 to 1491); n=43	0·51
CD4 percentage	21% (10 to 30); n=206	21% (10 to 29); n=164	20% (13 to 30); n=42	0·94
Severe immunosuppression†	84/201 (42%)	66/160 (41%)	18/41 (44%)	0·43
Weight-for-age Z score	−3 (−4 to −1); n=201	−3 (−4 to −1); n=155	−3 (−4 to −1); n=46	0·37
Severe acute malnutrition‡	118 (43%)	93 (43%)	25 (42%)	0·83
BCG vaccination	194/249 (78%)	150/192 (78%)	44/57 (77%)	0·41
Previous tuberculosis treatment	19 (7%)	14 (7%)	5 (8%)	0·74
Exposure to person with smear-positive or Xpert-positive tuberculosis	18/274 (7%)	17 (8%)	1/59 (2%)	0·13
Pulmonary infection in the past month	132 (48%)	117 (54%)	15 (25%)	<0·0001
Failure of broad-spectrum antibiotics for pneumonia	61/274 (22%)	51/214 (24%)	10 (17%)	0·24
Cough (any, ongoing)	237/274 (86%)	196 (91%)	41/59 (69%)	<0·0001
Cough >2 weeks	172/274 (63%)	151 (70%)	21/59 (36%)	<0·0001
Unremitting cough§	136/274 (50%)	119 (55%)	17/59 (29%)	0·0003
Fever (any, ongoing)	161/274 (59%)	138 (64%)	23/59 (39%)	0·0005
Fever >2 weeks§	90/274 (33%)	84 (39%)	6/59 (10%)	<0·0001
Haemoptysis in previous 4 weeks§	2/274 (1%)	2 (1%)	0/59	>0·99
Weight loss in previous 4 weeks§,¶	177/274 (65%)	142 (66%)	35/59 (59%)	0·34
Loss of appetite	143/274 (52%)	117 (54%)	26/59 (44%)	0·16
Fatigue or loss of playfulness	140/274 (51%)	115 (53%)	25/59 (42%)	0·13
Tachycardia§	62 (23%)	53 (25%)	9 (15%)	0·11
Cervical lymphadenopathy	63/274 (23%)	55 (26%)	8/59 (14%)	0·052
Hepatomegaly	47/274 (17%)	42 (20%)	5/59 (8%)	0·046
Chest radiography features consistent with tuberculosis	189/261 (72%)	176/205 (86%)	13/56 (23%)	<0·0001
Miliary§	32/261 (12%)	31/205 (15%)	1/56 (2%)	0·0070
Alveolar opacity§	136/261 (52%)	126/205 (61%)	10/56 (18%)	<0·0001
Lymph nodes§	126/261 (48%)	124/205 (60%)	2/56 (4%)	<0·0001
Cavitation	25/261 (10%)	23/205 (11%)	2/56 (4%)	0·085
Pleural effusion	13/261 (5%)	12/205 (6%)	1/56 (2%)	0·31
Airway compression	4/261 (2%)	4/205 (2%)	0/56	0·58
Abdominal lymph nodes§	36/258 (14%)	35/204 (17%)	1/54 (2%)	0·0039
Xpert test positive§	25/271 (9%)	24/212 (11%)	1/59 (2%)‖	0·024
Mycobacterium tuberculosis culture positive for any sample	8/228 (4%)	8/179 (4%)	0/49	0·21
PAANTHER TDA total score	208 (113 to 287)	242 (179 to 303)	63 (39 to 90)	<0·0001
Tuberculosis treatment initiated	197 (72%)	185 (86%)	12 (20%)	<0·0001
Tuberculosis treatment outcome				
Treatment successful	117/179 (65%)	114/167 (68%)	3/12 (25%)	..
Treatment unsuccessful	4/179 (2%)	4/167 (2%)	0/12	..
Died	25/179 (14%)	23/167 (14%)	2/12 (17%)	..
Lost to follow-up	6/179 (3%)	5/167 (3%)	1/12 (8%)	..
Not evaluated	27/179 (15%)	21/167 (13%)	6/12 (50%)	0·015

(Table 1 continues on next page)

	All children (n=275)*	Positive score (n=215)	Negative score (n=60)	p value
(Continued from previous page)				
Reference tuberculosis classification				
Confirmed	24/273 (9%)	24/213 (11%)	0	..
Unconfirmed	131/273 (48%)	127/213 (60%)	4 (7%)	..
Unlikely	118/273 (43%)	62/213 (29%)	56 (93%)	<0·0001
End-of-study status				
Alive	198 (72%)	158 (73%)	40 (67%)	..
Dead	47 (17%)	37 (17%)	10 (17%)	..
Transferred out	1 (<1%)	0	1 (2%)	..
Withdrawn	12 (4%)	9 (4%)	3 (5%)	..
Lost to follow-up	17 (6%)	11 (5%)	6 (10%)	0·24

