



Effect of decentralising childhood tuberculosis diagnosis to primary health centre versus district hospital levels on disease detection in children from six high tuberculosis incidence countries: an operational research, pre-post intervention study

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Summary

Background Childhood tuberculosis (TB) remains underdiagnosed largely because of limited awareness and poor access to all or any of specimen collection, molecular testing, clinical evaluation, and chest radiography at low levels of care. Decentralising childhood TB diagnostics to district hospitals (DH) and primary health centres (PHC) could improve case detection.

Methods We conducted an operational research study using a pre-post intervention cross-sectional study design in 12 DHs and 47 PHCs of 12 districts across Cambodia, Cameroon, Côte d'Ivoire, Mozambique, Sierra Leone and Uganda. The intervention included 1) a comprehensive diagnosis package at patient-level with tuberculosis screening for all sick children and young adolescents <15 years, and clinical evaluation, Xpert Ultra-testing on respiratory and stool samples, and chest radiography for children with presumptive TB, and 2) two decentralisation approaches (PHC-focused or DH-focused) to which districts were randomly allocated at country level. We collected aggregated and individual data. We compared the proportion of tuberculosis detection in

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children and young adolescents <15 years pre-intervention (01 August 2018–30 November 2019) versus during intervention (07 March 2020–30 September 2021), overall and by decentralisation approach. This study is registered with [ClinicalTrials.gov](https://clinicaltrials.gov), NCT04038632.

Findings TB was diagnosed in 217/255,512 (0.08%) children and young adolescent <15 years attending care pre-intervention versus 411/179,581 (0.23%) during intervention, (OR: 3.59 [95% CI 1.99–6.46], p-value<0.0001; p-value = 0.055 after correcting for over-dispersion). In DH-focused districts, TB diagnosis was 80/122,570 (0.07%) versus 302/86,186 (0.35%) (OR: 4.07 [1.86–8.90]; p-value = 0.0005; p-value = 0.12 after correcting for over-dispersion); and 137/132,942 (0.10%) versus 109/93,395 (0.11%) in PHC-focused districts, respectively (OR: 2.92 [1.25–6.81]; p-value = 0.013; p-value = 0.26 after correcting for over-dispersion).

Interpretation Decentralising and strengthening childhood TB diagnosis at lower levels of care increases tuberculosis case detection but the difference was not statistically significant.

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Keywords: Decentralisation; Child; Tuberculosis; Diagnosis

Research in context

Evidence before this study

We searched PubMed for decentralization of TB services from Jan 1 2000 to Dec 31 2022, with the terms ((decentral*[Title]) AND (TB [Title] OR tb [Title])) AND (servic*[Title] OR child*[Title]) AND ("2000/01/01" [Date-Entry]: "2022/12/31" [Date-Entry])) restricted to English. This search yielded 15 articles; studies that were not focused on decentralizing childhood TB services were excluded leaving 2 studies. One study showed a positive impact on TB detection while one study showed increased screening but not diagnosis of multidrug resistant TB. These studies demonstrating the positive impact of decentralizing TB services were limited to one country and geographical region. A study by Zawedde et al. in Uganda using a Before-and-after analysis showed that the proportion of child TB among all TB notified increased from 8.8% to 15%. Another study by Seddon et al. showed that decentralized care led to an increased number of child contacts being evaluated for MDR TB. None of the published studies addressed the important question of what, where and how much to decentralize while considering the health system structures and task shifting. In 2022, WHO recommended decentralised models of care to deliver TB services to children and adolescents. The recommendation referred to enhancing child and adolescent TB services at the peripheral health level nearer to the communities alongside the specialised paediatric TB services at higher levels. The WHO guideline development group rated the overall certainty of evidence as "very low" and emphasized key implementation considerations to decentralise TB services.

Added value of this study

This multi-country implementation study using a pre-post design assessed the effect on TB detection among sick children by decentralizing a comprehensive childhood TB

diagnosis package at primary health centres (PHC) and/or district hospital (DH) levels in districts from six countries with high or very TB incidence using two decentralised approaches. Implementing systematic screening for TB among sick children <15 years attending care, and a full clinical evaluation, Ultra testing of NPA and stool or expectorated sputum, and chest X-Ray using a standardised approach in those identified with presumptive TB led to nearly tripled the detection of children with TB as compared to pre-intervention data. After correcting for overdispersion the difference between the pre- and post-intervention TB detection was not statistically significant due to the variability in the contexts of the different countries. The DH-focused approach had a larger effect on the detection of children with TB than the PHC-focused approach. This study provides evidence across several countries with varying health systems strength, on the feasibility and effectiveness of decentralising childhood TB diagnosis.

Implications of all the available evidence

Together with evidence from previous studies assessing the feasibility of decentralising a single component, the effectiveness and feasibility of decentralising a comprehensive childhood TB diagnosis package in different settings and health systems further strengthens evidence supporting the WHO recommendation on decentralising childhood TB services. Decentralising childhood TB diagnosis is likely to reduce the gap between the number of estimated TB in children and the number notified to WHO, but the implementation of the decentralisation needs to be adapted to the relative low frequency of childhood TB and limited resources available in peripheral setting in order to maximize the access of children to molecular testing and Chest X-ray.

Introduction

The burden of childhood tuberculosis (TB) in children and young adolescents (aged below 15 years) is high worldwide, with an estimated 1.1 million new tuberculosis cases among children and 209,000 deaths in 2021.¹ Between 2018 and 2021, only 54% of the estimated childhood tuberculosis cases were notified to the World Health Organisation (WHO).¹

Low detection of tuberculosis in children is classically attributed to the difficulty to collect sputum in young children and to the low yield of current tuberculosis microbiological tests, due to the paucibacillary nature of tuberculosis in children.^{2–4} Alternative sputum specimen collection methods such as induced sputum or gastric aspirate are either poorly tolerated by children or difficult to implement in resource-limited settings. Another important factor for low detection of TB in children is structural. Childhood tuberculosis services are mostly centralized at high levels of care, thus poorly accessible to most children living in high incidence and resource-limited countries. Child-adapted respiratory specimen collection methods and rapid molecular testing are often lacking at lower levels of care. Chest X-ray, a useful tool for diagnosis of non-microbiologically confirmed tuberculosis, is often only available at referral hospitals, not affordable to patients, of poor quality and inadequately interpreted. In a survey of 15 secondary hospitals in Kenya, only 2% of children presenting with presumptive tuberculosis benefited from microbiological evaluation and a chest X-Ray.⁵ Few healthcare workers at district level are trained on childhood TB diagnosis resulting in low awareness of childhood TB and confidence in making a clinical diagnosis.

