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Cost-effectiveness of integrating paediatric tuberculosis services into child healthcare services in Africa: a modelling analysis of a cluster-randomised trial

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ABSTRACT

Background In 2021, over one million children developed tuberculosis, resulting in 214 000 deaths, largely due to inadequate diagnosis and treatment. The diagnosis and treatment of tuberculosis is limited in most high-burden countries because services are highly centralised at secondary/tertiary levels and are managed in a vertical, non-integrated way. To improve case detection and treatment among children, the World Health Organisation (WHO) recommends decentralised and integrated tuberculosis care models. The Integrating Paediatric TB Services Into Child Healthcare Services in Africa (INPUT) stepped-wedge cluster-randomised trial evaluated the impact of integrating tuberculosis services into healthcare for children under five in Cameroon and Kenya, compared with usual care, finding a 10-fold increase in tuberculosis case detection in Cameroon but no effect in Kenya.

Methods We estimated intervention impact on healthcare outcomes, resource use, health system costs and cost-effectiveness relative to the standard of care (SoC) using a decision tree analytical approach and data from the INPUT trial. INPUT trial data on cascades, resource use and intervention diagnostic rate ratios were used to parametrise the decision tree model. Health outcomes following tuberculosis treatment were modelled in terms of mortality and disability-adjusted life-years (DALYs).

Findings For every 100 children starting antituberculosis treatment under SoC, an additional 876 (95% uncertainty interval (UI) −76 to 5518) in Cameroon and −6 (95% UI −61 to 96) in Kenya would start treatment under the intervention. Treatment success would increase by 5% in Cameroon and 9% in Kenya under the intervention compared with SoC. An estimated 350 (95% UI −31 to 2204) and 3 (95% UI −22 to 48) deaths would be prevented in Cameroon and Kenya, respectively. The incremental cost-effectiveness ratio for the intervention compared with SoC was US$506 and US$1299 per DALY averted in Cameroon and Kenya, respectively.

Interpretation Although likely to be effective, the cost-effectiveness of integrating tuberculosis services into child healthcare services depends on baseline service coverage, tuberculosis detection and treatment outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Tuberculosis in children under 5 years of age is a substantial cause of disease and avaoidable death.
⇒ Innovative models of tuberculosis care for case detection and management in children are urgently required to address these challenges.
⇒ The WHO 2022 updated guidelines on tuberculosis management in children and adolescents conditionally recommended using innovative models of care (decentralised and family-centred, integrated models of care) for tuberculosis in children.
⇒ Evidence on the cost and cost-effectiveness of innovative models of care is limited but urgently required to inform policy decisions on their adoption and scale up.

WHAT THIS STUDY ADDS

⇒ We estimated the impact of an active case-finding intervention on healthcare outcomes, resource use, health system costs and cost-effectiveness relative to the standard of care using a decision-analytical approach and data from the Integrating Paediatric TB Services Into Child Healthcare Services in Africa study.
⇒ Integrating tuberculosis services into child healthcare services would improve tuberculosis diagnosis, treatment initiation and treatment completion in children under 5 years but the impact varies by country.
⇒ The intervention is likely to be cost-effective in settings where there is scope for improvements.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Baseline coverage of services, tuberculosis detection and treatment are likely to determine cost-effectiveness.
⇒ Targeting specific elements of interventions may improve cost-effectiveness in different settings.

INTRODUCTION

Tuberculosis (TB) in children under 15 years of age is a substantial cause of disease and death.[1] The WHO estimated that 1.3 million children developed TB and 214 000 died in 2022,[2] making TB a top 10 cause of death in children under 5 years.[3] The sub-Saharan Africa region accounts for about one-third of all paediatric TB cases with an incidence of 29–34/100 000, which is double the global average.[4] In the WHO African Region, about 20% of all TB patients are also infected with HIV.[2]

The majority of TB deaths in children are estimated to occur in children whose diagnosis has been missed and are, therefore, not treated.[1] The diagnosis of TB in children is particularly challenging due to the presence of non-specific symptoms, challenges in obtaining diagnostic samples and often the paucibacillary nature of the disease.[5–7] Furthermore, diagnostic and treatment services for children with active TB are largely centralised and provided as vertical, non-integrated services in many sub-Saharan African countries,[8 9] which limits access leading to underdiagnosis and under-reporting. In addition, primary healthcare facilities where most children initially seek care lack adequate services or capacity for diagnosing TB. Weak case findings, lack of and underutilisation of diagnostic tools, inadequate linkage to care and lack of appropriate paediatric TB formulations result in poor clinical outcomes.[9 10]

