

Effectiveness of a community-based approach for the investigation and management of children with household tuberculosis contact in Cameroon and Uganda: a cluster-randomised trial

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Summary

Background Globally, the uptake of tuberculosis-preventive treatment (TPT) among children with household tuberculosis contact remains low, partly due to the necessity of bringing children to health facilities for investigations. This study aimed to evaluate the effect on TPT initiation and completion of community-based approaches to tuberculosis contact investigations in Cameroon and Uganda.

Methods We did a parallel, cluster-randomised, controlled trial across 20 clusters (consisting of 25 district hospitals and primary health centres) in Cameroon and Uganda, which were randomised (1:1) to receive a community-based approach (intervention group) or standard-of-care facility-based approach to contact screening and management (control group). The community-based approach consisted of symptom-based tuberculosis screening of all household contacts by community health workers at the household, with referral of symptomatic contacts to local facilities for investigations. Initiation of TPT (3-month course of rifampicin–isoniazid) was done by a nurse in the household, and home visits for TPT follow-up were done by community health workers. Index patients were people aged 15 years or older with bacteriologically confirmed, drug-susceptible, pulmonary tuberculosis diagnosed less than 1 month before inclusion and who declared at least one child or young adolescent (aged 0–14 years) household contact. The primary endpoint was the proportion of declared child contacts in the TPT target group (those aged <5 years irrespective of HIV status, and children aged 5–14 years living with HIV) who commenced and completed TPT, assessed in the modified intention-to-treat population (excluding enrolled index patients and their contacts who did not fit the eligibility criteria). Descriptive cascade of care assessment and generalised linear mixed modelling were used for comparison. This study is registered with ClinicalTrials.gov (NCT03832023).

Findings The study included nine clusters in the intervention group (after excluding one cluster that did not enrol any index patients for >2 months) and ten in the control group. Between Oct 14, 2019 and Jan 13, 2022, 2894 child contacts were declared by 899 index patients with bacteriologically confirmed tuberculosis. Among all child contacts declared, 1548 (81.9%) of 1889 in the intervention group and 475 (47.3%) of 1005 in the control group were screened for tuberculosis. 1400 (48.4%) child contacts were considered to be in the TPT target group: 941 (49.8%) of 1889 in the intervention group and 459 (45.7%) of 1005 in the control group. In the TPT target group, TPT was commenced and completed in 752 (79.9%) of 941 child contacts in the intervention group and 283 (61.7%) of 459 in the control group (odds ratio 3.06 [95% CI 1.24–7.53]).

Interpretation A community-based approach using community health workers can significantly increase contact investigation coverage and TPT completion among eligible child contacts in a tuberculosis-endemic setting.

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Introduction

WHO estimates that more than 1 million children develop tuberculosis every year, but that the majority are undiagnosed or unreported.¹ The highest case detection gap and mortality rates in children are among young children (aged <5 years).^{2,3} Mathematical models estimate that 7.5 million children, of which 2 million

are younger than 5 years, are infected with *Mycobacterium tuberculosis* each year.⁴ Infection commonly takes place in the household and, if infected, progression to disease can be rapid.⁵ Therefore, to facilitate the early detection and treatment of contacts with disease, as well as the prevention of disease in those at risk following infection, contact investigation for all children living in the same

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Research in context

Evidence before this study

In tuberculosis-endemic countries, the uptake of tuberculosis-preventive treatment (TPT) among household child contacts remains low. One of the challenges is the necessity for parents to bring children to the health facility for contact investigation and management of TPT. Community-based approaches for household child contact screening and TPT management could increase the uptake of TPT and would be aligned with the WHO recommendations to use decentralised and family-centred approaches in children exposed to tuberculosis. Large trials had evaluated the effects of community-based tuberculosis household contact screening on tuberculosis detection rates, but very few have included TPT management at the household level. We searched PubMed up to Dec 29, 2022, for studies reporting community-based approaches for the management of TPT among household child contacts. We used the search terms ("tuberculosis preventive treatment" OR "tuberculosis preventive therapy") AND ("household child contacts") AND ("community"), with no language restrictions. We identified two relevant publications but no randomised control trials: one prospective cohort in Ethiopia reporting experience of delivering preventive isoniazid treatment using health extension workers, and one study reporting experience of a community-based programme for delivering a 3-month regimen of rifampicin-isoniazid preventive treatment by nurses in Eswatini. Both studies reported a high proportion of participants completing treatment (89% in Ethiopia and 93% in Eswatini) and good feasibility, but none compared the community-based approach with the facility-based standard of care.

Added value of this study

The CONTACT study is the first randomised controlled trial to compare a community-based approach for TPT management by community health workers with the facility-based standard of care. The study shows that community-based contact investigations and TPT management done by community health workers increases the coverage, initiation, and completion of TPT among child contacts at high risk (aged <5 years, or aged 5–14 years with HIV). The proportion of child contacts of all ages declared by the index patients who were screened for tuberculosis was increased in the intervention group (81.9%) versus the control group (47.3%). The proportion of declared child contacts in the TPT target group who commenced and completed TPT was also increased in the intervention group (79.9%) versus the control group (61.7%). Among all child contacts who commenced TPT, 93.5% completed treatment in the intervention group and 76.7% in the control group.