Recent advances in diagnostic approaches could contribute to improved childhood TB diagnosis at low levels of care and Clinical diagnosis of TB in children remains central. Simple symptom-based screening could identify children requiring further TB evaluation and the use of stool samples and nasopharyngeal aspirate (NPA) could improve microbiological sample collection among outpatients.⁶ Testing of NPA and stool samples with the newly developed rapid molecular assay Xpert MTB/RIF Ultra (Ultra; Cepheid, Sunnyvale, CA, USA), was recently recommended by WHO for the diagnosis of pulmonary TB in children.⁷ Combining NPA and stool testing using Xpert MTB/RIF achieves similar detection yield as gastric aspirates or induced sputum samples.^{8,9} Furthermore, there is evidence that the GeneXpert machines can be decentralized in peripheral centres using the battery-operated GeneXpert G1 Edge device.^{10,11} Lastly, simple digital system added to existing radiography could contribute to solve the problem of poor-quality chest X-ray, largely due to poor quality of reagents, and facilitate the interpretation and the transfer of images for double reading and quality assessment.

WHO recently recommended that decentralised models of care may be used to deliver TB services to

children and adolescents in high TB incidence settings.⁷ This was a conditional recommendation with a low level of certainty due to limited high quality evidence. Providing evidence on the effect of decentralising childhood TB diagnosis to district hospitals (DH)- and primary health centres (PHC)-levels and sharing of experience on diagnosis components to be decentralised is expected to contribute to informed decision-making by national TB programs (NTPs) in resource-limited settings.

In this study we assessed the effect of deploying a comprehensive childhood TB diagnosis package on TB detection at DH and PHCs in six high TB incidence and resource-limited countries. We also compared the uptake of different components of the diagnostic package along the cascade of TB care within two specific decentralisation approaches.

Methods

Study design and setting

The methods adhere to the WHO operational reporting guidelines.¹² We conducted an operational research study using a pre- and post-intervention cross-sectional design in two rural or semi-urban districts of six countries with high TB incidence (100–300/100,000 population, Cameroon, Côte d'Ivoire, Cambodia) or very high TB incidence (>300/100,000 population, Mozambique, Sierra Leone Uganda). The intervention was executed at two levels: at patient-level where a comprehensive childhood TB diagnosis package was implemented, and at health systems level where two distinct decentralisation approaches for deploying the patient-level intervention were randomly assigned to districts and compared. The two decentralisation approaches included (Fig. 1): i) the DH-focused approach in which the DH implemented the diagnosis package, while PHCs implemented TB screening only and referred children with presumptive TB to DH for further diagnostic assessment, and ii) the PHC-focused approach in which both the DH and PHCs implemented the childhood TB diagnosis package, except for CXR that was available at DH only. Two separate districts were selected to prevent risk of spillover effect between the two approaches. In each country, the two districts were randomly assigned to either the DH or PHC-focused approach based on a district randomization done by the central statistician stratified by country, at mid of the observation period.

Participating districts were selected with each country NTP, based on a baseline assessment of district capacities and on pre-defined selection criteria.¹³ Overall the study was implemented in 12 DH—of which 10 had analogue radiography available prior to the study; and 47 PHCs—of which 40 (85%) were rural, and 16 (34%) were TB diagnostic and treatment units (see [Supplementary Appendix](#)).

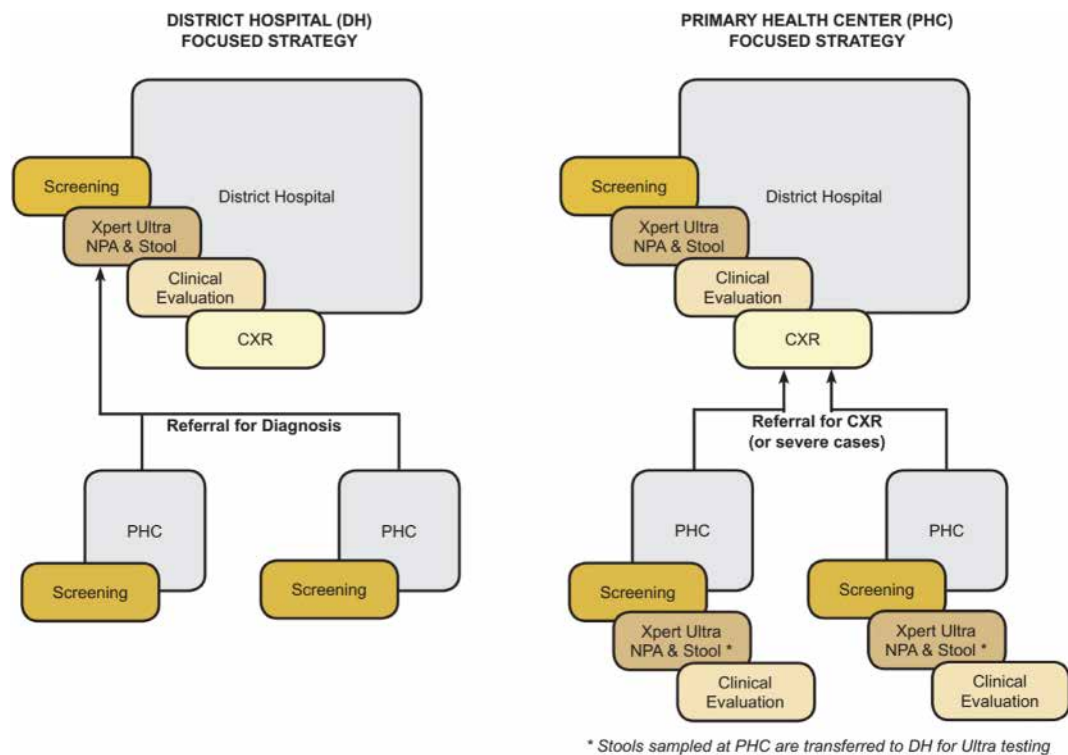


Fig 1: Study decentralisation approaches and health facility levels. DH focused strategy in which the PHCs only screen and refer presumptive TB to DH but the DH conducts screening, systematic CXRs, Xpert ultra on stool and NPA, and clinical evaluation for TB. PHC focused strategy in which at the PHC screening, xpert ultra testing on NPA and clinical evaluation are performed. Participants are referred to the DH for CXR when indicated and the collected stool is referred to DH for testing. DH, District Hospital; PHC, Primary Health Centre; NPA, Nasopharyngeal aspirate; CXR, Chest X-ray.