To address these challenges, innovative models of TB care for case detection and management in children are urgently required. Responding to this gap, the Catalysing Paediatric Tuberculosis Innovations (CaP-TB) project was developed and implemented with the aim of enhancing the detection of TB in children under the age of 15 years across nine sub-Saharan African countries. A detailed description of the CaP-TB project has previously been reported.[11] In short, the CaP-TB intervention integrated paediatric TB services into child healthcare services (such as outpatient departments, inpatient departments, maternal and child health, nutrition, and HIV services) both at the hospital and primary healthcare level and included a package of training, supportive supervision, job aids and logistical support for the integration of TB screening and diagnosis activities into paediatric services. The impact of the Cap-TB project was evaluated using a stepped-wedge cluster-randomised (SW-CRT) intervention study in the Integrating Paediatric TB Services Into Child Healthcare Services in Africa (INPUT) study.[11 12]

The WHO 2022 updated guidelines on TB management in children and adolescents[13] conditionally recommended using decentralised and family-centred, integrated models of TB care. However, evidence on the costs and cost-effectiveness of these models of care, key for their adoption by policy-makers, is minimal and has been highlighted as a research priority.[14] In this study, we use data from the INPUT study to quantify the impact of the Cap-TB intervention on mortality, health system costs and cost-effectiveness in comparison to the standard of care (SoC).

METHODS

Patient care pathways

Patient care pathways for children aged less than 5 years presenting for care at primary healthcare centres or district hospitals under the SoC and intervention were developed and represented as decision tree diagrams (online supplemental appendix figures S1-3). The aim was to develop common pathways that represent the care received in both countries and to inform that process, the description of patient pathways focuses on adequately capturing important aspects that were common in both countries. However, highlights of some important differences that might impact resource use and outcomes are also provided.

Standard of care

The SoC was defined as the cascade of TB care for children aged less than 5 years attending healthcare services before the introduction of the CaP-TB project. TB services in Cameroon were centralised at secondary or tertiary hospitals, and at specialised primary healthcare facilities with a physician while they were largely decentralised and provided from primary healthcare level in Kenya. In both countries, the cascade of TB diagnosis and care involved screening children presenting at healthcare facilities for symptoms of active disease. These symptoms were defined as a non-remitting cough of more than 2 weeks, fever of more than 10 days, night sweats of more than 2 weeks, fatigue, reduced playfulness or decreased activity, weight or appetite loss or failure to thrive during the last 3 months. TB screening was not recommended or done systematically in Cameroon while it was recommended at every healthcare entry point in Kenya.[11] In both countries, children identified with any TB suggestive symptoms were defined as presumptive TB cases and underwent diagnostic workup according to national guidelines or The Union's Desk Guide for Primary Health Care Workers on the diagnosis and management of TB in children and adolescents.[15]

TB investigations followed national guidelines, typically consisting of clinical assessment with or without chest X-ray, sample collection (including advanced procedures such as gastric aspirate, induced sputum and nasogastric aspirate) and bacteriological assessment. Xpert MTB/RIF diagnostic testing was available as SoC in most district hospitals in Kenya (but not in primary healthcare facilities) while it was not widely available in Cameroon. Clinical TB diagnosis, based on history and physical examination findings (with or without radiological investigations), was possible after a negative Xpert result or no Xpert testing. There was a possibility for sample referral from the collection site to the testing site in both models of care. Additional treatment or evaluation before starting a specific TB workup could include administering a course of broad-spectrum antibiotics followed by a re-evaluation after two weeks.

Children diagnosed with active TB were initiated on anti-TB treatment following national TB guidelines.

The clinical care pathways for sick children presenting to healthcare facilities are shown in online supplemental figures S1-3.

Intervention

The intervention was defined as a package of activities implemented during the CaP-TB project in both countries.[11 12] These activities included 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. The intervention integrated TB screening into all child healthcare services usually attended by children, improved TB diagnostic capacity through strengthening the use of clinical diagnosis algorithms, training on advanced specimen collection procedures and enhanced access to chest X-ray and Xpert MTB/RIF testing as the initial diagnostic test.

Intervention effect

The effect of the CaP-TB intervention was evaluated in the INPUT study (NCT03862261).[11] The study was a SW-CRT intervention study that assessed the effectiveness of the CaP-TB intervention (described above) on TB diagnosis and treatment outcomes in children under 5 years of age compared with the SoC. Full details of the INPUT study are provided elsewhere.[11 12] The INPUT SW-CRT was undertaken in six district-level hospitals and up to two of their affiliated primary healthcare centres in Cameroon and Kenya. The primary outcome of the INPUT SW-CRT study was the rate of children diagnosed with TB per thousand child consultations (or case detection rate). Secondary outcomes included the rate of children with TB signs and symptoms per thousand child consultations and the rate of children with presumptive TB and investigated for TB per thousand child consultations. The effect of the intervention on these outcomes was estimated using generalised linear mixed Poisson models adjusting for country and the time trend and accounting for within-site clustering.[12] The intervention effects were presented as adjusted rate ratios (aRRs) and their associated 95% confidence intervals (CIs). The INPUT SW-CRT reported overall rates of children diagnosed with TB per thousand child consultations of 0.64 per 1000 under the SoC and 0.68 per 1000 under the intervention. Overall, the study did not find a significant effect of the intervention on the rate of children diagnosed with TB (aRR 1.32 (95% CI 0.66 to 2.61)). However, in the country-stratified analysis, the study found a 10-fold increase in TB case detection rate in Cameroon (aRR 9.75 (95% CI 1.04 to 91.84)) but no effect in Kenya (aRR 0.94 (95% CI 0.44 to 2.01)).[12]