Implications of all the available evidence

This multicountry cluster-randomised trial confirms the feasibility of decentralising contact investigation and TPT management at the household level and shows that this community-based family-centred approach using community health workers is effective in increasing child contact screening coverage, TPT uptake, and treatment completion as compared with the facility-based standard of care. This approach could be integrated within other health interventions at the community level that involve community health workers.

household as a person with bacteriologically confirmed tuberculosis is strongly recommended by WHO.⁶

Among child contacts without tuberculosis disease, young children (aged <5 years) and children living with HIV are recognised as groups at high risk who should be started on tuberculosis-preventive treatment (TPT).⁷ However, TPT uptake among young children with household tuberculosis contact remains low—only 55% of the target set for the 2018–22 period at the UN high-level meeting on tuberculosis was reached by the end of 2022.¹ The health system-related and patient-related challenges that explain this low uptake of TPT in resource-limited countries are well described.⁸ The usual approach to contact investigation is that the index patient is asked to bring all household child contacts to the health facility for symptom screening and TPT initiation, if eligible. There are many barriers to this passive approach, such as scheduling or financial challenges, long waiting periods, and reluctance by families or health-care workers towards evaluation and initiation of TPT in a healthy child.⁹

WHO now recommends the use of family-centred approaches in children exposed to tuberculosis.⁶ Since 2006, WHO has recommended that symptom-based

screening alone can be used in resource-limited settings to detect child contacts who require further evaluation for tuberculosis and to determine eligibility for TPT.^{10–12} TPT can be provided to asymptomatic risk child contacts at high risk (children aged <5 years and children living with HIV) without requiring a chest x-ray to rule out disease or a test to confirm *M tuberculosis* infection.⁷ This approach could facilitate community-based implementation of child contact screening and management.¹³ However, no previous study has evaluated the effectiveness of symptom screening and TPT management of a community-based intervention with direct comparison to the facility-based standard of care.

We conducted a pragmatic, cluster-randomised, controlled trial (Community Intervention for TB Active Contact Tracing and Preventive Therapy Management; CONTACT) that evaluated a community-based intervention by community health workers for the investigation of children with household tuberculosis contact in Cameroon and Uganda. The primary objective of the study was to compare the proportion of children with household tuberculosis contact who commenced and completed TPT between a community-based intervention and the standard of care.

Methods

Study design and participants

The CONTACT study was a multicountry, two-arm, parallel, cluster-randomised, controlled trial comparing two approaches for household child contact investigation and management: a decentralised approach at the household level (intervention group) and the facility-based standard of care (control group).¹⁴ The cluster-randomised design was chosen for reasons dictated by the intervention, as it would not be possible to propose both community-based and facility-based interventions in the same health facility, and to avoid contamination between the two groups. Details of the study settings, population, and methodology have previously been published.¹⁴

Cameroon and Uganda are countries with high tuberculosis incidence and with less than 50% TPT coverage for child contacts younger than 5 years.¹⁵ Tuberculosis services are mainly provided at secondary and tertiary health-care facilities in Cameroon, and are decentralised to primary health-care facilities in Uganda. We included 20 clusters (ten per country) across health facilities, supported by the paediatric CaP-TB project, that registered at least 50 patients with bacteriologically confirmed tuberculosis in the year preceding the study implementation. Clusters were district hospitals in the Central and Littoral regions of Cameroon and district hospitals or primary health centres in four districts in the South-Western region of Uganda (some clusters included two facilities to meet the criterion of having at least 50 index patients).¹⁶ Participants were people living within a 50 km radius of the facilities.

Index patients were people aged 15 years or older with bacteriologically confirmed, drug-susceptible, pulmonary tuberculosis diagnosed less than 1 month before inclusion and who declared at least one child or young adolescent (aged 0–14 years) household contact, per the WHO definition of household contact (ie, sharing the same enclosed space for frequent or extended periods of time or having slept in the same bed during the past 3 months).¹⁷ Facility staff from both study groups and community health workers from the intervention group were trained to identify contacts using the WHO definition, and compliance with the definition was monitored. For study reporting, we defined contacts declared by the index patient at the time of their inclusion as “declared” contacts, and contacts actually enrolled in the study after obtaining informed consent as “enrolled” contacts. This distinction enabled comparison of the coverage of contact investigations between the two groups and the analysis of contacts who were not initially declared but who were subsequently identified through household visits.

The study was approved by the WHO Ethics Research Committee, the Advarra Institutional Review Board in the USA, the Cameroon National Ethics Committee for Human Health Research, the Research Ethics Committee

of the Mbarara University of Science and Technology in Uganda and the Uganda National Council for Science and Technology. Index patients, contacts’ parents and guardians (including those of children who were not family of the index patient), and contacts were asked to sign written informed consent and assent (for children aged 7–14 years in Cameroon and 8–14 years in Uganda) after receiving verbal and written information. Index patients were given the option to return home with the written information to discuss with household members before signing consent. If the index patient refused to consent, their contacts were invited for screening at the facility per the standard of care. If a participant was not literate, an impartial witness who was able to read was present during the informed consent discussion and signed the consent. Children’s parents or guardians and contacts could refuse HIV testing and still participate in the study.

