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Effect of integrating paediatric tuberculosis services into child healthcare services on case detection in Africa: the INPUT stepped-wedge cluster-randomised trial

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ABSTRACT

Introduction Paediatric tuberculosis (TB) underdiagnosis is a critical concern. The INPUT stepped-wedge cluster-randomised trial assessed the impact of integrating child TB services into child healthcare on TB case detection among children under age 5 years.

Methods We compared the standard of care, providing TB care in specific TB clinics (control phase), with the Catalysing Paediatric TB Innovations (CaP-TB) intervention, integrating TB services across all child health services (intervention phase). 12 clusters in Cameroon and Kenya transitioned from the standard of care to the intervention at randomly assigned times. Children with presumptive TB were enrolled after obtaining their parents' consent and were followed throughout TB diagnostic procedures and treatment. Study outcomes included the rate of children with presumptive TB receiving TB investigations and that of children diagnosed with TB (the primary outcome was case detection), per thousand children under 5 years attending facilities. Generalised linear mixed Poisson models estimated the intervention's effect as adjusted rate ratios (aRR) and associated 95% CIs. Ad hoc country-stratified analyses were conducted.

Results During control and intervention phases, respectively, 121 909 and 109 614 children under 5 years attended paediatric entry points, 133 (1.1 per thousand) and 610 (5.6 per thousand) children with presumptive TB received TB investigations, and 79 and 74 were diagnosed with TB, corresponding to a case detection rate of 0.64 and 0.68 per thousand, respectively. CaP-TB significantly increased TB investigations in both countries overall (aRR=3.9, 95% CI 2.4 to 5.4), and in each. Overall, TB case detection was not statistically different between intervention and control (aRR 1.32, 95% CI 0.66 to 2.61, p=0.43). Country-stratified analysis revealed a 10-fold increase (aRR 9.75, 95% CI 1.04 to 91.84, p=0.046) in case detection with CaP-TB in Cameroon and no significant effect in Kenya (aRR 0.94, 95% CI 0.44 to 2.01, p=0.88).

Conclusion CaP-TB increased TB investigations in both study countries and markedly enhanced TB case detection in one, underlining integrated TB services' potential to address paediatric TB underdiagnosis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In order to close the tuberculosis (TB) case detection gap in children, the WHO 2022 consolidated guidelines on the management of TB in children and adolescents recommend decentralised and integrated care models of care to deliver TB services to children.

⇒ We identified only two published comparative studies on the impact of integrating TB care into child healthcare services; one documented the impact of integrating TB services in IMCI clinics in Ethiopia, and the other documented the impact of collocating TB and ART services in Zambia, both of which demonstrated limited effect on case notification.

INTRODUCTION

In 2022, it was estimated that 1.3 million children aged <15 years had tuberculosis (TB) disease worldwide, which represents about 12% of all people with TB, of whom more than a quarter lived in Africa and 40% were aged below 5 years.[1 2] The COVID-19 pandemic has had a significant impact on TB, with 2020 being the first year since 2005 to see a year-on-year increase in TB deaths,[3] and 2021 even exceeding 2020 and reaching 1.6 million deaths, back to the level of 2017.[2] Although TB incidence decreased in 2022 compared with 2021, TB still caused the deaths of 214 000 children under the age of 15 globally in 2022, including 139 000 deaths

WHAT THIS STUDY ADDS

⇒ The INPUT stepped-wedge cluster-randomised study evaluated the impact of integrating child TB services into child health entry points on TB case detection in children aged under 5 years in Cameroon and Kenya.

⇒ We found that decentralised and integrated facility-based intensified case finding significantly increased identification of children investigated for TB in both countries and increased TB case detection in one of the study countries, highlighting the potential of this intervention to address the critical gap of underdiagnosis of TB in children and the importance of contextual influences on the impact of interventions.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study's finding that integrating TB services into child healthcare services has the ability to increase TB case detection and reduce the gap in children not started on TB treatment, as also supported by previous research, emphasises the need for continued investment in decentralised and integrated models of care to deliver child TB services in Africa, ensuring early detection and effective treatment of TB in children.

among children under the age of 5, making it one of the leading causes of death among children.[1]

Children aged less than 5 years and children living with HIV (CLHIV) are at the highest risk of progressing to TB disease after infection, developing disseminated forms of TB and dying.[4–6]

Diagnosing TB in children is more challenging than in adults, primarily due to the non-specific nature of symptoms and the difficulty in obtaining microbiological confirmation. This is a result of difficulties in specimen collection and paucibacillary disease, which make molecular diagnosis techniques such as the Xpert MTB/RIF assay less sensitive.[7] These challenges in diagnosis are among the key reasons why many children with TB remain undiagnosed or unreported to national TB programmes (NTPs).[8]

In many sub-Saharan African countries, paediatric TB services are centralised at the tertiary health facilities and provided in separate TB units in a vertical, non-integrated way.[8] Additionally, limited healthcare workers' confidence in recognising childhood TB, especially in lower-level facilities where the majority of children first access care, adds to the list of barriers to the identification of children with TB disease.[9] Paediatric services such as maternal and child healthcare/under-5 services, integrated management of childhood illnesses, outpatient and inpatient clinics for children, paediatric antiretroviral therapy (ART) services and nutrition rehabilitation services may represent a first entry point for children with TB disease.[10]

The WHO 2022 consolidated guidelines on the management of TB in children and adolescents recommend the use of decentralised and integrated models of care to deliver TB services to children.[8] These recommendations are based on growing evidence from resource-limited settings that strengthening TB diagnostic capacity at the primary healthcare level as well as strengthening linkages between communities and facilities increases TB diagnosis.[11–13]

Yet, the guidelines also point out that limited data are available on the feasibility of the integration of TB care into child healthcare services and its impact on paediatric TB case detection, the cascade of TB care and treatment outcomes. WHO conducted a systematic review and found only two comparative studies that documented the impact of integrating TB services in IMCI clinics in Ethiopia,[14] or collocating TB and ART services in Zambia,[15] both of which demonstrated limited impact.