Decision analytical modelling approach

In view of the acute nature of childhood TB, and the importance of representing detailed clinical pathways, a decision tree analytical modelling approach was used to represent the care cascades (figure 1) from the INPUT trial and extend them to capture mortality risk outcomes beyond the trial. The probabilities of following different pathways through the decision tree were assumed to depend on specific characteristics of children (attributes). The attributes included in the model are age (under 2 years or 2–5 years); HIV and antiretroviral treatment status (positive or negative) and true TB status (bacteriologically confirmed TB, bacteriologically unconfirmed TB, and no TB). Bacteriologically confirmed TB refers to TB that would be bacteriologically positive under ideal circumstances and with all samples available.

We calculated the number of children found with TB-suggestive symptoms, investigated for TB (ie, those with presumptive TB), initiated anti-TB treatment and achieved treatment success (figure 1). Treatment success was defined following WHO treatment outcome definitions as the sum of cured and treatment completed.[16 17] The impact of the intervention was estimated by applying country-level rate ratios for improvements in TB

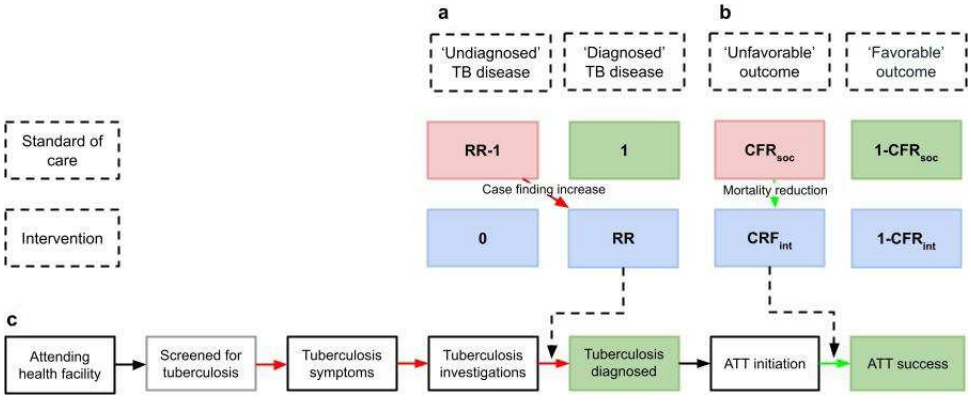

Figure 1 Conceptual diagram of the model used to estimate the impact and cost-effectiveness of integrating paediatric tuberculosis services into child healthcare services in Cameroon and Kenya. (a) The use of risk ratio estimates to model changes in tuberculosis diagnosis under the intervention. (b) The impact of the intervention on the case fatality rate. (c) The care cascade for tuberculosis modelled. The red lines describe changes in case detection activities under intervention. The green arrows show changes in mortality under the intervention. ATT, antituberculosis treatment; CFR, case fatality rate; RR, risk ratio; TB, tuberculosis.

diagnosis derived using generalised linear mixed Poisson models accounting for the time period and clustering and applying treatment outcomes obtained from the INPUT main trial analysis.[12] We used study cascade data to calculate the level of effort required per anti-TB treatment for initial care-seeking, screening for TB, TB-suggestive symptoms, TB investigations and anti-TB treatment (online supplemental appendix table S1–S3 and figure S4). We used these data and intervention effects to model resource use and costs under SoC and intervention. Primary data on the number of children systematically screened for TB symptoms on seeking care at health facilities were not available, hence we assumed the ratio of the number of children screened per presumptive TB observed in a parallel Cap-TB prestudy and poststudy implementation assessment at baseline and under the intervention.[18]

Country-specific and arm-specific estimates of treatment success and mortality for children on anti-TB treatment were derived from trial data using a Bayesian approach, with prior distributions defined based on pooled SoC data. Case fatality ratios for untreated TB were based on a literature review.[19 20] The average life years lost (with and without 3% discounting) were calculated using country-specific life expectancy from United Nations estimates. We neglected the contribution of morbidity associated with TB to disability-adjusted life-years (DALYs), previously shown to be a reasonable approximation.[18] We did not include post-TB morbidity. Drug-resistant TB or mortality in children without TB was not modelled. Model parameters are shown in online supplemental appendix table S2–4.

Country-specific and SoC/intervention-specific mean costs associated with resource use at each step of the care cascade were estimated and applied in the model (see online supplemental figures S5–10 and tables S6–9). Unit costs for activities involved in TB symptom screening, TB investigations and anti-TB treatments were estimated using study and published data.[21–28] We applied these unit costs to individual-level resource use data from the study to estimate costs per child engaging with each cascade step. Resource use costs were summed over the main cascade of care steps (TB symptom screening, TB investigations and anti-TB treatment) and mean costs (and SD) were estimated by country, age (<2 years or 2–5 years) and model of care. All costs were estimated in 2022 US dollars and were assumed to accrue in the present, with no discounting applied. The estimated mean costs were applied to the relevant cascade of care step in the model.