Randomisation and masking

Patients were randomly allocated (1:1) to receive a community-based approach (intervention group) or standard-of-care facility-based approach to contact screening and management (control group). The community-based approach consisted of symptom-based tuberculosis screening of all household contacts by community health workers at the household, with referral of symptomatic contacts to local facilities for investigations. TPT initiation was done by a nurse in the household, and home visits for TPT follow-up were done by community health workers. Randomisation was done by an independent statistician 3 months before inclusions commenced, and was stratified by country and covariate-constrained to account for the number of patients with bacteriologically confirmed tuberculosis notified per cluster during the previous year, using R software (cvcrand package).¹⁸ Participants, health-care providers, and study investigators were not masked to the allocation of the cluster.

Procedures

Study procedures are detailed in the published protocol and appendix 2 (pp 4–5).¹⁴ Investigators were informed of cluster allocation 1 month before inclusions commenced to allow for organisation of training. As part of the study, health-care providers from both groups were trained on the informed consent procedure, TPT adherence assessment, and safety management and reporting. Community health workers were trained on symptom screening, HIV testing, TPT adherence, and safety management.⁹

Index patients in both study groups were asked to list all household contacts by the tuberculosis focal person (TFP; the national tuberculosis programme focal person at the facility level, who was in charge of treatment, contact tracing, screening, and preventive treatment and recording of tuberculosis cases).

There were differences by country in the control group due to differences in the standard of care (appendix 2 pp 4–5). In Cameroon, the TFP asked the index patient to bring household child contacts to the health facility for symptom screening, with a focus on children younger than 5 years; in Uganda, the TFP could also screen at the community level.¹⁸ Asymptomatic children eligible for TPT were started on treatment by the TFP at the facility, and had monthly facility-based follow-up. For this study, a TPT treatment card was introduced to support adherence and provide data on the number of doses taken for comparison between study groups.

Activities in the intervention group were the same in both countries; the main difference from the control group was that services were provided at household level by community health workers. A trained community health worker and a research assistant visited the household to screen all contacts within 2 weeks after inclusion of the index patient. Community health workers were identified among existing community health workers involved in tuberculosis activities (Uganda) or other health activities (Cameroon).⁹ HIV testing was proposed for child contacts aged 5–14 years with unknown HIV status to identify if they would belong to the TPT target group (ie, were positive for HIV). Symptomatic contacts were referred to the facility for investigations with a referral slip, without transport refunds but with a tracking of referrals. Asymptomatic contacts eligible for TPT received another visit after 1 week by a nurse to initiate TPT. For contacts with symptoms not suggestive of tuberculosis, a follow-up screening visit was done by the community health workers after 2 weeks. The TPT follow-up and dispensation was done in the household by the community health workers after 1 week, 2 weeks, and then monthly, with assessment of tuberculosis symptoms, critical signs, and rifampicin and isoniazid tolerability using checklists (appendix 2 p 4). Children with critical signs or symptoms of poor TPT tolerability were immediately referred to the health facility and transport was refunded. Parents or guardians were briefed on how to record daily TPT doses on the treatment card, and cards were verified for completeness and consistency with the remaining pills at each follow-up visit.

In both groups, investigations for tuberculosis were done at the facility level including clinical examination, chest x-ray, and Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) testing of sputum, nasopharyngeal aspirate, or gastric aspirate. Children diagnosed with tuberculosis were treated in accordance with national guidelines, and those not diagnosed commenced TPT at the facility if eligible, with follow-up done in the household by the community health workers if the child was from an intervention cluster. In both groups, the TPT regimen consisted of 3 months of daily rifampicin and isoniazid and using the dispersible, fixed-dose combination formulation (75 mg rifampicin and 50 mg isoniazid for contacts weighing <25 kg), procured by the CaP-TB

project, as the national programme did not yet recommend this regimen when the study started.¹⁹ 6 months of daily isoniazid was given to children with HIV to prevent drug–drug interactions between antiretrovirals and rifampicin.

Between March 27 and Aug 28, 2020 in both countries, and between June 18 and Aug 11, 2021 in Uganda, enrolment was stopped due to COVID-19-related lockdowns. To ensure that all children who commenced TPT were able to complete treatment, the remaining doses were provided to caregivers and follow-up visits were replaced by telephone calls by research assistants in both groups.

Outcomes

The primary outcome was the proportion of children who commenced and completed TPT among child contacts younger than 5 years and children living with HIV aged 5–14 years (the TPT target group) declared by index patients. TPT completion was defined as intake of 90% of recommended doses within 133% of the planned TPT duration.¹⁷ The prespecified secondary outcomes included the proportion of contacts (all ages) screened for tuberculosis among those declared by index patients; the proportions of enrolled children investigated for tuberculosis and diagnosed with tuberculosis among those with tuberculosis symptoms; the proportion of enrolled children diagnosed with tuberculosis who started on tuberculosis treatment, and their outcomes; the proportion of enrolled child contacts in the TPT target group who commenced TPT; the proportion who completed TPT of those started on TPT; and the proportion of child contacts diagnosed with tuberculosis during 6 months of follow-up from the date of initial screening.¹⁴ Cost-effectiveness outcomes are reported in a separate Article.²⁰ Acceptability outcomes, tuberculosis case detection between the pre-intervention period (1 year before intervention) and post-intervention period (1 year during intervention per model of care) using aggregated data from tuberculosis registers, and fidelity outcomes are still under analysis and will be reported in future publications.