Data are n (%), n/N (%), or median (IQR). A positive score is defined as ≥100 and a negative score as <100. ART=antiretroviral therapy. PAANTHER=Pediatric Asian African Network for Tuberculosis and HIV Research. TDA=treatment decision algorithm. Xpert=Xpert MTB/RIF Ultra. *Of the 277 children enrolled in the study, two did not receive a PAANTHER TDA score owing to a data synchronisation failure in the electronic case report form. †WHO definition of severe immunosuppression: <25% CD4 cells in children aged ≤11 months, <20% CD4 cells in children aged 12–35 months, <15% CD4 cells in children aged 36–59 months, and <200 cells per mm^3 or <15% CD4 cells in children aged ≥5 years. ‡Weight-for-height Z score less than −3 SD in children younger than 5 years and BMI-for-age Z score less than −3 SD in children aged 5 years and older. §Scoring item. ¶As reported by parents or guardians. ||This child had a PAANTHER TDA score <100, a trace positive result on Xpert testing of nasopharyngeal aspirates, was not diagnosed with or treated for tuberculosis, and was alive at the end of the study.

Table 1: **Characteristics of participants with a calculated PAANTHER TDA score**

a greater proportion of clinicians in this setting over-diagnosing a chronic cough as unremitting. However, our results suggest that, for children living with HIV, the PAANTHER TDA could outperform TDA-A—a WHO algorithm that includes chest radiography—in terms of diagnostic accuracy. TDA-A proposes a single scoring approach for the general paediatric population (ie, not specific for HIV-positive or HIV-negative children), and has an estimated sensitivity of 86% and a specificity of 37% for the symptom and chest radiography scoring component.[11,17] A retrospective external evaluation of WHO TDAs using individual-patient data, which included this cohort, reported 84·3% (95% CI 74·8–90·6) sensitivity and 50·6% (95% CI 30·4–70·7) specificity for TDA-A in a general population. In comparison, the PAANTHER TDA had higher sensitivity (97·4% [93·6–99·0]) and similar specificity (47·5% [38·7–56·4]). However, given the overlap of the dataset and the different target population, this comparison should be interpreted with caution.[18]

To our knowledge, this study is the first prospective external validation of a data-driven TDA for tuberculosis. Since the publication of the PAANTHER algorithm, several data-driven TDAs for tuberculosis have been developed—in HIV-negative children,[19] in the general paediatric population,[17] and in children hospitalised with severe acute malnutrition[20]—and other TDAs have been developed for use when molecular testing is unavailable.[21,22] As far as we are aware, none of these algorithms have been externally validated to date. We prospectively implemented a TDA for real-life treatment decision making and therefore faced the methodological issues inherent to childhood tuberculosis diagnosis research, most crucially in relation to the absence of an independent reference standard. Indeed, owing to the treatment decision enforced by the TDA, the evolution

	Feasibility (uptake; N=277)	Time to score items (days)
Complete scoring*	272 (98%)	NA
Xpert test on nasopharyngeal aspirates	257 (93%)	1 (0–1)
Xpert test on stools and/or expectorated sputum	248 (90%)	1 (1–2)
Chest radiography	269 (97%)	0 (0–1)
Abdominal ultrasound	259 (94%)	1 (0–3)
Tuberculosis treatment initiation	197 (71%)	1 (0–4)

Data are n/N (%), n (%), or median (IQR). NA=not applicable. PAANTHER=Pediatric Asian African Network for Tuberculosis and HIV Research. TDA=treatment decision algorithm. Xpert=Xpert MTB/RIF Ultra. *Scoring was considered as complete if the total PAANTHER TDA score was ≥100 or, if <100, if all score items were assessed.

Table 2: **Feasibility and time to score for tuberculosis assessments**

under treatment or off treatment, which is a strong contributor to the classification of children as having either unconfirmed or unlikely tuberculosis,[23] could not be used as a classifying criterion for the reference standard.[12] To mitigate this, we used independent expert opinion to identify children with unlikely tuberculosis among those with a positive PAANTHER TDA score and negative microbiological test, and implemented a scheduled follow-up of children with negative scores to detect those with missed tuberculosis. Despite the challenges, and although more thorough implementation research on the use of TDAs is needed, this type of external validation study—even in tertiary care settings—is closer to real-world implementation scenarios than studies estimating the diagnostic accuracy of TDAs using retrospective data.[17] We found that a positive score did not automatically lead to the initiation of treatment for tuberculosis; this was notable in one of the countries, where treatment was initiated by a team from another programme that did not necessarily follow the clinician decision based on TDA scoring. Our