All model parameters were considered uncertain and described by probability distributions; 1000 samples of all inputs were used for probabilistic uncertainty analysis, with means and 95% quantiles reported. Calculations were performed using a decision tree framework in R.[29] Additional details are provided in online supplemental appendix. Plans for the analysis and reporting procedures used in this study were published in a health economic analysis plan.[30] All analysis code and data are available on GitHub.

Health economic outcomes

We calculated the relative number of children initially seeking care (and screened for TB symptoms), considered as presumptive TB, diagnosed with TB, initiated and completed anti-TB treatment. For every 100 children receiving anti-TB under SoC, we calculated the number of children starting and successfully completing anti-TB treatment, total costs, TB deaths averted, discounted (and undiscounted) DALYs averted and incremental costs under the intervention. We calculated the incremental cost-effectiveness ratios (ICERs) for each country in terms of incremental cost (US dollars) per DALY averted and the probability of the intervention being cost-effective at different cost-effectiveness thresholds. We complied with the Consolidated Health Economic Evaluation Reporting Standards 2022 reporting guidelines.[31]

Sensitivity analysis

We evaluated the impact of five modelling assumptions on cost-effectiveness outcomes in sensitivity and scenario analyses: (1) We applied alternative discount rates of 0% and 5% for the life-years and DALYs; (2) The main analysis assumed children lost to follow-up did not die, so we assessed the impact of including this mortality by applying a literature review case fatality ratios for untreated TB among children lost to follow-up; (3) We applied systematic review-based case fatality ratios instead of trial data to estimate mortality; (4) We applied pooled intervention effects (instead of country-specific estimates) and (5) We varied the relative number of children screened for TB by ±20%.

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 close-out.

RESULTS

The modelled cascade of care activities and overall cost associated with anti-TB treatment under SoC and during the intervention are shown in table 1 and figure 2. The INPUT study found that the CaP-TB intervention increased the rates of TB presumption in both countries (aRR 3.9 (95% CI 2.4 to 5.4)).[12] This represents an increase from 13.5 children in Cameroon and 1.38 in Kenya under SoC to 14.21 in Cameroon and 3.44 in Kenya under intervention per child initiating anti-TB treatment. The intervention also increased bacteriological testing rates by 30%–40% from 9.5 and 0.7 under SoC to 12.24 and 2.56 per child initiating anti-TB treatment under intervention in Cameroon and Kenya, respectively. Overall, Xpert MTB/RIF testing increased from 32% under SoC to 84% under intervention. The INPUT study found a 10-fold increase in TB case detection rate

Table 1 The cascade of care outcomes and costs for each child initiating antituberculosis treatment (ATT) under the intervention in comparison to the standard of care (SoC) in each country

		Cameroon		Kenya	
		Cascade	Unit cost	Cascade	Unit cost
ATT under SoC	Initial care seeking	21 887.5	–	1014.73	–
	TB symptom screening	1828.56	1.73 (2.03)	360.84	7.78 (2.98)
	TB signs and symptoms	38	–	5.4	–
	Presumptive TB	13.5	–	1.38	–
	Evaluated for TB	13.5	15.64 (13.59)	1.38	25.82 (20.48)
	Bacteriologically assessed	9.5	–	0.7	–
	Tested on Xpert*	2	–	0.51	–
	TB diagnosis	1	–	1	–
	DS-TB treatment	1	115.06 (15.88)	1	322.63 (143)
	Cost per ATT initiation, $ (SD)	1	3490 (3717)	1	3166 (1085)
ATT under intervention	Initial care seeking	1583.06	–	1399.34	0 (0)
	TB symptom screening	1214.21	2.76 (2.51)	642.29	7.11 (3.57)
	TB signs and symptoms	23.94	–	8.78	–
	Presumptive TB	14.21	–	3.44	–
	Evaluated for TB	13.7	164.57 (45.56)	3.34	88.17 (39.4)
	Bacteriologically assessed	12.24	–	2.56	–
	Tested on Xpert*	12.18	–	2.27	–
	TB diagnosis	1	–	1	–
	DS-TB treatment	1	371.82 (153.32)	1	389.8 (134.21)
	Cost per ATT initiation, $ (SD)	1	5977 (3115)	1	5251 (2301)

The costs per ATT initiation were calculated by multiplying resource use for each cascade step by their respective unit costs and summing over the entire cascade. Unless specified, all values are counts (n) presented for one child starting ATT. Costs are presented in 2021 US dollars (US$).
*Tested on Xpert is a subset of bacteriologically assessed.