Statistical analysis

For the sample size calculation, we used an estimated 60% TPT completion rate in the control group, based on a systematic review, and a 10% difference in the intervention group, considered to be the minimal clinically relevant difference.²¹ We considered a cluster coefficient variability of 50%, based on the variation in the number of bacteriologically confirmed tuberculosis patients between the clusters in the year before the intervention. An intracluster correlation of 0.01 was used. With these parameters, we needed at least 1500 declared child contacts of the TPT target group to have a power of 85% overall across the two countries. The study was not powered within the country. The type 1 error rate, α , was fixed at 5%.

Characteristics of index patients and contacts at enrolment were presented per study group and per country. We used a modified intention-to-treat (mITT) analysis for the primary outcome to exclude enrolled index patients and their contacts who did not fit eligibility criteria. Children who were lost to follow-up were included in the mITT analysis. The analysis was done at individual level with a logistic mixed model with a binomial distribution and logit link function, including the fixed effects of study group, country, and number of index patients per cluster (variable used for randomisation), and one random effect for the cluster. 95% CIs and p values were calculated on the basis of a t distribution with a degree-of-freedom correction to deal with the type 1 error inflation due to the small number of

clusters (≤ 30).²² The intraclass correlation coefficient was reported overall and per group. Four sensitivity analyses were done for the primary outcome: (1) using the number of enrolled children in the TPT target group as the denominator; excluding children who could not undergo the study procedures per their cluster allocation due to the COVID-19 pandemic (per-protocol approach) among (2) the declared child contacts and (3) the enrolled child contacts; and (4) with covariate adjustment on the location of cluster (rural vs urban) and the household size (number of contacts per household). As a secondary analysis, we did a cluster-level analysis of the primary outcome using risk ratio as the effect estimate.

For the analysis of the secondary outcomes, similar individual-level analyses using mixed models were