The comprehensive childhood TB diagnosis package, consisted of; 1) systematic screening for TB among sick children and young adolescents <15 years attending care, and, for those identified with presumptive TB: 2) a full clinical evaluation, 3) microbiological testing of NPA and stool or expectorated sputum using Ultra, and 4) chest X-Ray using a simplified and standardized interpretation approach.

The study comprised: 1) pre-intervention (01 August 2018–30 November 2019); an observation period in which we documented 3-month prospective and 9-month retrospective facility attendance and TB detection, 2) a lead-in phase for district and health facility set-up and capacity building, and 3) an intervention period (07 March 2020–30 September 2021) during which we decentralized the comprehensive childhood TB diagnosis package and documented TB diagnosis at facility- and at individual-level. The start and end dates of periods varied across countries. The study included a nested prospective cohort to assess the diagnostic performance of the patient-level intervention and an implementation research component (data not presented).

During the observation period, field research assistants collected aggregated data on children attendance

from Outpatient department registers and TB diagnosis from unit TB registers, without interfering with the routine childhood TB diagnosis processes. Extracted aggregated data were recorded in paper study forms. The data was checked and verified NTP District TB focal person and country project managers. During the lead-in phase, we set up clinical and coordination study teams, equipment, patient and sample flow systems, and trained health care workers on TB screening, clinical diagnosis, NPA and stool sample collection, Ultra and CXR interpretation. Simple digital system and quality assurance of CXR reading by national re-readers was also set-up.

During the intervention period, the comprehensive childhood TB diagnosis package was implemented within routine programmatic setting, without hiring of any additional staff. Sick children were screened for presumptive TB by either a healthcare worker or a community health volunteer at the health facility outpatient department entry point. At DH, children with presumptive TB were fully evaluated for TB and those at PHCs were either i) referred to the DH for full diagnostic assessment in DH-focused districts, or ii) assessed on site in PHC-focused districts. In

DH-focused districts, in PHCs that were already diagnosing TB before the study intervention, only children not diagnosed as per routine were referred to the DH for further evaluation. The study strengthened existing referral systems and provided no funds for transport to the DH at the initial visit.

Once consent and assent for enrolment of children with presumptive tuberculosis, was obtained, children had NPA collected immediately and were provided a container for stool samples or expectorated sputum in older children. NPA and expectorated sputum were tested with Ultra at the PHC using GeneXpert G1 Edge battery-operated devices or at DH laboratory using regular GeneXpert 4-module devices. Stool samples collected at PHCs were referred to the DH for Ultra testing after specimen processing using a centrifuged-based sucrose floatation method. Children had a clinical evaluation and those enrolled at DH a systematic chest X-Ray. Children were initiated on TB treatment as per national guidelines with support of diagnosis algorithms adapted from the Uganda TB guidelines.¹⁴ Children had another clinical assessment at day 7. At PHC, those not diagnosed with TB whose symptoms persisted at day 7 were referred to DH for CXR with transportation costs covered by the study.

Support supervision visits were conducted jointly by NTP and country research units to oversee study activities, identify challenges and discuss solutions with health facility teams. Clinical mentoring visits were conducted alongside supervision visits to sustain clinical skills through patient and CXR discussions.

All sick children aged below 15 years were included in the analysis of the effect on TB detection. Children with presumptive TB and parental/guardian consent as well as individual assent, as per national ethics guidelines, obtained were enrolled for individual data collection. We excluded children who had received TB treatment in the previous 6 months. Presumptive TB was defined by a positive TB screening (either cough for ≥ 2 weeks, fever for ≥ 2 weeks, documented weight loss, or history of TB contact with any duration of cough) or by clinician's decision, irrespective of the mentioned screening criteria.

Outcomes

The primary outcome for the study was the proportion of children with TB detected among sick children attending outpatient services overall. Secondary outcomes for comparing decentralization approaches included the proportion of i) children screened for TB among sick children; ii) presumptive TB among children screened; iii) children with TB detected among children with presumptive TB; iv) enrolled children with presumptive TB receiving the different components of the diagnostic package; v) children with positive Ultra; vi) children initiating TB treatment among TB

diagnosed; and vii) time from TB positive screening (enrolment) to treatment initiation.

Statistical analysis

We estimated the study power based on an estimated number of 260,000 sick children attending outpatient departments of the participating health facilities at study period (observation and intervention), assuming the following estimates: 10% presumptive TB among sick children, 20% TB among presumptive TB, 20% TB detection pre-intervention and an increase to 50% post-intervention, i.e., TB detection in sick children increasing from 0.4% to 1.0%, and an intra-class correlation (ICC) of 0.005. With a significance level of 0.05, and with the estimated attendance, we would have >0.99 power to show the expected difference of the primary endpoint.

We analysed the primary and secondary outcomes using unadjusted comparisons using Pearson's chi-squared test and adjusted comparison generalized linear mixed effects model (GLMM) with binomial function. For the primary outcome analysis, the model included study period (12-months observation *versus* 12-months intervention) as fixed effect, and facility, districts, and countries as random effects to account for repeated measures and multi-level (countries, districts, sites) study design. For the secondary endpoint analyses comparing the two decentralisation approaches, the model included decentralisation approaches as fixed effects, and districts and countries as random effects. Sites-level random effect was added if there was significant effect on the outcome. We systematically verified for over-dispersion to account for greater variability in data than what would be expected in a binomial distribution and used quasi-binomial model when over-dispersion occurred.¹⁵

We conducted *post hoc* analyses of our study outcomes by levels of facility, i.e. PHC-level versus DH-level instead of PHC-focused versus DH-focused approaches to further explain the variability of the primary outcome results between countries and between decentralisation approaches. We also estimated *post-hoc* our study power using the observed attendance, proportion of children with TB, and ICC calculated using a one-way ANOVA.

A significance level of 0.05 was used for all analyses. No imputation was done and all analyses were complete case analyses. There was no strategy to mitigate impact of missing data. Analyses were done using the R software 4.1.2.

The study protocol was approved by the WHO's and the sponsor's (Inserm) Ethics Review Committees, as well as the country ethics committees (See Supplementary material). Administrative clearance was obtained from the NTPs, districts and the institutions of the participating countries. This study is registered with clinicaltrials.gov (NCT04038632).