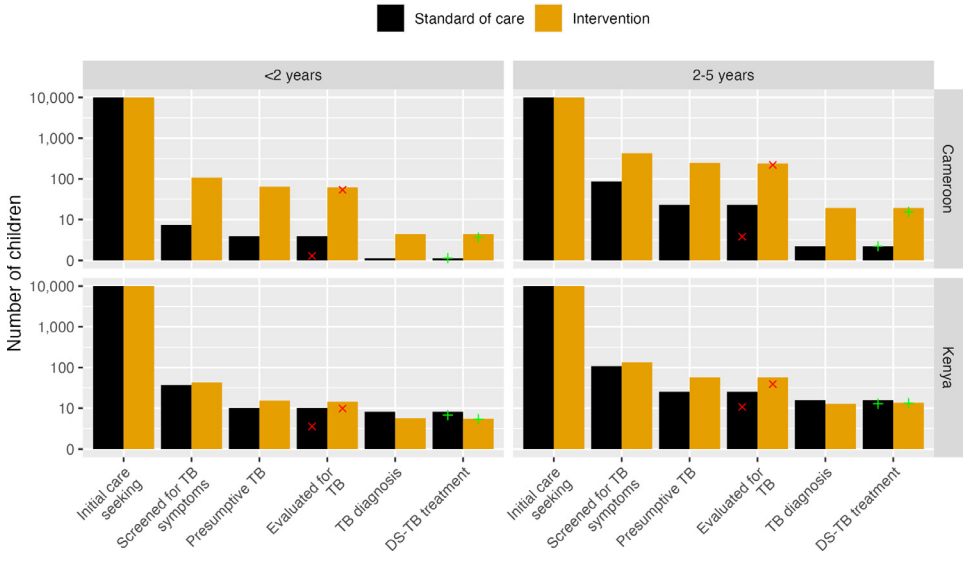

Figure 2 The cascade of care for initial care-seeking, TB symptom screening and diagnosis for children attending healthcare facilities in the INPUT study by country, age and model of care. Data are presented per 10 000 children seeking care at healthcare facilities. The red cross indicate the number of children tested on Xpert. The green plus sign indicate the number of children successfully treated. DS-TB, drug-susceptible tuberculosis; INPUT, Integrating Paediatric TB Services Into Child Healthcare Services in Africa; TB, tuberculosis.

Table 2 Healthcare resource use, health outcomes, costs and cost-effectiveness of the intervention in comparison to standard of care (SoC)

	Cameroon			Kenya		
	SoC	Intervention	Difference	SoC	Intervention	Difference
Healthcare resource use						
TB signs and symptoms	3800	37 178 (25 475–52 394)	33 378 (21 675–48 594)	570.5	2431 (1828–3193)	1860 (1258–2622)
Presumptive TB investigated	1350	5538 (130–31 721)	4188 (–1220–30 371)	142.5	128 (50–275)	–14 (–92–133)
Started treatment	100	976 (24–5618)	876 (–76–5518)	100	94 (39–196)	–6 (–61–96)
Treatment success (cured or completed treatment)	85 (67–96)	792 (20–4550)	708 (–65–4465)	82 (74–89)	87 (36–181)	5 (–46–99)
Health outcomes						
TB deaths	413 (–30–2523)	63 (1–370)	–350 (–2204–31)	5 (–22–52)	2 (0–7)	–3 (–48–22)
Disability-adjusted life-years (DALYs)	25 837 (–1870–157 794)	3928 (63–23 117)	21 909 (–1966–137 897)	351 (–1484–3570)	134 (6–510)	217 (–1546–3312)
Discounted DALYs	10 598 (–767–64 722)	1611 (26–9482)	8987 (–806–56 563)	140 (–592–1425)	54 (2–204)	87 (–617–1322)
Healthcare system costs and cost-effectiveness						
Cost	167 837 (18 627–505 182)	4 718 988 (101 047–28 364 861)	4 551 152 (–107 796–28 188 885)	103 258 (63 441–153 924)	215 639 (69 854–508 550)	112 381 (–43 834–408 347)
ICER (US$/DALY averted)	–	–	506	–	–	1299

All outcomes are presented per 100 initiating antituberculosis treatment under SoC. Data are presented as means and 95% uncertainty interval from probabilistic sensitivity analysis unless otherwise stated. Uncertainty in cost-effectiveness is presented in figure 2. All costs are presented in 2022 US dollars (US$). The ICER is presented as US$ per discounted DALY averted.
ICER, incremental cost-effectiveness ratio; TB, tuberculosis.

in Cameroon (aRR 9.75 (95% CI 1.04 to 91.84)) but no effect in Kenya (aRR 0.94 (95% CI 0.44 to 2.01)).[12] However, the intervention improved treatment success in both countries (aRR 1.32 (95% CI 0.01 to 210.12)). The total costs for identifying and initiating one child on anti-TB treatment were US$3490 (SD; US$3717) in Cameroon and US$3166 (SD; US$1085) in Kenya under SoC. These costs increased by more than 65% to US$5977 (SD; US$3,115) in Cameroon and US$5251 (SD; US$2301) in Kenya under the intervention.