In response to the need for controlled randomised studies with robust designs that can assess the effect of the integration of TB services on TB case detection and treatment outcomes in children, we developed the Catalysing Paediatric TB Innovation project (CaP-TB). CaP-TB is a multipronged intervention aimed at enhancing the detection of paediatric TB in children under the age of 15 years across nine sub-Saharan African countries. This project focused on the integration and decentralisation of TB screening and diagnosis capabilities, coupled with community contact tracing efforts. In this report, we share the results of the 'integrating paediatric TB services into child healthcare services in Africa' (INPUT) study, which assessed the impact of the facility-based intensified case finding (a component of the CaP-TB package) on TB case detection in children under 5 years of age in Cameroon and Kenya.

METHODS

Study design

This study used a stepped-wedge cluster-randomised trial design. Clusters were composed of district or regional hospitals (the hubs) and up to two of their affiliated health centres (the spokes) referring patients or specimens to the hubs for TB services.

A total of 12 clusters in Cameroon and Kenya (six from each country) started the study under the standard of care (control phase), and four clusters (two in each country) were randomly assigned to transition to the intervention every 4 months (intervention phase) (online supplemental material 1). A transition phase of 1 month was factored in for preparations of the sites, training and logistical support.[15]

Enrolment began in May 2019, with the first four clusters transitioning to the intervention phase in October 2019 and the next randomised clusters transitioning in March 2020. The COVID-19 pandemic disrupted the third step, resulting in a study halt from April to July 2020. During this time, participants who had already been enrolled were followed as per the study protocol; however, no new participants were enrolled, and these months were not considered part of the study steps. Enrolments resumed in early August 2020, and the last clusters transitioned

in October 2020. Enrolment stopped in all clusters in March 2021.

Definitions

Children with TB signs and symptoms

Children presenting with symptoms and signs of active TB disease according to national guidelines in Cameroon and Kenya: cough, fever, night sweats, fatigue, reduced playfulness or decreased activity, weight or appetite loss or failure to thrive during the last 3 months.

Children with presumptive TB and investigated for TB

Children with TB signs and symptoms who remained symptomatic at their 2-week reassessment after an antibiotic course and warranted TB investigations. These children were eligible for enrolment in the study's prospective follow-up.

Children diagnosed with TB

Children with presumptive TB who went through clinical, sometimes radiological and microbiological investigations, and for whom the clinician made a diagnosis of TB.

Microbiologically confirmed diagnosis

This applies to children diagnosed with TB using rapid molecular tests recommended by WHO, lateral flow urine lipoarabinomannan assays, sputum smear microscopy or culture.[1]

Treatment success

Defined by WHO 2021 revised definition as the sum of 'cured' and 'treatment completed'.[16] 'Cured' applies to a patient with pulmonary TB with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy with evidence of bacteriological response and no evidence of failure. 'Treatment completed' applies to a patient who completed treatment as recommended by the national policy and whose outcome does not meet the definition of cure or treatment failure.

Moderate acute malnutrition

Weight for height z-score between 2 and 3 SD below the mean.

Severe acute malnutrition

Weight for height z-score more than 3 SD below the mean, arm circumference <110 mm or the presence of nutritional oedema.

Study sites and participants

Study sites comprised 12 district hospitals and 20 referring health centres, 32 facilities overall. Study facilities were purposively selected in collaboration with the NTPs and Ministry of Health (MoH) according to predefined criteria, and the overall number was determined according to feasibility with available resources.[17]

The study population comprised all children aged less than 5 years who presented for care at the study sites. These children served as the denominator to calculate the rates per thousand child consultations.

Children with presumptive TB who met the following eligibility criteria were enrolled in a prospective follow-up study: (1) age less than 5 years; (2) with presumptive TB as per the above definition; (3) had TB diagnostic investigations initiated; (4) committed to receive treatment in the clinic of enrolment or another INPUT study site; and (5) had parental/caregiver consent for the child to participate in the study. Children who are TB contacts but without symptoms or signs of TB disease were excluded.

Randomisation and masking

The site's stepped-wedge randomisation sequence determining when each of the sites would transition from the control to the intervention phase was generated by the study biostatistician using Stata V.15.0, with stratification by country.[17] It remained concealed from all investigators until the last month before sites were transitioned to the next step. The 1-month notice given before starting into the transition phase allowed sites to adequately prepare for the roll-out of the CaP-TB intervention. The study design did not allow the site investigators to be blinded after assignment to interventions.

Interventions

Standard of care of TB services before CaP-TB

In Cameroon, TB services were offered at secondary or tertiary hospitals and at specialised primary healthcare facilities with a physician. TB screening was not recommended nor done systematically at each entry point. Conversely, in Kenya, TB services were offered at the primary healthcare level, and TB screening was recommended at every entry point. In both countries, children identified as having presumptive TB would be referred to the TB clinic to receive TB diagnostic investigations and treatment from the TB focal person. In Kenya, Xpert MTB/RIF diagnostic testing was available as a standard of care in most district hospitals, but not in primary healthcare facilities. In Cameroon, Xpert testing was not available.