Role of the funding source

The study funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

During the pre-intervention period 255,512 children attended care in the 59 participating health facilities, including 122,570 and 132,942 in DH-focused and PHC-focused districts, respectively. During the intervention period from 7 March 2020 to 31 September 2021, with a 3-month study interruption due to COVID-19 from April 2020 to June 2020, 177,166 children attended care, including 86,367 and 90,799 in DH-focused and PHC-focused districts, respectively (Table 1).

Overall, 217/255,512 (0.08%) children were diagnosed with TB pre-intervention and 419/177,166 (0.24%) post-intervention (OR: 3.60; 95% CI: 2.00–6.48; p-value < 0.0001; p-value = 0.054 after correcting for overdispersion). Facility attendance and children with TB detected in pre-intervention and intervention periods varied widely across countries (Supplement, Table S1).

In DH-focused districts, 80/122,570 (0.07%) and 311/86,367 (0.36%) children were diagnosed with TB pre-intervention and post-intervention, respectively (OR: 4.07; 95% CI: 1.85–8.91; p-value = 0.0005; p-value = 0.122 after correcting for overdispersion). In PHC-focused districts, 137/132,942 (0.10%) and 108/90,799 (0.12%) children were diagnosed with TB pre-intervention and post-intervention, respectively (OR: 2.92; 95% CI: 1.26–6.79; p-value = 0.013; p-value = 0.256 after correcting for overdispersion) (See country details

in Supplement, Table S1). A *posteriori* power was estimated to be 41.50%, and the ICC to be 0.015.

During the intervention period, 149,599 (84.4%) of 177,166 children attending care were screened, and 3849 (2.6%) were identified as presumptive TB (Table 2). There was no difference in screening rates (83.4% versus 85.4%, p-value = 0.281) and presumptive TB rates (2.7% versus 2.5%, p-value = 0.359) between DH-focused and PHC-focused districts. TB screening rates were above 80% in most countries. The presumptive TB rate was below 3% in all countries except Cameroon where it reached 10% (Supplement, Table S2). Among children with presumptive TB, 311 (16.3%) and 108 (5.6%) were diagnosed with TB in the DH-focused and PHC-focused districts, respectively (OR: 0.43; 95% CI: 0.21–0.87; p-value = 0.019; p-value = 0.369 after correcting for overdispersion) (Supplement, Table S2).

Overall, 1189/1910 (62.3%) children with presumptive TB in DH-focused districts and 1915/1939 (98.8%) children in PHC-focused districts were enrolled in the study. There were more children presenting with severe acute malnutrition (22.0% versus 13.9%; p-value < 0.0001) and with TB suggestive signs (81.8% versus 73.4%, p < 0.001) in DH-focused versus PHC-focused districts (Table 3). Sample collection and testing rates were similar, with 1175/1189 (98.8%) children in DH-focused districts and 1906/1915 (99.5%) children in PHC-focused districts with at least one sample collected (p-value = 0.357), and 1126 (94.7%) and 1890 (98.7%) with at least one Ultra test performed, respectively (p-value = 0.141). There were more children with Ultra positive samples in the DH-focused districts than in the PHC-focused districts [37/1126 (3.3%) versus 34/1891 (1.8%); p-value: 0.053] (Table 4). Overall, 273/1189 (23.0%) children enrolled in DH-focused districts were

	Pre-intervention		Intervention period		Variation of TB case proportion delta in point (minimum; maximum)	Unadjusted p-value ^a	Impact of decentralisation (Reference = Pre-intervention) ^b		
	Facility attendance	TB cases n (%)	Facility attendance	TB cases n (%)			OR (95% CI)	p-value	Corrected p-value for overdispersion
Overall	255,512	217 (0.08)	177,166	419 (0.24)	0.16 (–0.22; 3.22)	<0.0001	3.60 (2.0–6.48)	<0.0001	0.054
Cambodia	32,837	14 (0.04)	18,441	18 (0.1)	0.06 (–0.13; 3.22)	0.100	3.97 (1.89–8.35)	0.0003	0.142
Cameroon	8114	15 (0.2)	6866	29 (0.4)	0.2 (–0.22; 1.27)	0.045	2.30 (1.23–4.31)	0.009	0.170
Côte d'Ivoire	54,863	5 (0.01)	36,816	89 (0.2)	0.19 (0; 1.02)	<0.0001	24.80 (10.07–61.10)	<0.0001	0.0008
Mozambique	67,609	114 (0.2)	37,889	89 (0.2)	0 (–0.15; 0.5)	0.111	1.50 (1.14–1.97)	0.004	0.308
Sierra Leone	39,856	43 (0.1)	31,883	152 (0.5)	0.4 (0.05; 0.6)	<0.0001	4.75 (3.37–6.70)	<0.0001	0.0004
Uganda	52,233	26 (0.05)	45,271	42 (0.09)	0.04 (–0.08; 0.2)	0.067	1.86 (1.14–3.04)	0.013	0.301
DH-focused districts	122,570	80 (0.07)	86,367	311 (0.4)	0.33 (–0.13; 1.93)	<0.0001	4.06 (1.85–8.91)	0.0005	0.122
PHC-focused districts	132,942	137 (0.1)	90,799	108 (0.1)	0 (–0.22; 3.22)	0.293	2.92 (1.26–6.79)	0.013	0.256

DH, district hospital; PHC, primary health centre. ^aPearson's chi-squared test. ^bGLMM modelling impact of decentralisation approach.

Table 1: Comparison of tuberculosis case detection between pre-intervention and intervention periods—overall, by country and by DH-focused or PHC-focused decentralisation approach.

	DH-focused approach n (% on upper level)	PHC-focused approach n (% on upper level)	Unadjusted p-value ^a	Impact of decentralisation approach (Ref = DH-focused) ^b		
				OR (95% CI)	p-value	Corrected p-value for overdispersion
Facility attendance	86,367	90,799				
At DHs	35,447	25,180				
At PHCs	50,920	65,619				
Screened	72,036 (83.4)	77,563 (85.4)	<0.0001	4.32 (0.30, 61.61)	0.281	0.929
At DHs	28,585 (80.6)	19,686 (78.2)				
At PHCs	43,451 (85.3)	57,877 (88.2)				
Presumptive TB	1910 (2.7)	1939 (2.5)	0.067	0.80 (0.51, 1.28)	0.359	0.872
At DHs	1099 (3.8)	666 (3.4)				
At PHCs	811 (1.9)	1273 (2.2)				
TB cases	311 (16.3)	108 (5.6)	<0.0001	0.43 (0.21, 0.87)	0.019	0.369
At DHs	249 (22.5)	66 (9.7)				
At PHCs	62 (7.7)	42 (3.4)				

DH, district hospital; PHC, primary health centre. ^aPearson's chi-squared test. ^bGLMM modelling impact of decentralisation approach.