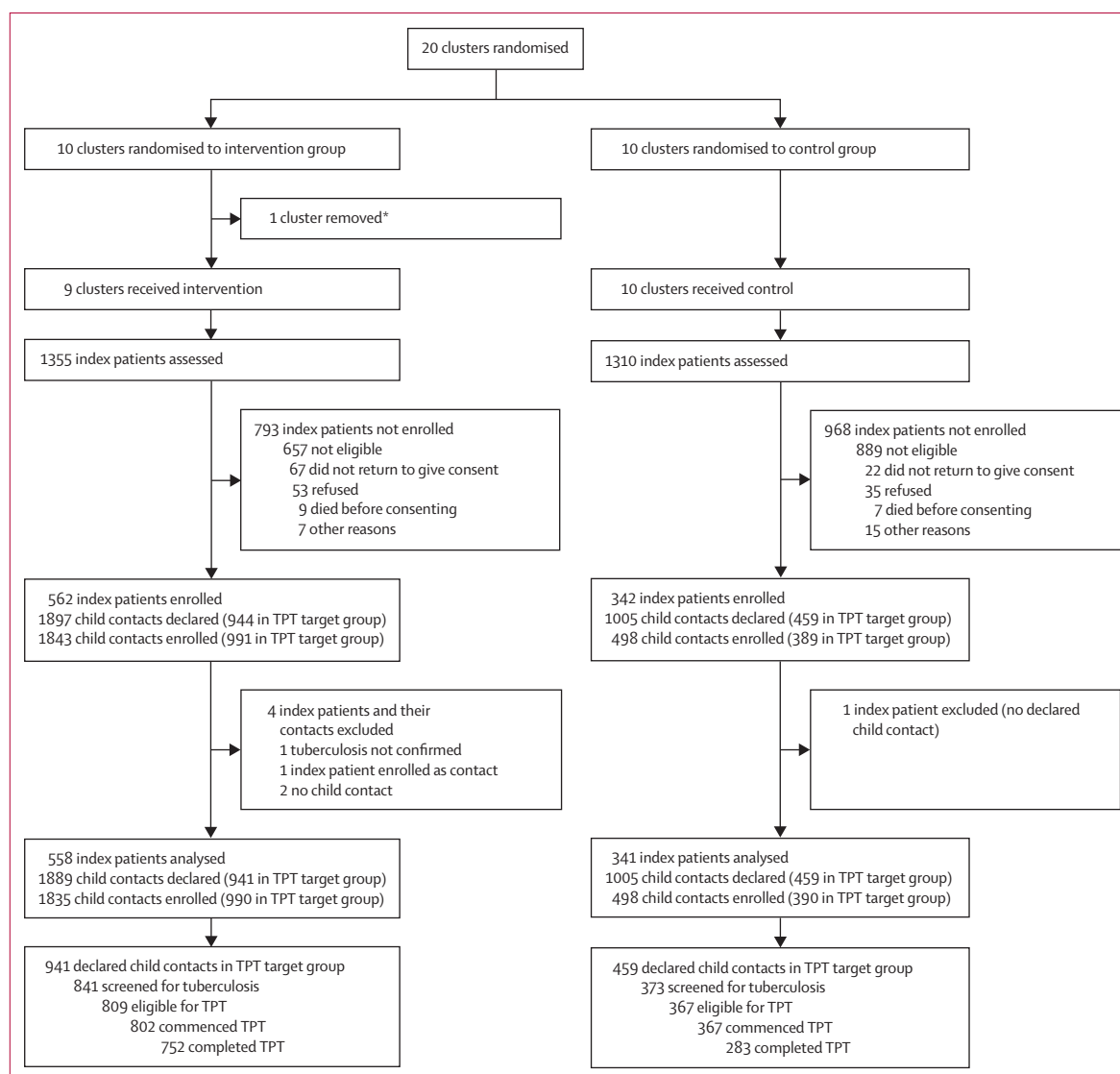


Figure 1: Trial profile

TPT=tuberculosis-preventive treatment. *One cluster in Cameroon was removed, per the protocol, because no index patients were identified who met the eligibility criteria for 2 consecutive months.

	Intervention group	Control group
Clusters		
Total	9	10
Health facilities	12	12
Rural clusters	6	6
Median households per cluster	67 (50–73)	31 (21–42)
Index patients		
Total	558	341
Living in rural cluster	312/558 (55.9%)	174/341 (51.0%)
Median age, years	38.4 (29–49)	36.5 (29–49)
Sex		
Female	207/558 (37.1%)	119/341 (34.9%)
Male	351/558 (62.9%)	222/341 (65.1%)
HIV positive*	139/556 (25.0%)	72/338 (21.3%)
Declared child contacts†		
Total	1889	1005
Age, years		
Median	5 (2–9)	5 (3–10)
<5	938/1889 (49.7%)	458/1005 (45.6%)
Sex		
Female	948/1889 (50.2%)	500/1005 (49.8%)
Male	941/1889 (49.8%)	505/1005 (50.2%)
Relation to index case‡		
Close family direct	781/1889 (41.3%)	501/1005 (49.9%)
Family other	1062/1889 (56.2%)	501/1005 (49.9%)
Not family	46/1889 (2.4%)	3/1005 (0.3%)
Enrolled child contacts§		
Total	1835	498
Age, years		
Median	4.6 (2–8)	3.1 (2–5)
<5	985/1835 (53.7%)	389/498 (78.1%)
Sex		
Female	921/1835 (50.2%)	238/498 (47.8%)
Male	914/1835 (49.8%)	260/498 (52.2%)
HIV positive*	7/1108 (0.6%)¶	1/216 (0.5%)¶
Relation to index case, n (%)		
Close family direct	602/1835 (32.8%)	260/498 (52.2%)
Family other	1167/1835 (63.6%)	238/498 (47.8%)
Not family	66/1835 (3.6%)	0/498

Data are n, median (IQR), or n/N (%). *Denominator is individuals with known HIV status. †Household child contacts declared by index patients, including those who were not enrolled afterwards. ‡“Close family direct” was for child contacts who were siblings, sons, or daughters of the index patient; “Family other” included all other family relations between the index patient and the child contact; “Not family” was for child contacts without a family relation with the index patient. §All household child contacts enrolled, including those who might not have been declared by the index patient. ¶Five HIV-positive child contacts in the intervention group and one in the control group were aged 5–14 years.

Table 1: Baseline characteristics for each group at the cluster and individual levels

used with the same fixed and random effects and correction method, focusing on the main outcomes of the cascade of care for symptom screening, detection, and TPT management. Cascade of care for TPT

management among enrolled child contacts was described before (October, 2019, to March, 2020) and during (September, 2020, to January, 2022) the COVID-19 pandemic period. Primary and secondary outcomes were also presented per country without comparison between the two groups. Analyses were done with R (version 4.1.2) and Stata (version 15.0).¹⁴

This study is registered with ClinicalTrials.gov (NCT03832023).

Role of the funding source

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

Results

Of the 20 clusters included, ten were allocated to the intervention group and ten to the control group. In accordance with the protocol, one cluster in the intervention group in Cameroon was withdrawn because it did not enrol any index patients for more than 2 months after randomisation (figure 1). Between Oct 14, 2019 and Jan 13, 2022, 2665 bacteriologically confirmed index patients were assessed for study eligibility (65–203 patients per cluster in Uganda and 111–313 in Cameroon), 903 (33.9%) were enrolled, and 899 were retained for analysis (558 in the intervention group and 341 in the control group; figure 1; appendix 2 p 6). The main reason for index patients' ineligibility was that they reported having no household child contacts (1317 [74.7%] of 2665; appendix 2 p 7). The median age of analysed index patients was 37.4 years (IQR 29.1–48.7), 326 (36.3%) were female, 573 (63.7%) were male, and 211 (23.6%) of 894 with a known HIV status were HIV positive (table 1; appendix 2 p 8). Analysed index patients declared 2894 child contacts younger than 15 years, among whom 1400 (48.4%) were in the TPT target group: 941 (49.8%) of 1889 declared child contacts in the intervention group (938 children aged <5 years and three children aged 5–14 years with HIV; mean 105 per cluster [SD 43]) and 459 (45.7%) of 1005 in the control group (458 children aged <5 years and one child aged 5–14 years with HIV; mean 46 per cluster [SD 30]; figure 1).