	Confirmed and unconfirmed tuberculosis (n=155)		Unlikely tuberculosis (n=118)		Sensitivity (95% CI)	p value*	Specificity (95% CI)	p value*	Positive predictive value (95% CI)	p value*	Negative predictive value (95% CI)	p value*
	Positive score	Negative score	Positive score	Negative score								
Overall	151	4	62	56	97·4% (93·6–99·0)		47·5% (38·7–56·4)		70·9% (64·5–76·6)		93·3% (84·1–97·4)	
Age groups (years)												
0–4	72	4	28	27	94·7% (87·2–97·9)	..	49·1% (36·4–61·9)	..	72·0% (62·5–79·9)	..	87·1% (71·2–94·9)	..
5–9	42	0	15	14	100% (91·6–100)	..	48·3% (31·4–65·6)	..	73·7% (61·0–83·4)	..	100% (78·5–100)	..
10–14	35	0	19	15	100% (90·1–100)	0·12	44·1% (28·9–60·6)	0·90	64·8% (51·5–76·2)	0·54	100% (79·6–100)	0·13
Immunosuppression												
None to advanced	59	1	32	21	98·3% (91·1–99·9)	..	39·6% (27·6–53·1)	..	64·8% (54·6–73·9)	..	95·6% (78·2–99·8)	..
Severe†	54	3	12	15	94·7% (85·6–98·2)	0·57	55·6% (37·3–72·4)	0·26	81·8% (70·9–89·3)	0·031	83·3% (60·8–94·2)	0·46
Nutritional status												
Severe acute malnutrition‡	67	1	24	24	98·5% (92·1–99·9)	..	50·0% (36·4–63·6)	..	73·6% (63·8–81·6)	..	96·0% (80·5–99·8)	..
No severe acute malnutrition	84	3	38	32	96·6% (90·4–98·8)	0·79	45·7% (34·6–57·3)	0·79	68·9% (60·2–76·4)	0·54	91·4% (77·6–97·0)	0·86
ART at inclusion												
On ART	91	2	40	41	97·9% (92·5–99·4)	..	50·6% (40·0–61·2)	..	69·5% (61·1–76·7)	..	95·4% (84·5–98·7)	..
Not on ART	46	0	19	9	100% (92·3–100)	0·81	32·1% (17·9–50·7)	0·14	70·8% (58·8–80·4)	0·98	100% (70·1–100)	1·0
Country												
Côte d'Ivoire	18	0	2	6	100% (82·4–100)	..	75·0% (40·9–92·9)	..	90·0% (69·9–97·2)	..	100% (61·0–100)	..
Mozambique	17	1	11	11	94·4% (74·2–99·7)	..	50·0% (30·7–69·3)	..	60·7% (42·4–76·4)	..	91·7% (64·6–99·6)	..
Uganda	49	1	25	8	98·0% (89·5–99·9)	..	24·2% (12·8–41·0)	..	66·2% (54·9–76·0)	..	88·9% (56·5–99·4)	..
Zambia	67	2	24	31	97·1% (90·0–99·2)	0·75	56·4% (43·3–68·6)	0·0099	73·6% (63·8–81·6)	0·11	93·9% (80·4–98·3)	0·85

A positive score is defined as ≥100 and a negative score as <100. ART=antiretroviral therapy. PAANTHER=Pediatric Asian African Network for Tuberculosis and HIV Research. TDA=treatment decision algorithm. *Two-sample, three-sample, or four-sample test for equality of proportions without continuity correction, depending on the number of subgroups. †WHO definition of severe immunosuppression: <25% CD4 cells in children aged <11 months, <20% CD4 cells in children aged 12–35 months, <15% CD4 cells in children 36–59 months, and <200 cells per mm^3 or < 15% CD4 cells in children older than 5 years. ‡Weight-to-height Z score less than –3 SD in children younger than 5 years and BMI-for-age Z score less than –3 SD in children aged 5 years and older.

Table 3: **Overall diagnostic performance of the PAANTHER TDA score in the full cohort and in subgroups**

study also highlighted challenges in accurate reporting of clinical findings in the scoring system, which calls for more user-friendly digital tools for use of TDAs.