Table 2: Screening to diagnosis cascade during the intervention period by decentralisation approach (aggregated data).

diagnosed with TB versus 106/1915 (5.5%) in the PHC-focused districts (p-value: <0.0001), with 37/273 (3.1%) microbiologically confirmed TB in DH-focused districts and 34/106 (1.8%) in PHC-focused districts. TB detection rates ranged between 5.9% in Cameroon (40/677) and Uganda (43/732), and 32.7% (133/407) in Sierra Leone (Supplement, Table S3).

In facility level analysis, systematic screening rates were similar in DH and PHCs (79.6% versus 87.0%; p-value = 0.618) but there were higher rates of presumptive TB at DH compared to PHCs (3.7% versus 2.1%; p-value = 0.0001) (Table 5). Overall, the 1936 children enrolled at DH had more clinical TB features than the 1168 children enrolled at PHC, with higher

	Overall		DH-focused approach		PHC-focused approach		p-value
	Available in N (if #N')	n (%) (N' = 3104)	Available in N (if #N')	n (%) (N' = 1189)	Available in N (if #N')	n (%) (N' = 1915)	
Age (median)	3094	3.75 (1.33–7.42)	1189	3.54 (1.33–7.17)	1915	3.83 (1.33–7.65)	0.336
Age <5 years	3094	1813 (58.6)	1184	716 (60.5)	1910	1097 (57.4)	0.095
Gender female		1490 (48)		557 (46.8)		933 (48.7)	0.310
Gender male		1614 (52.0)		632 (53.2)		982 (51.3)	0.310
First care seeking facility level							<0.0001
District hospital		1555 (50.1)		808 (67.9)		747 (39.0)	
Primary health centre		1549 (49.9)		381 (32.0)		1168 (61.0)	
Severe acute malnutrition ^a	3074	522 (16.8)	1180	259 (22.0)	1894	263 (13.9)	<0.0001
WHZ <-3 SD (age <5 years)	1732	303 (9.8)	695	157 (22.6)	1037	146 (14.1)	<0.0001
MUAC <115 (age 6–59 months)	1502	216 (7.0)	588	121 (20.6)	914	95 (10.4)	<0.0001
BMI for age Z score <-3 SD (age ≥5 years)	1280	141 (4.5)	468	62 (13.3)	812	79 (9.7)	0.0528
TB contact history		990 (31.9)		492 (41.4)		498 (26.0)	<0.0001
Contact with smear or Xpert positive case in the previous year		644 (20.8)		312 (26.2)		332 (17.3)	<0.0001
Cough >2 weeks		1956 (63)		850 (71.5)		1106 (57.8)	<0.0001
Unremittent cough	2521	1303 (51.7)	981	523 (53.3)	1540	780 (50.6)	0.192
Fever >2 weeks		1109 (35.7)		578 (48.6)		531 (27.7)	<0.0001
Lethargy/reduced appetite		831 (26.8)		503 (42.3)		328 (17.1)	<0.0001
Weight loss documented	3103	1085 (34.9)		533 (44.8)	1914	552 (28.8)	<0.0001
TB symptoms per child (med (IQR))		2 (1–4)		3 (1–4)		2 (1–3)	<0.0001
At least 1 TB symptom ^b		2801 (90.2)		1072 (90.2)		1729 (90.3)	0.907

^aDefined as WHZ <-3 SD in those aged ≤5 or BMI for age <-3 SD in those aged >5 years, or MUAC <115 in those aged 6–59 months. ^bCough, Fever, Weight loss, Lethargy or fatigue.

Table 3: Characteristics of enrolled children (intervention period).

	DH-focused approach		PHC-focused approach		Unadjusted p-value ^a	Effect of decentralisation approach (Reference = DH- focused) ^h	
	Available in N (if #N')	n (%) (N' = 1189)	Available in N (if #N')	n (%) (N' = 1915)		OR (95% CI)	p-value
Sample collection and testing							
NPA collected		1100 (92.5)		1876 (98.0)	<0.0001	3.92 (1.00, 15.36)	0.049
Stool collected		957 (80.5)		1278 (66.7)	<0.0001	0.52 (0.10, 2.74)	0.437
Sputum collected		76 (6.4)		275 (14.4)	<0.0001	1.32 (0.19, 9.32)	0.782
Stool or sputum collected		978 (82.3)		1504 (78.5)	0.014	0.87 (0.18, 4.34)	0.869
At least 1 sample collected		1175 (98.8)		1906 (99.5)	0.043	1.57 (0.60, 4.14)	0.357
≥2 samples collected		925 (77.8)		1488 (77.7)	0.987	1.09 (0.22, 5.35)	0.914
≥1 specimen tested with Ultra		1126 (94.7)		1890 (98.7)	<0.0001	1.54 (0.87, 2.72)	0.141
Ultra positive result on any sample	1126	37 (3.3)	1891	34 (1.8)	0.013	0.60 (0.36, 1.01)	0.053
Time to 1st Xpert result	1126	1 (0.3) ^a	1890	0 (0.1) ^b	<0.0001	1.63 (0.97, 2.74)	0.066
Clinical evaluation							
Clinical evaluation performed ^c		1189 (100)		1915 (100)	NA	NA	NA
Presumptive TB clinical features ^f		1018 (85.6)		1529 (79.8)	<0.0001	0.46 (0.15, 1.38)	0.166
Presumptive TB clinical features except weight loss		973 (81.8)		1406 (73.4)	<0.0001	0.35 (0.06, 2.06)	0.247
D7 visit done		665 (55.9)		1550 (80.9)	<0.0001	5.70 (1.76, 18.46)	0.004
Still symptomatic at day 7	663	241 (36.4)	1550	575 (37.1)	0.775	0.53 (0.11, 2.44)	0.414
Chest X-ray (CXR)							
CXR done		1011 (85.0)		625 (32.6)	<0.0001	0.01 (0.001, 0.08)	<0.0001
CXR result interpreted		1011 (85.0)		625 (32.6)	<0.0001	0.01 (0.001, 0.08)	<0.0001
CXR suggestive of TB	1011	318 (31.5)	625	92 (14.7)	<0.0001	0.47 (0.16, 1.41)	0.180
TB diagnosis and treatment							
TB diagnosed		273 (23.0)		106 (5.5)	<0.0001	0.19 (0.09, 0.42)	<0.0001
TB microbiologically diagnosed		37 (3.1)		34 (1.8)	0.022	0.61 (0.36, 1.02)	0.062
TB clinically diagnosed		236 (19.9)		72 (3.8)	<0.0001	0.15 (0.06, 0.43)	0.0003
TB treatment initiated		255 (21.5)		87 (4.5)	<0.0001	0.15 (0.07, 0.36)	<0.0001
Time to treatment initiation (days)	255	1 [0-4] ^c	87	2 [0-7] ^d	0.125	0.83 (0.54, 1.29)	0.400