Among the children in the TPT target group declared by the index patients, 841 (89.4%) of 941 in the intervention group and 373 (81.3%) of 459 in the control group were screened for tuberculosis. After ruling out tuberculosis (asymptomatic or symptomatic but not diagnosed with tuberculosis), 809 (96.2%) of 841 contacts in the intervention group and 367 (98.4%) of 373 in the control group were eligible for TPT. Of those eligible, 802 (99.1%) and 367 (100%) commenced TPT, and 752 (93.8%) and 283 (77.1%) of those who commenced TPT completed the treatment in the intervention and control groups, respectively (figure 1). Therefore, treatment was commenced and completed in 752 (79.9%) of 941 declared child contacts in the intervention group and 283 (61.7%) of 459 in the control group (odds ratio [OR] 3.06 [95% CI

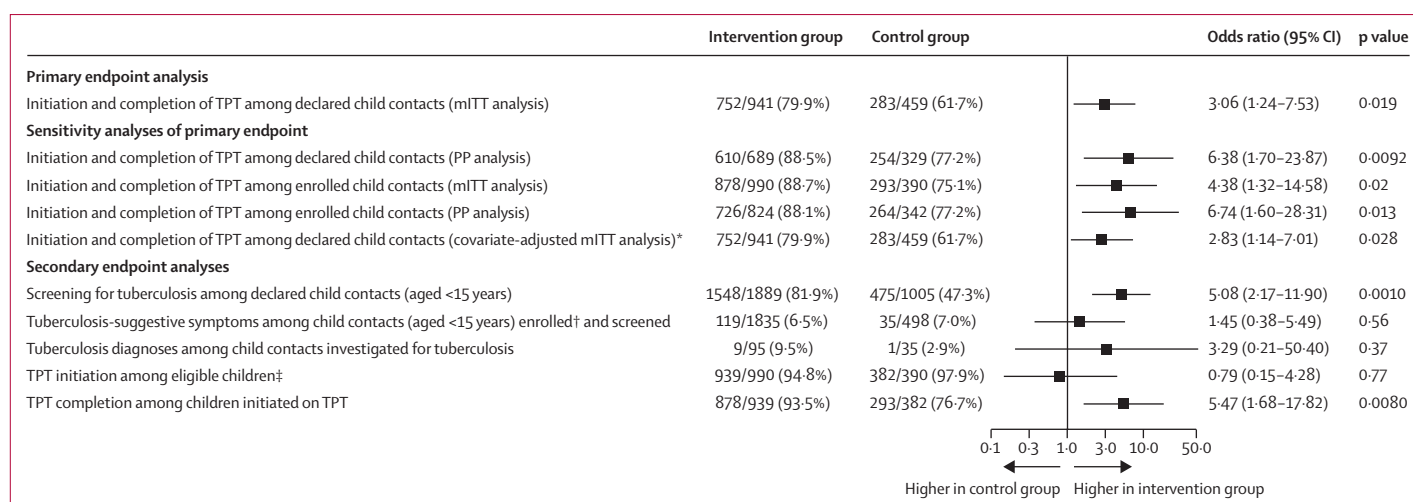


Figure 2: Results of primary and secondary outcome analyses

Primary endpoint analyses (including sensitivity analyses) were based on declared or enrolled child contacts in the TPT target group (defined as children aged <5 years, and children aged 5–14 years with HIV). mITT analyses excluded contacts of index patients excluded because of deviation from eligibility criteria. PP analyses excluded contacts who could not receive the intervention or control due to COVID-19 pandemic-related restrictions. Intracluster correlation for the primary outcome analysis was 0.1 (0.01 for the control group and 0.13 for the intervention group). TPT=tuberculosis-preventive treatment. mITT=modified intention-to-treat. PP=per-protocol. *Covariate-adjusted analysis for location of cluster (rural vs urban) and household size. †Includes contacts who were enrolled but not declared. ‡Eligible children were those in the TPT target group with tuberculosis disease ruled out.

1.24–7.53], $p=0.019$; figure 2; appendix 2 p 9). In the cluster-level analysis, consistent results using risk ratio were obtained, although the sensitivity analysis results did not meet the significance threshold (appendix 2 p 10). The effect of the intervention persisted after exclusion of children who did not receive the intervention or control per protocol due to COVID-19 pandemic-related restrictions (figure 2). Primary outcome results at the country level are presented in appendix 2 (p 11).