Our model projected an increase in children identified with TB signs and symptoms by 33 378 (95% uncertainty interval (UI) 21 675 to 48 594) in Cameroon and 1860 (95% UI 1258 to 2622) in Kenya under intervention compared with SoC. The number of children investigated for TB increased to 5538 (95% UI 130 to 31 721) in Cameroon but decreased to 128 (95% UI 50 to 275) in Kenya (table 2). The observed intervention effect in Cameroon increased the number of children starting anti-TB treatment by 876 (95% UI to 76 to 5518), while the absence of an effect in Kenya resulted in a reduction in the number of children starting anti-TB treatment of 6 (95% UI –96 to 61) in Kenya.[12] More children were projected to successfully complete treatment under intervention in both countries: 792 (95% UI 20 to 4548) in Cameroon and 87 (95% UI 36 to 181) in Kenya, compared with 85 (95% UI 67 to 96) in Cameroon and 82 (95% UI 74 to 89) in Kenya under SoC. This significant intervention effect on treatment success resulted in more than 60% reduction in mortality: an estimated 350 (95% UI –31 to 2204) deaths avoided in Cameroon and 3 (95% UI –22 to 48) deaths in Kenya. Subsequently, 8987 (95% UI –806 to 56 563) discounted DALYs in Cameron and 87 (95% UI –617 to 1322) in Kenya would be averted.

The total economic cost required to initiate 100 children on anti-TB treatment under the SoC was US$167 837 (95% UI US$18 627 to US$505 182) in Cameroon and US$103 258 (95% UI US$63 441 to US$153 924) in Kenya. With the intervention, these costs increased by US$4 551 152 (95% UI US$–107 796 to US$28 188 885) and US$112 381 (95% UI US$–43 834 to US$408 347) to US$4 718 988 (95% UI US$101 047 to US$28 364 861) and US$215 639 (95% UI US$69 854 to US$508 550) in Cameroon and Kenya, respectively.

Compared with the SoC, the ICER for implementing the intervention was US$506 per DALY averted in Cameroon and US$1299 per DALY averted in Kenya. The probability of the intervention being cost-effective compared with SoC over a range of willingness-to-pay thresholds (representing decision uncertainty) is shown in figure 3. Assuming a cost-effectiveness threshold of 0.5×GDP per capita (equivalent to US$750 in Cameroon and US$910 in Kenya) resulted in a probability of the intervention being cost-effective of 68% in Cameroon and 34% in Kenya. The maximum probability of the intervention being cost-effective over the entire range of thresholds achieved in Cameroon was 83% at a cost-effectiveness threshold of US$11 628/DALY averted. The probability of the intervention being cost-effective exceeds 45% at a cost-effectiveness threshold of US$3000/DALY averted in