NA, not applicable. ^aRange (min, max) = (0, 374). ^bRange (min, max) = (-238, 59). ^cRange (min, max) = (0, 193). ^dRange (min, max) = (0, 385). ^eAt least one TB sign assessed. ^fPresumptive TB clinical features defined as having at least one of the following symptoms: Cough more than 2 weeks, Fever more than 2 weeks, Night sweat, Lethargy, Weight loss. ^gPearson's chi-squared test or Wilcoxon test. ^hGLMM modelling impact of decentralisation approach.

Table 4: Uptake and results of the diagnostic evaluation process in enrolled children by decentralization approach.

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proportions of severe acute malnutrition, cough >2 weeks, and history of TB exposure. Samples were collected in more than 98% of children both at DH and PHC, but more children had positive Ultra at DH than at PHC (58/1860, 3.1% versus 13/1157, 1.1%, p-value = 0.005). Additionally, there were more children clinically diagnosed with TB at DH than at PHC, 280/1936 (14.5%) versus 28/1168 (2.4%) (p-value = 0.0002).

Discussion

This multi-country implementation study showed that decentralising childhood TB diagnosis at PHC and DH levels increased detection of children with TB. Overall, the DH-focused approach had a larger effect on detection of children with TB than the PHC-focused approach.

Implementing a comprehensive childhood TB diagnosis package at DH and PHC level nearly tripled the detection of children with TB with variability between

countries. The use of systematic screening at facility entry-point to identify children with presumptive TB together with the strengthening of clinical skills and better access to microbiological tests and CXR contributed to reducing missed opportunities for diagnosis. Overall, our findings are similar to those of the DETECT TB project that showed increase in proportions of children among all TB notification from 9% to 15% after strengthening and decentralisation of TB services within routine integrated child health services in Uganda.¹⁶ Unlike DETECT TB that was implemented in a few sites in one country, our study was deployed in six countries with different TB incidences and health systems organization. At country level, the effect of the intervention was larger in countries with no or limited prior decentralization of childhood TB services, such as in Cameroon, Côte d'Ivoire and Sierra Leone where there were almost no childhood TB screening activities at PHC level. On the other hand, in Mozambique and

	District hospital		Primary health centre		Unadjusted p-value ^e	Effect of type of facility (Ref = DH) ^f		
	N	n/N (%)	N	n/N (%)		OR (95% CI)	p-value	Corrected p-value for overdispersion
Diagnosis cascade (aggregated data)								
OPD attendance		60,627		116,539				
Screened	60,627	48,271 (79.6)	116,539	101,328 (87.0)	<0.0001	1.21 (0.58, 2.51)	0.618	0.888
Presumptive TB	48,271	1765 (3.7)	101,328	2084 (2.1)	<0.0001	0.38 (0.23, 0.63)	0.0001	0.254
Treated for TB	1765	315 (0.52)	2084	104 (0.09)	<0.0001	0.30 (0.23, 0.39)	<0.0001	<0.0001
Characteristics of children enrolled (individual data)		(N' = 1936)		(N' = 1168)				
Age <5 years	1929	1148 (59.5)	1165	665 (57.0)	0.169			
Gender female		907 (46.8)		583 (49.9)	0.098			
Gender male		1029 (53.2)		585 (50.1)	0.098			
SAM ^g	1917	386 (20.1)	1157	136 (11.8)	<0.0001			
TB contact history		766 (39.6)		224 (19.2)	<0.0001			
Contact with smear positive adult in the previous year		488 (25.2)		156 (13.4)	<0.0001			
Cough >2 weeks		1310 (67.7)		646 (55.3)	<0.0001			
Fever >2 weeks		828 (42.8)		281 (24.1)	<0.0001			
Lethargy/reduced appetite		606 (31.3)		225 (19.3)	<0.0001			
Weight loss documented		729 (37.6)	1167	356 (30.5)	0.0001			
Sample collection and testing								
NPA collected	1867	1829 (98.0)	1150	1147 (99.7)	0.0001	4.61 (0.62, 34.36)	0.136	NA
Stool collected		1506 (77.8)		729 (62.4)	<0.0001	0.83 (0.27, 2.54)	0.739	NA
At least 1 sample collected		1917 (99.0)		1164 (99.7)	0.073	2.05 (0.67, 6.27)	0.211	NA
≥2 samples collected		1517 (78.4)		896 (76.7)	0.306	1.11 (0.43, 2.87)	0.824	NA
≥1 specimen tested with Ultra		1859 (96.0)		1157 (99.1)	<0.0001	1.89 (0.95, 3.75)	0.068	NA
Ultra positive result on any sample	1860	58 (3.1)	1157	13 (1.1)	0.0007	0.40 (0.21, 0.75)	0.005	NA
Clinical evaluation								
Clinical evaluation performed ^c		1937 (100)		1168 (100)	NA	NA	NA	NA
TB suggestive clinical features ^d		1595 (82.4)		952 (81.5)	0.568	1.29 (0.43, 3.81)	0.648	NA
TB suggestive clinical features without weight loss		1521 (78.6)		858 (73.5)	0.001	1.07 (0.35, 3.25)	0.900	NA
D7 visit done		1237 (63.9)		978 (83.7)	<0.0001	5.21 (1.99, 13.67)	0.0008	NA
Still symptomatic at day 7	1228	535 (43.6)	970	281 (29.0)	<0.0001	0.32 (0.10, 1.07)	0.064	NA
CXR								
CXR done		1563 (80.7)		73 (6.3)	<0.0001	0.01 (0.01, 0.03)	<0.0001	NA
TB suggestive CXR features	1563	387 (24.8)	73	23 (31.5)	0.245	4.34 (2.39, 7.86)	<0.0001	NA
TB diagnosis and treatment								
TB diagnosed		338 (17.5)		41 (3.5)	<0.0001	0.35 (0.23, 0.52)	<0.0001	NA
TB microbiologically diagnosed		58 (3.0)		13 (1.1)	0.001	0.41 (0.22, 0.76)	0.005	NA
TB clinically diagnosed		280 (14.5)		28 (2.4)	<0.0001	0.18 (0.07, 0.44)	0.0002	NA
TB treatment initiation		313 (16.2)		29 (2.5)	<0.0001	0.16 (0.16, 0.16)	<0.0001	NA
Time to treatment initiation (days)	313	1 [0–5] ^a	29	7 [1–14] ^b	0.003	0.60 (0.39, 0.94)	0.025	NA