Of the 2894 declared child contacts younger than 15 years, tuberculosis screening was done in 1548 (81.9%) of 1889 in the intervention group and 475 (47.3%) of 1005 in the control group (OR 5.08 [95% CI 2.17–11.90]). The proportion of screened child contacts among those declared was similar in the intervention group in both countries (821 [82.9%] of 990 in Cameroon and 727 [80.9%] of 899 in Uganda), but was lower in the control group in Cameroon (262 [39.7%] of 660) than in Uganda (213 [61.7%] of 345). An additional 310 child contacts were screened who had not been declared by the index patient, of whom 287 (92.6%) were in the intervention group (appendix 2 p 12). Therefore, a total of 2333 child contacts were enrolled and screened, of whom 1835 (78.7%) were in the intervention group. The ratio of child contacts screened per index case was higher in the intervention group (3.3) than in the control group (1.5).

Of the 2333 child contacts enrolled, 1159 (49.7%) were female, and eight (0.6%) of 1324 with a known HIV status had HIV (two children aged <5 years and six aged 5–14 years), with similar distributions between the two groups (table 1; appendix 2 p 8). Tuberculosis symptoms were observed in 119 (6.5%) of 1835 screened child contacts in the intervention group and 35 (7.0%) of

498 in the control group (OR 1.45 [95% CI 0.38–5.49], $p=0.56$; table 2). In both groups, the most common symptom was a cough lasting for more than 2 weeks (appendix 2 p 13).

Among enrolled child contacts with tuberculosis symptoms, 95 (79.8%) of 119 and 35 (100%) of 35 were investigated, and nine (9.5%) of 95 and one (2.9%) of 35 of those investigated were diagnosed with tuberculosis in the intervention and control groups, respectively (table 2). Overall, nine (0.5%) of 1835 and one (0.2%) of 498 enrolled child contacts were diagnosed with tuberculosis in the intervention and control groups, respectively (OR 1.82 [95% CI 0.13–26.24]). Results by country are presented in appendix 2 (p 14). Of the 85 child contacts investigated for tuberculosis in Cameroon, 73 (85.9%) had an Xpert MTB/RIF test and ten (11.8%) had a chest x-ray; in Uganda, 39 (86.7%) of the 45 children investigated were tested with Xpert MTB/RIF and one (2.2%) by x-ray.

Among 907 enrolled contacts in the TPT target group in the intervention group who were deemed negative on screening by community health workers, 906 (99.9%) were confirmed negative by a nurse during the TPT initiation visit.

Among contacts aged 15 years or older declared by index patients, 1137 (80.2%) of 1417 in the intervention group and 60 (7.5%) of 805 in the control group were screened. Only two contacts, in the intervention group, were diagnosed with tuberculosis (appendix 2 p 15).

Among the enrolled contacts in the TPT target group who were screened, TPT was started in 939 (94.8%) of 990 children in the intervention group and 382 (97.9%) of 390 in the control group (OR 0.79 [95% CI 0.15–4.28]). Among those who started TPT, 878 (93.5%) of 939 in the

	Intervention group (n=1835)*	Control group (n=498)*	Odds ratio (95% CI)†	p value
Screened for tuberculosis	1835/1835 (100%)	498/498 (100%)
Positive on initial screening	96/1835 (5.2%)	35/498 (7.0%)
Positive on initial or repeat assessment‡	119/1835 (6.5%)	35/498 (7.0%)	1.45 (0.38–5.49)	0.56
Investigated for tuberculosis	95/119 (79.8%)§	35/35 (100%)	NA	NA
Clinical examination	94/95 (98.9%)	35/35 (100%)
Tuberculosis suggestive	84/94 (89.4%)	34/35 (97.1%)
Sample collected	82/95 (86.3%)	34/35 (97.1%)
Xpert MTB/RIF test done	78/95 (82.1%)	34/35 (97.1%)
<i>Mycobacterium tuberculosis</i> detected	6/78 (7.7%)	0/34
Chest x-ray done	9/95 (9.5%)	2/35 (5.7%)
Tuberculosis suggestive	2/9 (22.2%)	1/2 (50.0%)
Final diagnosis of tuberculosis	9/95 (9.5%)	1/35 (2.9%)	3.29 (0.21–50.40)	0.37
Tuberculosis treatment started	8/9¶	1/1
Tuberculosis treatment success	8/8	1/1

Data are n/N (%) except where otherwise specified. NA=not available (analysis not valid due to presence of data separation). *Denominators are the number of children enrolled, including children not declared by the index case but who were seen either at a facility or in the household and were enrolled and screened because they met the case definition for household contact. †Using a logistic mixed model with a binomial distribution and logit link function including the fixed effects of study group, country, and number of bacteriologically confirmed index patients per cluster (variable used for randomisation), and one random effect for the cluster for specific study outcomes, per the study protocol. ‡In the intervention group, of 194 children who need reassessment, 174 were reassessed and 23 had a positive result on reassessment; in the control group, three needed reassessment, one was reassessed, and none had a positive result. §24 children did not reach the facility. ¶One child diagnosed with tuberculosis did not start treatment (due to parental refusal).

Table 2: Cascade of care for case detection and treatment for tuberculosis disease in children (aged <15 years) with tuberculosis contact

intervention group and 293 (76.7%) of 382 in the control group completed the treatment (5.47 [1.68–17.82]; table 3, figure 3). Of enrolled contacts in the TPT target group who were screened, TPT was commenced and completed in 878 (88.7%) of 990 in the intervention group and 293 (75.1%) of 390 in the control group (4.38 [1.32–14.58]). The difference in TPT completion between the intervention and control groups was 11.5% (88.5% vs 77.0%, respectively) in Cameroon and 20.0% (96.2% vs 76.2%, respectively) in Uganda (appendix 2 p 16).