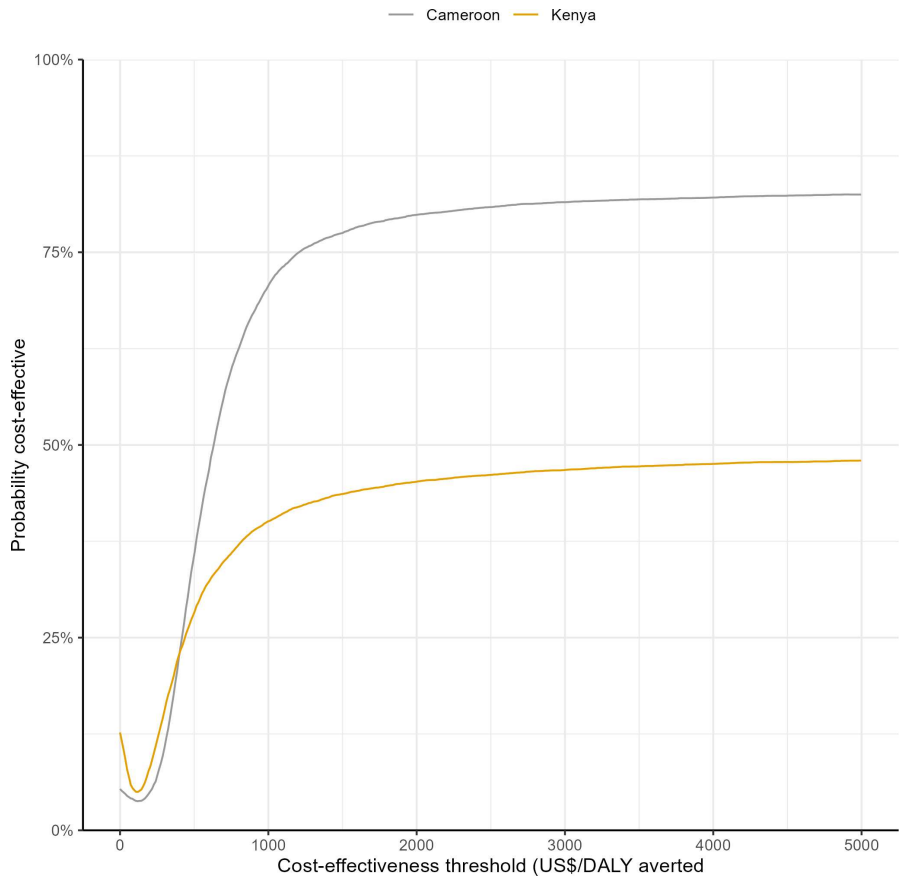

Figure 3 Cost-effectiveness acceptability curves for the intervention in comparison to the standard of care. The figure shows the probability that an intervention is cost-effective (y-axis) in each country, based on the proportion of simulations in which the comparison of the intervention to the standard of care falls below the cost-effectiveness threshold (y-axis). DALY, disability-adjusted life-year.

Kenya. Age-specific results are provided in online supplemental appendix tables S10–11 and figures S11–13.

Sensitivity analyses

The ICERs dropped to US$208/DALY averted in Cameroon and US$518/DALY averted in Kenya with no discounting and increased to US$765/DALY averted in Cameroon and US$1981/DALY averted in Kenya with a 5% discount rate (online supplemental appendix table S12). Assuming lower screening rates lowered the ICERs to US$470/DALY averted in Cameroon and US$1095/DALY averted in Kenya. Conversely, higher (+20%) screening rates increased the ICERs to US$551/DALY averted in Cameroon and US$1502/DALY averted in Kenya. Pooling data across the two countries diluted the intervention effects for Cameroon while improving it for Kenya. This resulted in ICERs of US$1450/DALY averted in Cameroon and US$363/DALY averted in Kenya. Incorporating mortality in children lost to follow-up increased the ICER to US$548/DALY averted in Cameroon but lowered it to US$884/DALY averted in Kenya. Assuming systematic review-based case fatality rates did not change the ICER in Cameroon but resulted in the intervention being more costly and less effective in Kenya with an ICER of—US$1650/DALY averted.

DISCUSSION

Our modelling suggests that integrating TB services into child healthcare services would improve TB diagnosis and treatment initiation in children under 5 years of age compared with SoC. In addition, improvements in such services would increase treatment completion and reduce TB-related mortality. The intervention is likely to be cost-effective from a health systems perspective compared with the SoC at a willingness to pay threshold of US$750/DALY averted in Cameroon. For Kenya, the lack of improvements in TB diagnosis and treatment initiation compared with the increased costs means the intervention, as implemented, is unlikely to be cost-effective at typical threshold choices (US$910/DALY averted representing 0.5×GDP per capita).

These findings suggest that the cost-effectiveness of integrating TB services into child healthcare services is likely to differ by setting and may reflect varying levels of baseline integration and/or decentralisation, the different health systems and policy/operational contexts. These differences also highlight the importance of considering context when planning and implementing interventions. Large improvements in TB diagnosis and treatment initiation observed in Cameroon suggest that

there was a substantial baseline case detection gap for TB in children. Although similar improvements were not achieved in Kenya, the intervention improved treatment outcomes leading to a reduction in mortality and DALYs.

Several factors can explain the lack of intervention effect observed in Kenya. Although active case finding was already occurring as SoC, TB diagnosis in children was mostly clinical and overdiagnosis was possible. Improvements brought in by the CAP-TB intervention potentially reduced overdiagnosis resulting in the observed no effect. The widespread healthcare worker strikes experienced in Kenya during the INPUT study adversely impacted the intervention. These resulted in fewer children being screened, diagnosed and subsequently treated. The enrolment period for the INPUT study overlapped with the COVID-19 pandemic which could have influenced intervention performance. During the COVID-19 pandemic, TB notifications decreased, with larger decreases for children, due to disruptions in health services and attendance, increased stigma around respiratory symptoms and fear of infection. The magnitude of this impact differed across countries.

These differences in detection and treatment success were the major determinants of cost-effectiveness in this analysis. Although the observed 10-fold increase in case detection in Cameroon significantly increased resource use and costs, the associated huge increases in life years saved resulted in the intervention being cost-effective. These results were robust to different assumptions including case fatality rate (see online supplemental appendix table S12).

Despite significantly improved treatment outcomes in Kenya, the observed lack of improvements in case detection meant the intervention was not cost-effective there. Cost-effectiveness results for Kenya were sensitive to different assumptions, due to this lack of change in detection. Assuming systematic review-based case fatality rates with no improvements in treatment outcomes resulted in the intervention being dominated by the SoC there (became more costly and less effective). These results suggest that interventions that improve case detection are likely to be cost-effective in settings where there is the most scope for improvement.

Our study draws major strength from the use of primary data collected alongside a randomised control study to inform pathways of care, resource use and intervention effects. The diverse nature of the two settings in terms of service integration and decentralisation, and the organisation of national TB control and TB care suggest these findings may be generalisable to other settings. However, context-specific adaptation of such interventions, based on existing levels of integration and decentralisation, is required to improve cost-effectiveness. Intervention costs were estimated using comprehensive country-specific budget and expenditure data for implementing the intervention activities. These approximated the additional costs that a public health system would incur to improve the utilisation of paediatric TB services (through increased access and improved services), beyond what the system currently provides. Therefore, these costs provide an estimate of programmatic costs required for scaling up the intervention such as costs for training and supervision, logistics or investment in resources beyond what is available to the healthcare system in these settings.