Implementing the PAANTHER TDA in primary and secondary health-care settings is expected to bring challenges. One such challenge will be the availability of both radiography and ultrasonography in decentralised settings. Notably, owing to the low specificity of clinical features, both of these investigations contributed to improvements in the specificity of the TDA development models and derived scores by 7–20%.[9,17] Increased specificity is important in vulnerable children, such as those living with HIV, in whom the diagnosis and prompt treatment of other conditions in addition to tuberculosis is important. The specific contributions of TDA components, particularly abdominal ultrasonography and chest radiography, to treatment decisions will be addressed in future work. Expanding the implementation of the PAANTHER TDA, alongside WHO-recommended TDAs, in the health system could be challenging for health-care professionals. Clinical decision support systems, enabling the use of multiple TDAs, could help to alleviate the cognitive load on the physician and to move towards more individualised approaches in global health. In addition to supporting diagnostics, these systems could support decision making regarding the type of treatment needed—an important consideration given the introduction of a shorter treatment regimen for less severe tuberculosis in children.[24,25]

This study has limitations. First, owing to the COVID-19 pandemic and to logistical and budgetary constraints, we recruited a smaller sample than initially planned. Although we were able to reach the TDA validation criteria per protocol, this smaller sample could have biased our results, leading to less precise estimates, limited subgroup analyses, and introduced selection bias. Second, we validated the tool in tertiary referral hospitals, whereas it is intended to be implemented mostly in secondary health-care settings. The use of tertiary settings could have positively affected the feasibility, turnaround time to results, and diagnostic accuracy compared with routine conditions in lower health-care settings. Third, we did not conduct qualitative assessments of acceptability and feasibility from the clinician's perspective, two aspects that are considered essential in the evidence requested by WHO to inform the GRADE process for guideline development.[26] Fourth, the classification process for the reference standard could have contributed to biased estimates of the prevalence of tuberculosis and hence the diagnostic accuracy of the PAANTHER TDA. Fifth, we did not collect data on the screening step, and are therefore unable to determine how this algorithm integrates with the WHO-recommended four-symptom screen that targets acute symptoms.[24] Finally, although the 75% negative predictive value was prespecified in our protocol, it is a pragmatic and context-specific threshold for this validation study, and should be interpreted with caution when comparing across settings. Participants were recruited from four sub-Saharan countries, which could limit generalisability to other settings.

Despite improved access to ART, an increase in tuberculosis screening through the WHO-recommended four-symptom screen, and increased access to urine lipoarabinomannan testing at the point of care, children living with HIV remain at high risk of developing tuberculosis, of being undiagnosed, and of tuberculosis-related mortality. The PAANTHER TDA, which has been specifically developed—and now validated—for children living with HIV with presumptive tuberculosis, aims to guide clinicians through a standardised process for improved diagnosis and subsequent access to treatment. This study provides evidence for the external validation of tuberculosis TDAs as requested by WHO, and shows that the PAANTHER TDA has the potential to have a substantial impact on public health through its widescale use, by HIV and tuberculosis programmes, in children living with HIV. Given its current performance, with a sensitivity above the WHO target for diagnostic tests but suboptimal specificity, the PAANTHER TDA could be improved by including the analysis of biomarkers, such as urine lipoarabinomannan or a host–response immunological biomarker, or by recalibrating scores and making adjustments to account for the local context and the availability of diagnostic resources, such as microbiological analysis or ultrasonography. The reading of radiographs or point-of-care ultrasonographs by artificial intelligence could make these approaches more widely available. Validating new versions of the TDA might warrant novel approaches to shorten the time for evidence generation, allowing more rapid transfer of scientific evidence into policy and practice and enabling an impact on tuberculosis-related mortality in children.

Contributors

OM, MB, and EW conceived and designed the study and led the study at the international level. CR coordinated study implementation at the international level. Practical study implementation was coordinated by NN in Uganda, PS in Zambia, SC in Mozambique, and EK in Côte d'Ivoire, under scientific leadership from JM-A, CC, CK, and RM, respectively. ACH provided scientific guidance and expertise through the scientific advisory board. JM-A, CC, RM, DN, BN, EM, MAF, DR, and GM implemented the study and enrolled participants. JAS and APS served on the international expert review committee and classified children. MHTNN did the statistical analysis. CK, OM, MHTNN, MB, and EW contributed to the interpretation of the results. CK wrote the first draft of the manuscript, which was reviewed and approved by all authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Equitable Partnership Declaration

The authors of this paper have submitted an Equitable Partnership Declaration (appendix 4). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of The Lancet Group's broader goal to decolonise global health.

See Online for appendix 4

Declaration of interests

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Research on AIDS and Viral Hepatitis, the US Agency for International Development, the Medical Research Foundation, Janssen Pharmaceuticals, and the Bill & Melinda Gates Foundation. All other authors declare no competing interests.

Data sharing

Individual-participant data related to the reported results, including data on all presented variables, will be made available via a secure repository. Access will be granted to researchers who submit a methodologically sound proposal to the corresponding author, subject to review and approval by the study steering committee and the signing of a data access agreement.

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