Intervention under evaluation

The CaP-TB intervention has been defined for every level of care and has been extensively described elsewhere.[17] Briefly, the subset of CaP-TB interventions assessed as part of the INPUT study included a package of healthcare worker training, supportive supervision, monitoring tools, job aids and logistical support for the integration and decentralisation of TB screening and diagnosis services into child healthcare services at the different levels of care. This included (1) integration of TB screening into all the child healthcare services usually attended by children and (2) improvement of TB diagnostic capacity through strengthened use of clinical diagnosis algorithms, training on advanced specimen collection procedures[18] and strengthened availability of Xpert testing (Xpert Ultra at the end of the intervention)

and chest X-ray (CXR) either on-site or through referral systems.

Data collection

Trained study nurses prospectively collected weekly aggregates of the overall number of children receiving services, including information on their entry points and age categories (<2 years and 2–5 years).

Additionally, study nurses checked site registers and records to identify children under the age of 5 years for whom TB signs and symptoms had been recorded, approached mothers or caregivers of children who had presumptive TB symptoms to assess the child's eligibility as per inclusion criteria and enrolled him/her after obtaining written consent. Baseline characteristics were entered in an electronic case report form (eCRF). Subsequently, as the child was investigated and potentially treated for TB, the study nurse prospectively abstracted follow-up data from TB records and entered them in the eCRF. Study termination occurred at the collection of the final TB treatment outcome 2 months after treatment completion, or for enrolled children without TB, once they had been determined not to have active TB, or at the latest, 3 months after enrolment. In case of early termination, the date and reasons (ie, relocation, withdrawal, death and loss to follow-up) were collected.

Study outcomes

Cluster-level outcomes were calculated over the aggregated number of children under age 5 years attending the child healthcare services during each study step and included, as per the definitions given above: (1) the rate of children with TB signs and symptoms per thousand child consultations; (2) the rate of children with presumptive TB and investigated for TB per thousand child consultations; and (3) the rate of children diagnosed with TB per thousand child consultations (or case detection rate, the primary study outcome).

Individual-level outcomes considering TB presumptive children investigated for TB as the denominator included the proportion of children who had a sample collected for microbiological diagnosis and the proportion of children diagnosed with TB.

Individual-level outcomes considering children diagnosed with TB as the denominator included the proportion of children with a bacteriologically confirmed diagnosis, time from symptoms onset to diagnosis (dichotomised to ≤1 versus >1 month) and proportion with treatment success.

Sample size

Sample size and power estimation were based on the primary outcome of the TB case detection rate. We assumed a TB case detection rate of 2 per thousand child consultations under the standard of care. Assuming 500 child consultations per cluster per month, an intracluster correlation of 0.001 in case detection between clusters and four clusters transitioning to the intervention every 4 months in three steps, we had more than 90% power to detect a doubling of the case detection rate due to CaP-TB intervention.[17] With these same assumptions, we expected to diagnose overall 96 children with TB under the standard of care and 192 under intervention (online supplemental material 1), which gave 80% power to detect a 20% increase in favourable TB treatment outcomes, from 70% to 90% (the secondary outcome).

Statistical methods

In a stepped-wedge study, exposed (intervention) and unexposed (standard of care) observation periods, or steps, take the place of 'arms' in parallel cluster trials.[19 20] Characteristics of the clusters were summarised in the different steps of intervention and standard of care to assess for potential selection biases and lack of balance. This included the average cluster size and variance and cluster characteristics in terms of the TB care cascade. The baseline characteristics of enrolled children, along with their TB diagnostic investigations and outcomes, were also presented according to the study phases. This allowed for the visualisation of changes before and after the intervention, as all clusters initially received the standard of care and eventually transitioned to the intervention.

Data collected during the 1-month transition phase from the standard of care to the intervention were not considered in the analysis in order to minimise contamination between study periods.

We displayed the summary statistics of TB detection rates (the primary outcome) during each step and intervention period using boxplot graphs.

To estimate the effect of the intervention on the different outcomes, we used generalised linear mixed Poisson models adjusting for the country and the time trend while also accounting for within-site clustering (the model equation is given in online supplemental material 2). Those were generated at the cluster level or at the individual level depending on the outcomes. The effect was presented as an adjusted rate ratio (aRR) and associated 95% CI. Because of important differences across countries, we also adjusted or stratified results by country when appropriate.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting of our research. Dissemination meetings involving the communities were organised at the study sites during the study closeout.

RESULTS

Study enrolments and flow

Overall, 231 523 child attendees below 5 years of age attended a consultation at the study sites during the enrolment period, of whom 1642 (0.7%) were identified as having TB signs and symptoms (figure 1). Of those, 819 (50%) were prescribed a course of antibiotics. Overall, 923/1642 (56%) of symptomatic children were