This study has some limitations worth highlighting. Data on the number of children systematically screened for TB symptoms on seeking care at health facilities were not available. Without these data, we used approximations based on data from the CaP-TB pre/post study done in parallel to the INPUT study across nine sub-Saharan African countries including Cameroon and Kenya.[18] While the assumptions better approximate screening under the intervention where systematic TB screening for all children seeking care was actively promoted, they may be less appropriate under the SoC. Our cost estimates may, therefore, be an underestimate or an overestimate. Our sensitivity analyses show our results are robust to these assumptions in Cameroon, but more sensitive to them for Kenya, where a lower effect of the intervention was found.

For pragmatic reasons, country-specific primary cost analyses were only performed to establish the additional costs associated with procedures introduced as part of the intervention. We applied unit costs for the core healthcare services available under the SoC estimated from publicly available sources. We made all necessary adjustments for costs derived from previous years or other countries, however, more recent and country-specific costs would closely reflect resource use and opportunity costs.

The INPUT study included some household child TB contacts who could have been initiated on TB preventive therapy after active disease was excluded. These were not followed in the study, therfore our analysis did not capture potential costs and benefits associated with TB preventive therapy. We did not model false positive TB, a potentially important factor in the context of the well-established challenges in the diagnosis of paediatric TB and the huge reliance on clinical diagnosis. False-positive TB can have potential adverse consequences including increased costs directly from unnecessary TB treatment and indirectly from second-line treatment for emerging drug-resistant TB. However, bacteriological testing (including Xpert) significantly increased under intervention although a statistically non-significant increase in bacteriological confirmation was observed (from 6/79 under SoC to 11/74 under intervention). Our analysis excluded drug-resistant TB which is associated with higher costs but is rare in children in these settings.

Evidence on the costs and cost-effectiveness of decentralised and family-centred, integrated models of TB care for children is very limited and has been highlighted as a research priority by the WHO Guideline Development Group on the management of TB in children and adolescents.[14] Very few studies with a focus on children have been published to

date. A systematic review by Alsdurf *et al*[32] of studies providing cost and outcome data for systematic TB screening, found ICERs of between US$281 and US$698 per DALY averted among the general population, US$619/quality-adjusted life-year (QALY) gained among children and US$372–US$3718/DALY averted among close contacts. A few studies report ICERs of TB case-finding interventions in children. These include Mafirakureva *et al*[33] who considered Xpert Ultra on stool and found ICERs of US$132 and US$94 per DALY averted in Ethiopia and Indonesia, respectively; Mupere *et al*[34] who reported US$538 per QALY gained in Uganda; and Debes *et al*[35], who found ICERs ranging from US$106 to US$184 per life-year gained in Uganda. In an analysis of a combined intervention of intensified case finding and strengthened household contact management and TPT provision across nine sub-Saharan African countries, Mafirakureva *et al*[18] reported ICERs of between US$135 and US$6804/DALY averted. More recently, d'Elbée *et al*[36] reported ICERs ranging between US$263 and US$342 per DALY averted for decentralising childhood TB diagnosis at district hospital compared with SoC. Our study is the first cost–utility analysis of TB case finding in children based on a randomised trial comparing the integration of paediatric TB services into child healthcare services (intervention) to current approaches to offering paediatric TB services (the SoC).

Judgements on whether an intervention represents good value for money are commonly based on comparing the estimated ICER to a cost-effectiveness threshold, and interventions with ICERs falling below the threshold are considered cost-effective. However, most countries, especially in the low-income and middle-income category, do not have explicit thresholds specified. In the absence of explicit cost-effectiveness thresholds in Cameroon and Kenya, as in most low-income and middle-income countries, we assumed a threshold of 0.5×GDP per capita for each country. This assumption generally aligns with empirically estimated thresholds based on health spending data for these countries.[37–39] Specific estimates for these countries differ in their assumptions and results, including: for Cameroon, US$49–US$654,[37] US$112–US$140[38] and US$155–US$386[40]; and for Kenya, US$$32–US$519,[37] US$491–US$647[38] and US$270–US$671.[40] However, the final choice of a cost-effectiveness threshold rests with decision-makers. Cost-effectiveness acceptability curves (figure 3) can be used to evaluate the probability of cost-effectiveness at any chosen threshold.

Integrating TB services into child healthcare services can potentially improve TB diagnosis and treatment initiation and may be cost-effective depending on existing levels of health services for paediatric TB and the choice of threshold. Baseline coverage of services and TB detection and treatment are likely to determine cost-effectiveness. Future empirical work could explore targeting specific elements of interventions that may improve cost-effectiveness in different settings.

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