NA, not applicable. ^aRange (min, max) = (0, 385). ^bRange (min, max) = (0, 88). ^cAt least one TB sign assessed. ^dPresumptive TB clinical features defined as having at least one of the following symptoms: Cough more than 2 weeks, Fever more than 2 weeks, Night sweat, Lethargy, Weight loss. ^ePearson's chi-squared test or Wilcoxon test. ^fGLMM modelling impact of type of facility. ^gDefined as WHZ <-3 SD in those aged ≤5 or BMI for age <-3 SD in those aged >5 years, or MUAC <115 in those aged 6–59 months.

Table 5: Diagnosis cascade, patient characteristics and uptake by facility level.

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Uganda, children with presumptive TB could be diagnosed and treated for TB at PHC level and only complicated or severe cases were referred to DH. The variability in TB care practice, facility attendance and TB incidence may explain differences in TB detection rates between countries, as well as the data heterogeneity underlying the (need of correcting for) overdispersion.

The effect of the DH-focused approach on TB detection was higher than that of the PHC-focused approach. There are several possible explanations for our study findings. First, the screening and presumptive TB rates were similar between the two approaches and thus do not account for this finding. Second, in DH-focused districts, a large proportion of children

referred from PHC did not reach DH and most likely the sickest reached. Indeed, there were more children with TB suggestive symptoms and severe acute malnutrition, hence more likely to be diagnosed with TB, at DH than at PHC. Third, skills of medical doctors at DH for clinical assessment may account for higher TB detection than that done by clinical officers or nurses at PHC. Despite training and clinical mentoring in the study, clinicians at PHC may have not been empowered enough to initiate treatment for TB without microbiological confirmation, as implied by the higher proportion of microbiologically confirmed TB in children at PHC level (32%) compared to DH (17%). This is also likely to explain the low proportion of children started on treatment at PHC in the PHC-focused approach where the diagnosis is made by a nurse as compared to the DH-focused approach in which children with presumptive TB from PHC were referred to the DH where diagnosis was made by a doctor. Finally, all children enrolled in DH-focused districts had a CXR performed while in PHC-focused districts only children with persisting symptoms after 7 days were referred for CXR at DH; this is likely to have contributed to higher TB detection in DH-focused districts.

Contextual factors probably played a role in low TB detection in PHC-focused districts. As the intervention was deployed in a small number of health facilities per country, site-specific events related to human resources and management, might have led to variations in the implementation of the intervention and/or negatively impacted the effect of the intervention globally. The impact of the COVID-19 pandemic, including movement restrictions (with limited access to transport means, and increase in transport costs), may explain the decrease in facility attendance and the decline in the number of children detected with TB, with heterogeneous effect between and within countries.¹⁷

This study brings evidence about the feasibility and yield of different diagnostic interventions at lower levels of healthcare. Systematic screening for TB among children attending care was feasible both at DH and PHC levels. Nonetheless up to a quarter of children presenting at DH were not screened, which may indicate challenges in patient flows or constraints in implementing the simple question-based screening, in often overburdened district hospitals.¹⁸ Except in Cameroon, the presumptive TB rate after systematic screening was lower for all countries than we had hypothesized (10%). The uptake of NPA and stools collection as well as Ultra testing on NPA was high at PHC level, showing the feasibility of decentralising child-adapted sample collection and molecular testing.

Our study has limitations. First, the pre-post design has inherent weaknesses as it does not allow to distinguish between the effect of the intervention,

the effect of time, change of policy, and other confounding factors such as the COVID-19 pandemic to reliably establish the causal effect of the intervention on TB detection in children. Second, aiming to maximize the external validity of the study, we included many countries, thereby increasing heterogeneity, which contributed to increasing data overdispersion and diluted the intervention effect when we corrected for it in analysis. Third, our study included a low number of districts per country, which may have hampered documentation of country specificities as well as negatively impacted study results. Lastly, we were unable to properly document details of the standard of care for diagnosis of TB in children during the observation period hence unable to document changes in clinical practices compared to the intervention period.

Despite its limitations, our study conducted in six high TB incidence countries across different regions in Africa and in South-East Asia using an integrated approach within routine care provides key evidence to further strengthen the WHO recommendation on decentralising childhood TB services. Beyond previous studies^{10,16,19} assessing the feasibility of decentralising a single diagnostic component, we documented the effectiveness and feasibility of decentralizing a comprehensive childhood TB diagnosis package. Furthermore, considering the potential low TB detection at PHC level, the diagnostic approach chosen in our study could be further adapted depending on local resources and health systems organization and alternative hybrid decentralisation models proposed. For example, despite its low detection yield in children, decentralising Ultra testing can be highly relevant and effective for TB diagnosis in adults and thus could be integrated with other services for diagnosis or quantification of other pathogens.²⁰ Alternatively, child-adapted sample collection could be implemented at PHC with sample transportation and testing in centralized hubs at DH-level.²¹ Given the persisting poor microbiological detection yield from respiratory samples, clinical diagnosis remains the cornerstone of TB diagnosis in children. Access to CXR remains a major problem in many countries and alternative approaches using portable X-rays and computer aided detection programs need to be further evaluated for diagnosis of pulmonary TB in children. Task shifting from physicians to nurses at PHC, that was shown to be effective in the field of malaria and HIV, may be more challenging for TB in the absence of highly sensitive TB point of care test and poorly specific clinical presentation.²² Treatment decision algorithm (TDA), as recently recommended by WHO, are likely to help TB treatment decision at low level of care but warrants further research on their effectiveness and feasibility.⁷ Our cost effectiveness and budget impact analyses also provide important information for

adapting decentralization approaches and models to country resources. Additional implementation research analyses are specifically assessing the feasibility and perceived sustainability of the different diagnosis package components and evaluating implementation strategies used to deploy diagnosis at decentralised levels; these findings will be useful to NTPs in their operational and financial planning to scale-up and sustain decentralised services.