	Period	Indicator	Sequence 1 (0-1-1-1) N=4 clusters	Sequence 2 (0-0-1-1) N=4 clusters	Sequence 3 (0-0-0-1) N=4 clusters
Step 1	May-Sep 2019	Number of clusters receiving intervention	0	0	0
		Number of under 5 attendees	**22,948**	**11,899**	**24,978**
		Average cluster size	5,737	2,974.75	6,244.50
		Cluster size variance	3,737	974.75	4244.5
		Screened positive with TB signs and symptoms	149	64	117
		Enrolled with presumptive TB	9	25	32
		Diagnosed with TB	8	19	23
Step 2	Nov-19-Feb-20 Oct-19-Jan-20	Number of clusters receiving intervention	4	0	0
		Number of under 5 attendees	**19,184**	**13,040**	**21,158**
		Average cluster size	4,796	3,260	5,289.50
		Cluster size variance	2,796	1,260	3,289.50
		Screened positive with TB signs and symptoms	144	54	58
		Enrolled with presumptive TB	61	37	13
		Diagnosed with TB	6	23	3
Step 3	Mar-20-Oct-20 Feb-20-Sep-20	Number of clusters receiving intervention	4	4	0
		Number of under 5 attendees	**22,990**	**16,950**	**27,886**
		Average cluster size	5,747.50	4,237.50	6,971.50
		Cluster size variance	3,747.50	2,237.50	4,971.50
		Screened positive with TB signs and symptoms	128	146	50
		Enrolled with presumptive TB	69	75	17
		Diagnosed with TB	3	13	3
Step 4	Nov-20-Mar-21	Number of clusters receiving intervention	4	4	4
		Number of under 5 attendees	**16,731**	**14,530**	**19,229**
		Average cluster size	4,182.75	3,632.50	4,807.25
		Cluster size variance	2,182.75	1,632.50	2,807.25
		Screened positive with TB signs and symptoms	263	194	275
		Enrolled with presumptive TB	128	135	142
		Diagnosed with TB	14	17	21

Figure 1 INPUT Consolidated Standards of Reporting Trials flow chart. TB, tuberculosis.

assessed for eligibility for the prospective follow-up study at their 2-week reassessment, and 744 were children with presumptive TB warranting TB investigations, therefore eligible for the prospective follow-up study. One caregiver withdrew participation just after the consent, so the final number of enrolled children with presumptive TB who underwent TB investigations was 743 (online supplemental material 3).

Baseline characteristics

Baseline characteristics of participants enrolled with presumptive TB by study phases are shown in table 1. During the control phase, 106/133 (80%) were enrolled in Kenya, and during the intervention phase, 469/610 (77%) were enrolled in Cameroon.

The median age of enrolled children was 18.7 months (IQR 10.4–35.3 months), and 407/743 (55%) were male. Overall, 88/743 (12%) of children were born from a mother living with HIV, and 47/743 (6%) were CLHIV.

The most frequent clinical features experienced by children were cough (88%), fever (60%), fatigue (36%) and appetite loss or failure to thrive (33%).

TB diagnosis and treatment

The TB diagnostic investigations done among the 743 children enrolled with presumptive TB by study phases and aRRs and p values measuring the effect of the intervention for the variables that were defined as individual-level outcomes are shown in table 2.

Overall, 83% of enrolled children had a sample collected for TB diagnosis, 62% in the control phase and 88% in the intervention phase, an increase that was not statistically significant (aRR, 1.28, 95% CI 0.86 to 1.90, p=0.232). Xpert or Xpert Ultra was done in 84% of children in the intervention phase versus 32% in the control. Overall, the proportion of positive Xpert tests (the yield) was 2.4%.

Half of the children received a CXR in both phases. A majority (69%) of CXRs in the control phase showed abnormal images, 43/45 (95%) of which were interpreted as consistent with TB. During the intervention, 49% of the CXRs were considered abnormal, 41/150 (27%) of which were interpreted as consistent with TB and 109/150 (73%) leading to a differential diagnosis.

Four children were terminated before TB diagnosis investigations were completed (online supplemental material 3): one child relocated, one died, and two were lost to follow-up. Finally, 586 had TB ruled out, and 153 were diagnosed with TB, 79/133 (59%) in the control phase and 74/610 (12%) in the intervention phase. The aRR measuring the effect of the intervention on the proportion of children investigated for TB who were diagnosed with TB was 0.54 (95% CI 0.27 to 1.09), p=0.0866.

The types of diagnosis and treatment received among the 153 children diagnosed with TB and associated aRRs and p values for individual-level study outcomes are shown in table 3.

Overall, 17 (11%) children had a microbiologically confirmed TB diagnosis. The increase in the proportion of children with microbiological confirmation (6/79, 8% in control and 11/74, 15% in intervention) was not significantly different between control and intervention (aRR 0.77, 95% CI 0.07 to 8.19, p=0.83) after adjusting for study design and country.

The median time from symptom onset to diagnosis was 2 months in the control phase and 1 month in the intervention phase, and the difference was not statistically significant (aRR 1.20, 95% CI 0.02 to 66.39, p=0.61).

All children diagnosed with TB were initiated on treatment, with 87% starting on treatment the same day the diagnosis was made. The treatment outcome was in 65/79 (82%) children in the control phase and 68/74 (92%) in the intervention phase, an increase that was not statistically significant (aRR 1.32, 95% CI 0.01 to 210.12, p=0.61).

Study cluster-level outcomes

The results of the intervention on cluster-level outcomes, analysed using mixed Poisson modelling to account for clustering and time effects, both overall and by country, are presented in table 4.

We observed a significant increase in the proportion of children identified with TB signs and symptoms and in the proportion of children with presumptive TB undergoing TB diagnostic investigations among children under age 5 years in the intervention group compared with the control group (aRR 2.95, 95% CI 2.39 to 3.67) and aRR 3.90, 95% CI 2.40 to 5.42, respectively). These findings were consistent when analysing Cameroon and Kenya separately.