Overall, our study supports the recent WHO recommendation on decentralising TB services by providing evidence on its effect on TB detection and feasibility and showing that decentralising and strengthening childhood TB diagnosis at lower levels of care increases tuberculosis detection, especially at DH-levels accompanied by screening activities at PHC levels. The difference disappeared after adjusting for over-dispersion with marginal significance due the high variability of the TB diagnosis between the countries. Though not statistically significant, implying there could be a real effect going on, the three-fold increase in the absolute TB cases is programmatically significant. Although not shown by the effectiveness results, decentralisation at PHC level could be interesting in setting with high TB prevalence and high facility testing volumes as suggested by the cost-effectiveness results.

Contributors

OM, MB, EW conceived and designed the study. MN coordinated and contributed to the implementation of the study protocol. OM, MB, EW, AD, MS, GB, RM, J-VT, and JOG contributed to the development of the study protocol. OM, MB, and EW led the study at international level. LB and TEM led the study in Cambodia, J-VT and MB led the study in Cameroon, RM led the study in Côte d'Ivoire, CK led the study in Mozambique, EW and JM-A led the study in Uganda, AM led the study in Sierra Leone, ML and EN coordinated laboratory aspects at international level, ADL and BD coordinated study implementation in Cambodia, SKN coordinated study implementation in Cameroon, EAK coordinated study implementation in Côte d'Ivoire, SC coordinated study implementation in Mozambique, NN coordinated study implementation in Uganda. PN, LT developed the chest X-ray section and course. JP coordinated the TB-Speed project at international level. BJ conducted implementation research work. AD provided scientific guidance and expertise for the study. J-VT, JM-A, AM, CK, JM, NN, GB, ADL and SC implemented the study and enrolled participants. ST, SS, LF, KKA, IM supported study implementation in country. EB developed and maintained the study database. MH did the statistical analysis. OM and MH accessed and verified the data and prepared the report. AD, SV provided scientific expertise and guidance. OM, MN, MH, MB, AD, JOG and EW contributed to the interpretation of the results. EW wrote the first draft and all authors reviewed and approved the final version of the manuscript. OM, MB, EW were responsible for the decision to submit the manuscript.

Data sharing statement

Study data will not be publicly available. Data could be made available by the sponsor (Inserm) to interested researchers on request to the corresponding author under a data transfer agreement.

Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2024.102527>.

References

- 1 Bagcchi S. WHO's global tuberculosis report 2022. *Lancet Microbe*. 2023;4(1):e20.
- 2 Wobudeya E, Bonnet M, Walters EG, et al. Diagnostic advances in childhood tuberculosis-improving specimen collection and yield of microbiological diagnosis for intrathoracic tuberculosis. *Pathogens*. 2022;11(4):389.
- 3 Gous N, Scott LE, Khan S, Reubenson G, Coovadia A, Stevens W. Diagnosing childhood pulmonary tuberculosis using a single sputum specimen on Xpert MTB/RIF at point of care. *S Afr Med J*. 2015;105:1044–1048.
- 4 Zar HJ, Workman L, Isaacs W, et al. Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. *Clin Infect Dis*. 2012;55(8):1088–1095.
- 5 Oliwa JN, Gathara D, Ogero M, et al. Diagnostic practices and estimated burden of tuberculosis among children admitted to 13 government hospitals in Kenya: an analysis of two years' routine clinical data. *PLoS One*. 2019;14(9):e0221145.
- 6 Owens S, Abdel-Rahman IE, Balyejusa S, et al. Nasopharyngeal aspiration for diagnosis of pulmonary tuberculosis. *Arch Dis Child*. 2007;92(8):693–696.
- 7 WHO. WHO operational handbook on tuberculosis: module 5: management of tuberculosis in children and adolescents. WHO operational handbook on tuberculosis: module 5: management of tuberculosis in children and adolescents. 2022.
- 8 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):1161–1168.
- 9 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;175(5):e206069.
- 10 Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet*. 2011;377(9776):1495–1505.
- 11 Theron G, Zijenah L, Chanda D, et al. Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet*. 2014;383(9915):424–435.
- 12 Hales S, Leshner-Trevino A, Ford N, Maher D, Ramsay A, Tran N. Reporting guidelines for implementation and operational research. *Bull World Health Organ*. 2016;94(1):58–64.
- 13 Wobudeya E, Niangoran S, Borand L, et al. Childhood TB diagnostic capacities in primary healthcare facilities in high TB-burden countries: results from the TB-Speed cross-sectional descriptive survey. Hyderabad. 50th World conference on lung health of the international union against tuberculosis and lung disease (The Union). 2019.
- 14 MoH. Uganda management of tuberculosis in children; a health worker guide. 2015.
- 15 Hinde J, Demétrio CG. Overdispersion: models and estimation. *Comput Stat Data Anal*. 1998;27(2):151–170.
- 16 Zawedde-Muyanja S, Nakanwagi A, Dongo JP, et al. Decentralisation of child tuberculosis services increases case finding and uptake of preventive therapy in Uganda. *Int J Tuberc Lung Dis*. 2018;22(11):1314–1321.

- 17 Abayneh M, HaileMariam S, Asres A. Low tuberculosis (TB) case detection: a health facility-based study of possible obstacles in kaffa zone, southwest district of Ethiopia. *Can J Infect Dis Med Microbiol.* 2020;2020:7029458.
- 18 Deya RW, Masese LN, Jaoko W, et al. Yield and coverage of active case finding interventions for tuberculosis control: a systematic Review and meta-analysis. *Tuberc Res Treat.* 2022;2022:9947068.
- 19 Wei X, Liang X, Liu F, Walley JD, Dong B. Decentralising tuberculosis services from county tuberculosis dispensaries to township hospitals in China: an intervention study. *Int J Tuberc Lung Dis.* 2008;12(5):538–547.
- 20 Ndlovu Z, Fajardo E, Mbofana E, et al. Multidisease testing for HIV and TB using the GeneXpert platform: a feasibility study in rural Zimbabwe. *PLoS One.* 2018;13(3):e0193577.
- 21 Kiyaga C, Sendagire H, Joseph E, et al. Uganda's new national laboratory sample transport system: a successful model for improving access to diagnostic services for early infant HIV diagnosis and other programs. *PLoS One.* 2013;8(11):e78609.
- 22 Penazzato M, Davies MA, Apollo T, Negussie E, Ford N. Task shifting for the delivery of pediatric antiretroviral treatment: a systematic review. *J Acquir Immune Defic Syndr.* 2014;65(4):414–422.