The proportion of TB cases diagnosed among children aged under 5 years was not statistically different between intervention and control (aRR 1.32, 95% CI 0.66 to 2.61, p=0.43). Furthermore, country-stratified analysis demonstrated a substantial 10-fold increase (aRR 9.75, 95% CI 1.04 to 91.84, p=0.046) in case detection in Cameroon, with no significant increase in Kenya (aRR 0.94, 95% CI 0.44 to 2.01, p=0.88).

Boxplots of the cluster-level analysis on primary outcomes are shown in online supplemental material 4.

Serious adverse events

Of 90 adverse events recorded among the 743 enrolled children, 37 were serious adverse events occurring among 35 (5%) children (25 were hospitalised and 10 died; online supplemental material 5). These were all reported to institutional review boards, and none was considered related to the study procedures as per their assessment. 53 additional non-serious adverse events were reported among 42 children, all of mild or moderate intensity. The most frequent were signs and symptoms of TB (cough, fever and weight loss) experienced by 25 children (3.4%). Two moderate adverse events were considered related to the study procedures: a sore throat after a gastric aspirate

Table 1 Characteristics of enrolled children (children with presumptive TB investigated for TB) by study phases (n=743)

Variable	Overall (n=743) n (%) or median (IQR)	Control (n=133) n (%) or median (IQR)	Intervention (n=610) n (%) or median (IQR)
Site characteristics			
Country			
Cameroon	496 (66.8)	27 (20.3)	469 (76.9)
Kenya	247 (33.2)	106 (79.7)	141 (23.1)
Level of care where seeking services			
Secondary hospital	592 (79.7)	111 (83.5)	481 (78.8)
Primary Healthcare centre	151 (20.3)	22 (16.5)	129 (21.2)
Service where seeking care			
Outpatient department/emergency room	393 (52.9)	57 (42.9)	336 (55.1)
Inpatient department	111 (14.9)	23 (17.3)	88 (14.4)
TB clinic	98 (13.2)	18 (13.5)	80 (13.1)
Of whom, referred from contact tracing*	71 (72.4)	5 (27.8)	66 (82.5)
Mother and child health services (for under 5)	88 (11.8)	20 (15.0)	68 (11.1)
HIV clinic	38 (5.1)	8 (6.0)	30 (4.9)
Nutrition rehabilitation clinic	5 (0.7)	2 (1.5)	3 (0.6)
Other	10 (1.4)	5 (3.8)	5 (0.8)
Demographic characteristics			
Gender			
Male	407 (54.8)	78 (58.7)	329 (53.9)
Female	336 (45.2)	55 (41.3)	281 (46.1)
Age in months	*18.7 (10.4–35.3)*	*19.3 (12.0–36.6)*	*18.7 (9.8–35.0)*
Age under 2 years	435 (58.5)	75 (56.4)	360 (59.0)
Place of residence			
Rural	337 (45.4)	88 (66.2)	249 (40.8)
Urban	406 (54.6)	45 (33.8)	361 (59.2)
Less than 1 hour travel time to facility (n=739)	551 (74.6)	76 (57.6)	475 (78.3)
Caregiver's highest level of education			
Unknown/never attended school/primary school	264 (35.5)	83 (62.4)	181 (29.7)
Secondary school and above	479 (64.5)	50 (37.6)	429 (70.3)
Medical history and comorbidities			
Child born from a mother living with HIV	88 (11.8)	23 (17.3)	65 (10.7)
Child HIV status			
Negative	301 (40.5)	81 (60.9)	220 (36.1)
Unknown	395 (53.2)	38 (28.6)	357 (58.5)
Positive	47 (6.3)	14 (10.5)	33 (5.4)
Of whom, on antiretroviral therapy	34 (72.3)	10 (71.4)	24 (72.7)
History of asthma or chronic lung disease	45 (6.1)	7 (5.3)	38 (6.2)
History of severe or moderate acute malnutrition	102 (13.7)	36 (27.1)	66 (10.8)
TB contact history			
Household source case diagnosed with TB	124 (16.7)	35 (26.3)	89 (14.6)
Of whom, on TB treatment	105 (84.7)	29 (82.9)	76 (85.4)
Clinical signs and symptoms†			
Cough	651 (87.6)	101 (**75.9**)	550 (90.2)
Cough for more than 2 weeks	484 (65.1)	88 (66.2)	396 (64.9)

Continued

Table 1 Continued

Variable	Overall (n=743) n (%) or median (IQR)	Control (n=133) n (%) or median (IQR)	Intervention (n=610) n (%) or median (IQR)
Fever	446 (60.0)	62 (46.6)	384 (63.0)
Fever for more than 10 days	256 (34.5)	39 (29.3)	217 (35.6)
Night sweats	209 (28.1)	53 (39.8)	156 (25.6)
Night sweats for more than 10 days	151 (20.3)	39 (29.3)	112 (18.4)
Appetite loss/failure to thrive	245 (33.0)	39 (29.3)	206 (33.8)
Fatigue/reduced playfulness/decreased activity	267 (35.9)	39 (29.3)	228 (37.4)
Dyspnoea	96 (12.9)	19 (14.3)	77 (12.6)
Wheeze	84 (11.3)	10 (7.5)	74 (12.1)
Abnormal pulmonary auscultation/percussion	178 (24.0)	30 (22.6)	148 (24.3)
Peripheral lymphadenitis	44 (5.9)	14 (10.5)	30 (4.9)
Dehydration	25 (3.4)	3 (2.3)	22 (3.6)
Pallor	41 (5.5)	6 (4.5)	35 (5.7)
Diarrhoea/vomiting	33 (4.4)	1 (0.8)	32 (5.2)
Rhinitis/cold	47 (6.3)	0	47 (7.7)
Received antibiotics prior to TB investigations	345 (46.4)	64 (48.1)	281 (46.1)

*These children have been identified through contact tracing activities (close contact of someone diagnosed with TB) and have been referred to the facility for TB care.
†Here we report only signs and symptoms with more than 2.5% prevalence overall (≥20 occurrences).
TB, tuberculosis.

and an episode of vomiting after a change of drug formulation.

DISCUSSION

Our study showed that integration and decentralisation of child TB services into paediatric healthcare services increased TB symptoms screening and TB diagnostic workup among all child attendees, leading to a marked increase in TB case detection in Cameroon, whereas in Kenya, we did not observe a significant increase in TB case detection.

The study's finding that integrating and decentralising TB services into child healthcare services has the ability to increase TB case detection and improve treatment outcomes was supported by previous research.[13 21] However, the INPUT study represents a pioneering effort in using the stepped-wedge cluster-randomised design to demonstrate the efficacy of integrating paediatric TB services. This robust study design has gained traction in public health research and has proven effective in evaluating multifaceted interventions.[22]

In analysing the difference in the effect on TB case detection between the two countries, it is crucial to consider the contrasting baseline situations. In Kenya, prior to the study implementation, efforts had already been made at the MoH level to establish decentralised TB care services, resulting in a relatively efficient and established system for TB case identification. This pre-existing infrastructure and decentralised approach likely contributed to the higher case detection rate during the standard of care in Kenya. Conversely, in Cameroon, there had been no attempt to decentralise TB services before the roll-out of the CaP-TB intervention, hence the very low detection rate of TB found during the control phase, which markedly increased during the intervention phase.

These contextual differences across countries highlight the importance of considering the existing healthcare landscape when interpreting the outcomes of multi-country interventions.

Before conducting the study, we discussed the possibility of an initial increase in case finding at study initiation, even before the roll-out of the intervention.[15] The increase could be due to the use of new TB registers and monitoring and evaluation forms, which by themselves could raise awareness about paediatric TB, as well as the capture of a reservoir of previously undiagnosed prevalent cases. While the paucity of TB diagnoses in standard of care rules out this hypothesis for Cameroon, we cannot exclude the possibility that this confounding effect may have contributed to decreasing our ability to show a difference in case detection in Kenya.

Another factor that could have impeded our ability to show an effect in Kenya is the occurrence of massive healthcare worker strikes, which significantly impacted the final step when all sites were implementing the CaP-TB intervention. In December 2020, study sites in Kenya faced a severe decline in attendees and were unable to enrol children with presumptive TB due to the strikes. We extended the duration of the last step by a few

Table 2 TB investigations by study phases among enrolled children with presumptive TB (n=743)

	Overall (n=743) n (%) or median (IQR)	Control (n=133) n (%) or median (IQR)	Intervention (n=610) n (%) or median (IQR)	Adjusted rate ratio*	P value
Specimen collected	618 (83.2)	83 (62.4)	535 (87.7)	1.28 (0.86–1.90)	0.2321
Specimen type					
Sputum	38 (6.1)	20 (24.1)	18 (3.4)		
Induced sputum	20 (3.2)	12 (14.5)	8 (1.5)		
Nasopharyngeal aspirate	104 (16.8)	4 (4.8)	100 (18.7)		
Gastric aspirate	443 (71.7)	40 (48.2)	403 (75.3)		
Other†	13 (2.1)	7 (8.4)	6 (1.1)		
Xpert assay performed	553 (74.4)	43 (32.3)	510 (83.6)		
Xpert assay result					
Positive	13 (2.4)	2 (4.7)	11 (2.2)		
Negative	538 (97.3)	41 (95.3)	497 (97.4)		
Indeterminate	1 (0.2)	0	1 (0.2)		
Missing	1 (0.2)	0	1 (0.2)		
Smear microscopy performed	157 (21.1)	33 (24.8)	124 (20.3)		
Smear microscopy result					
Positive	0	0	0		
Negative	156 (99.4)	32 (97.0)	124 (100)		
indeterminate	1 (0.6)	1 (3.0)	0		
X-ray performed	373 (50.2)	65 (48.9)	308 (50.5)		
X-ray result					
Normal	161 (43.2)	19 (29.2)	142 (46.1)		
Abnormal, consistent with TB	84 (22.5)	43 (66.2)	41 (13.3)		
Abnormal, not consistent with TB	111 (29.8)	2 (3.1)	109 (35.4)		
Unknown	17 (4.6)	1 (1.5)	16 (5.2)		
Diagnosed with TB	153 (20.6)	79 (59.4)	74 (12.1)	0.54 (0.27–1.09)	0.0866

*Adjusted rate ratios of the effect of the intervention and associated p values are calculated from mixed Poisson models adjusting for country, clustering and time effects. These are calculated for variables that are defined as study outcomes.
†Others include gastric lavage, bronchoscopy, lymph node aspirate and urine (collected for lateral flow urine lipoarabinomannan test in five children living with HIV).
TB, tuberculosis.

weeks to approximate a full 4 months of normal activity in these clusters. However, as shown in figure 1, the number of attendees in step 4 was still lower compared with other steps.

Unfortunately, another notable limitation of the INPUT study's stepped-wedge design was the unforeseen onset of the COVID-19 pandemic during the later phases of the trial, which mainly encompassed the intervention periods. It is reasonable to hypothesise that the impact of the COVID-19 pandemic, weighing heavily on the intervention phases, could have impeded our ability to fully demonstrate the true impact of the intervention.[23] We can observe from boxplots (online supplemental material 4) that during phase III, both control and intervention sites appeared to have lower case detection than what was achieved during phases I and II and pre-COVID. Indeed, the COVID-19 pandemic has had a profound disruptive effect on all healthcare services, including TB-related services.[24–26]

One of the key objectives of the CaP-TB intervention was to provide training to healthcare workers in primary healthcare facilities, enabling them to confidently diagnose and initiate treatment for paediatric TB, even in the absence of bacteriological confirmation. Even though specimen collection was more frequent during CaP-TB, bacteriological confirmation of the TB diagnosis was not more frequent. This study confirms that bacteriological confirmation is rare in children, despite the use of molecular tests and improved sample collection methods.[27]

In this context, CXR plays a crucial role. In our study, although the proportion of presumptive children undergoing CXR remained consistent between study phases (approximately half of them), the intervention phase saw a substantial increase in children with presumptive

Table 3 TB diagnosis and treatment by study phases

	Overall (n=153) n (%) or median (IQR)	Control (n=79) n (%) or median (IQR)	Intervention (n=74) n (%) or median (IQR)	Adjusted rate ratio*	P value
Microbiological confirmation	17 (11.1)†	6 (7.6)†	11 (14.9)	0.77 (0.07–8.19)	0.83
TB type					
Pulmonary	119 (77.8)	58 (73.4)	61 (82.4)		
Extrapulmonary: adenitis	31 (20.3)	20 (25.3)	11 (14.8)		
Extrapulmonary: disseminated	2 (1.3)	1 (1.3)	1 (1.4)		
Extrapulmonary: osteoarticular	1 (0.7)	0	1 (1.4)		
Time from symptom onset to diagnosis (months) (n=149) (median, IQR)	2.0 (1.0–5.0)	2.0 (1.0–6.5)	1.0 (1.0–3.0)		
Time from symptoms onset to diagnosis (dichotomic) (n=149)					
≤1 month	72 (48.3)	34 (44.7)	38 (52.1)	1.20 (0.02–66.39)	0.67
>1 month	77 (51.7)	42 (55.3)	35 (47.9)	1	
Initiated on TB treatment	153 (100)	79 (100)	74 (100)		
Time from diagnosis to treatment initiation (days)					
Same day	133 (86.9)	71 (89.9)	62 (83.8)		
1–3 days	15 (9.8)	6 (7.5)	9 (12.1)		
4–7 days	2 (1.3)	1 (1.3)	1 (1.4)		
>7 days‡	3 (2.0)	1 (1.3)	2 (2.7)		
Treatment regimen§					
2RHZE-4RH	141 (92.2)	74 (93.7)	67 (90.6)		
2RHZ-4RH	11 (7.2)	5 (6.3)	6 (8.1)		
2RHZE-10RH	1 (0.7)	0	1 (1.3)		
Treatment outcome					
Cured¶	0	0	0		
Treatment completed	133 (86.9)	65 (82.3)	68 (91.9)		
Died	7 (4.6)	6 (7.6)	1 (1.4)		
Lost to follow-up	8 (5.2)	4 (5.1)	4 (5.4)		
Not evaluated	5 (3.3)	4 (5.1)	1 (1.4)		
Dichotomic treatment outcome					
Treatment success	133 (86.9)	65 (82.3)	68 (91.9)	1.32 (0.01–210.12)	0.61
No treatment success	20 (13.1)	14 (17.7)	6 (8.1)	1	

N=153 children diagnosed with TB.
*Adjusted rate ratios of the effect of the intervention and associated p values are calculated from mixed Poisson models adjusting for country, clustering and time effects. These are calculated for variables that are defined as study outcomes.
†Among microbiological confirmations, 13 positive Xpert and 4 positive lateral flow urine lipoarabinomannan tests (in control phase), performed in children living with HIV in one of our study sites as an intervention that was not part of Catalysing Paediatric TB Innovations.
‡These times were 8, 12 and 17 days.
§R: rifampin; H: isoniazid; Z: pyrazinamide and E: ethambutol. Numbers indicate the duration in months of intensive and continuation phase. The 10-month continuation phase was for the child with osteoarticular TB.
¶No smear or culture was positive at initiation making it impossible to observe cure in children.
TB, tuberculosis.

TB, elevating the absolute number of CXRs conducted from 65 to 308. During the intervention phase, there were fewer abnormal CXR findings attributed to TB, and conversely, more abnormal CXR findings attributed to other causes than TB, compared with the control phase. This may be due to the broader range of differential diagnoses considered during the intervention because of broader screening for respiratory symptoms, as well as due to the positive impact of the training provided by CaP-TB in improving the interpretation of X-rays, thus increasing their specificity to detect TB. Also, looking at the absolute numbers of CXR findings with abnormal

Table 4 Effect of the intervention on cluster-level outcomes, overall and disaggregated by country

	Control		Intervention			
	N (workload)	n (rate per thousand child consultations)	N (workload)	n (rate per thousand child consultations)	Adjusted rate ratio (95% CI)*	P value
Screened positive with TB symptoms among attendees						
Overall	121 909	492 (4.04)	109 614	1150 (10.49)	2.95 (2.39 to 3.67)	<0.001
Kenya	78 134	416 (5.32)	57 373	360 (6.27)	2.13 (1.60 to 2.80)	<0.001
Cameroon	43 775	76 (1.74)	52 241	790 (15.12)	4.88 (3.42 to 6.96)	<0.001
With presumptive TB investigated for TB among attendees						
Overall	121 909	133 (1.09)	109 614	610 (5.56)	3.90 (2.40 to 5.42)	<0.0001
Kenya	78 134	106 (1.36)	57 373	141 (2.46)	2.05 (1.23 to 3.39)	0.005
Cameroon	43 775	27 (0.62)	52 241	469 (10.71)	6.86 (4.22 to 11.13)	<0.0001
Primary outcome: diagnosed with TB among attendees						
Overall	121 909	79 (0.64)	109 614	74 (0.68)	1.32 (0.66 to 2.61)	0.43
Kenya	78 134	77 (0.99)	57 373	41 (0.71)	0.94 (0.44 to 2.01)	0.88
Cameroon	43 775	2 (0.05)	52 241	33 (0.63)	9.75 (1.04 to 91.84)	0.046

*Adjusted rate ratio obtained from mixed Poisson mixed after adjustment for clustering and time.
TB, tuberculosis.

images not consistent with TB (109 in the intervention compared with two in the control), we can expect that the use of CXR, in turn, contributed to a more accurate diagnosis of pulmonary infections in these children. Notably, before TB investigations, only half of the children had received antibiotics, contrary to guidelines recommending a 2-week course for all those with TB signs. Abnormal X-ray images likely prompted appropriate antibiotic courses.

These considerations become particularly relevant considering the new conditional recommendation by the WHO to use treatment decision algorithms based on clinical symptoms and CXR when available and the concern that this approach may lead to overtreating children who do not have TB.[8 28] However, given the potential consequences of missing a TB diagnosis and the low frequency of serious adverse reactions to anti-TB treatment in children,[29] it is considered reasonable to prioritise high sensitivity and accept a lower specificity[26] even though that implies a degree of overtreatment.[30]

While a larger number of children with presumptive TB were identified during the intervention and underwent TB investigations, the intervention decreased the probability of a child investigated for TB being ultimately diagnosed with TB. This occurred because the increase in the number of children with presumptive TB undergoing TB investigations (denominator) outpaced the increase in actual TB diagnoses (numerator). Although the lower yield of TB diagnosis among those investigated may seem counterintuitive, we view this as a positive outcome of the intervention, suggesting that investigating more children led to more accurate diagnoses and appropriate treatments, even when TB was ruled out. Our study follow-up focused on confirmed TB cases; therefore, we were unable to document the outcomes of children who were not diagnosed with TB. We strongly advocate for studies investigating the outcomes of all children with presumptive TB, irrespective of the final diagnosis. We do believe that increasing the number of children identified with pulmonary symptoms and undergoing TB diagnostic examination should in turn contribute to improving their health outcomes, whether the diagnosis was TB or not.

It is important to acknowledge that the number of children diagnosed with TB in our study was below our expectations, which has limited our power to show significant differences between the intervention and control periods. It was especially the case for treatment outcomes, for which we failed to find a significant association, although the proportion of favourable treatment outcomes rose from 82% to 92% between the control and intervention phases, a 10% increase that can certainly be considered clinically important.

Nevertheless, our findings provide important evidence of the potential benefits of integrating TB services into child healthcare services. In the view of scaling up such interventions, it will be critical to take logistical challenges and cost implications into account. The main logistical challenges identified within CaP-TB were to ensure adequate training and retraining of healthcare workers, including at the low level of care, and to ensure the availability of TB diagnostic tools and medications. Costing considerations, both from a patient and from a health system perspective, as well as cost-effectiveness, have also been studied in INPUT.[31 32] This analysis showed that the cost-effectiveness of integrating TB services into child healthcare services depends on baseline service coverage, TB detection and treatment outcomes. These additional

findings are crucial for reinforcing the importance of continued investment in TB control efforts in Africa.

CONCLUSION

This study provides compelling evidence that decentralising and integrating TB screening and diagnosis within child healthcare services can lead to a substantial increase in the identification of children with TB signs and symptoms, as well as in the number of children with presumptive TB undergoing TB diagnostic investigations. Moreover, this approach has resulted in a remarkable 10-fold increase in TB case detection in Cameroon. Although no significant difference was observed in TB case detection rates between CaP-TB and the standard of care in Kenya, the study findings emphasise the importance of context-specific factors. These findings have significant implications for policy and practice, emphasising the value of integrating TB services into child healthcare to improve the identification and management of TB in under-5 children.

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Contributors LDN, RMas, RMac, BT, MC and AT conceptualised the study. MO, SJP, ROM and BT collected the data. NH, SS and LS validated the data. NH and RM performed the statistical analysis. All authors (LDN, RMas, RMac, BT, MC, MO, SJP, NH, SS, LS, PT, ACZKB, GOO and AT) contributed to the interpretation of data. LDN prepared the original draft. All authors (LDN, RMas, RMac, BT, MC, MO, SJP, NH, SS, LS, PT, ACZKB, GOO and AT) reviewed and edited the draft. ROM, BT, LDN and AT administered the project. AT and MC acquired funding. All authors (LDN, RMas, RMac, BT, MC, MO, SJP, NH, SS, LS, PT, ACZKB, GOO and AT) have read and approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. LDN is the guarantor.

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