In both groups, treatment discontinuation was due to a parent's or guardian's decision in more than 85% of cases, with refusal to continue treatment (38 [70.4%] of 54 children with TPT interruption due to decisions by parent or guardian) being the most common reason in the intervention group and operational issues related to travel or transport (45 [54.9%] of 82) most common in the control group. Of the 1321 children started on TPT, treatment was discontinued due to suspicion of drug toxicity in two (0.2%) participants (one with suspicion of peripheral neuropathy and one with suspicion of hepatotoxicity), diagnosis of tuberculosis in one (0.1%) participant, and poor TPT adherence in three (0.2%) participants (appendix 2 p 17). The cascade of care for TPT management before and during the COVID-19 period is shown in appendix 2 (p 1).

After 6 months of follow-up, two children (from the intervention group) were diagnosed with clinical tuberculosis after being started on TPT (two [0.2%] of 1321): one (3 months old) had completed TPT and one (16 months old) was on TPT. There were no tuberculosis incident cases among 1002 child contacts (954 aged ≥ 5 years without HIV) who did not commence TPT.

Discussion

We report evidence from a cluster-randomised trial that a community-based approach increased screening coverage and improved TPT completion compared with a facility-based approach among children with household tuberculosis contact in Cameroon and Uganda. The findings are robust, with consistent results across different sensitivity analyses, including a per-protocol analysis that excluded child contacts followed up during the country COVID-19-related lockdowns. With a good balance of rural and urban clusters and different levels of health facilities, the CONTACT study findings are generalisable as they reflect the variety of settings that might be encountered in a national scale-up. Previous randomised controlled trials have evaluated the effects of household contact symptom screening on tuberculosis detection, but none has evaluated TPT management.^{22–26} In the CONTACT study, the primary endpoint was assessed among all declared child contacts in the TPT target group to account for potential increased enrolment under the community-based approach and to have a more stringent comparison between the two groups.

Compared with the standard of care, the community-based approach significantly improved the screening coverage and assessment of child contacts for TPT eligibility. The household visit identified additional children who were not declared by the index patient. Screening coverage was also much higher among older child contacts (aged 5–14 years) and adult contacts in the intervention group. Older child and adult contacts not living with HIV have not been priority groups for screening under programmatic conditions in either Cameroon or Uganda, which might explain why most screened child contacts in the control group were in the TPT target group. WHO has recently recommended that all contacts without tuberculosis should be considered eligible for TPT, including those not living with HIV.⁷ Globally, TPT coverage in this group of contacts is less than 5%,¹ and the recommendation for chest x-ray in addition to symptomatic assessment to rule out tuberculosis might be a barrier for implementation in many resource-limited settings.¹⁶

Notably, all but one child screened negative by community health workers in this study were confirmed as asymptomatic at the TPT initiation visit by the nurse, suggesting that task shifting of symptom screening to community health workers is potentially feasible.

The case detection rate of tuberculosis among child contacts of only 0.5% is similar to that found in a

	Intervention group (n=990)*	Control group (n=390)*	Odds ratio (95% CI)†	p value
Screened for tuberculosis	990/990 (100%)	390/390 (100%)
Negative on initial screening	827/990 (83.5%)	364/390 (93.3%)
Negative on initial and repeat assessment‡	913/990 (92.2%)	365/390 (93.6%)	1.61 (0.42–6.20)	0.46
Positive on screening, tuberculosis not diagnosed§	62/990 (6.3%)	22/390 (5.6%)
Tuberculosis disease ruled out	975/990 (98.5%)	387/390 (99.2%)
Assessed for contraindication to TPT	946/975 (97.0%)	384/387 (99.2%)
Eligible for TPT	946/946 (100%)	382/384 (99.5%)
Commenced TPT	939/946 (99.3%)¶	382/382 (100%)	NA	NA
Completed TPT	878/939 (93.5%)	293/382 (76.7%)	5.47 (1.68–17.82)	0.0080

Data are n/N (%) except where otherwise specified. NA=not available (analysis not valid due to presence of data separation). TPT=tuberculosis-preventive treatment.
 *Denominators are the number of children enrolled, including children not declared by the index case but who were seen either at a facility or in the household and were enrolled and screened because they met the case definition for household contact (two in the intervention group and one in the control group). †Using a logistic mixed model with a binomial distribution and logit link function including the fixed effects of study groups, country, and number of bacteriologically confirmed index patients per cluster (variable used for randomisation), and one random effect for the cluster for specific secondary outcomes, per the study protocol. ‡In the intervention group, 110 children needed reassessment, 102 were reassessed, and 87 had a negative screening after reassessment; in the control group, only one child needed reassessment and the result was negative. §Six of 68 children positive on screening in the intervention group and one of 23 in the control group were diagnosed with tuberculosis.
 ¶Seven children did not commence TPT due to parental refusal (six children) or having moved to another region (one child).

Table 3: Cascade of care for TPT of child contacts in the TPT target group

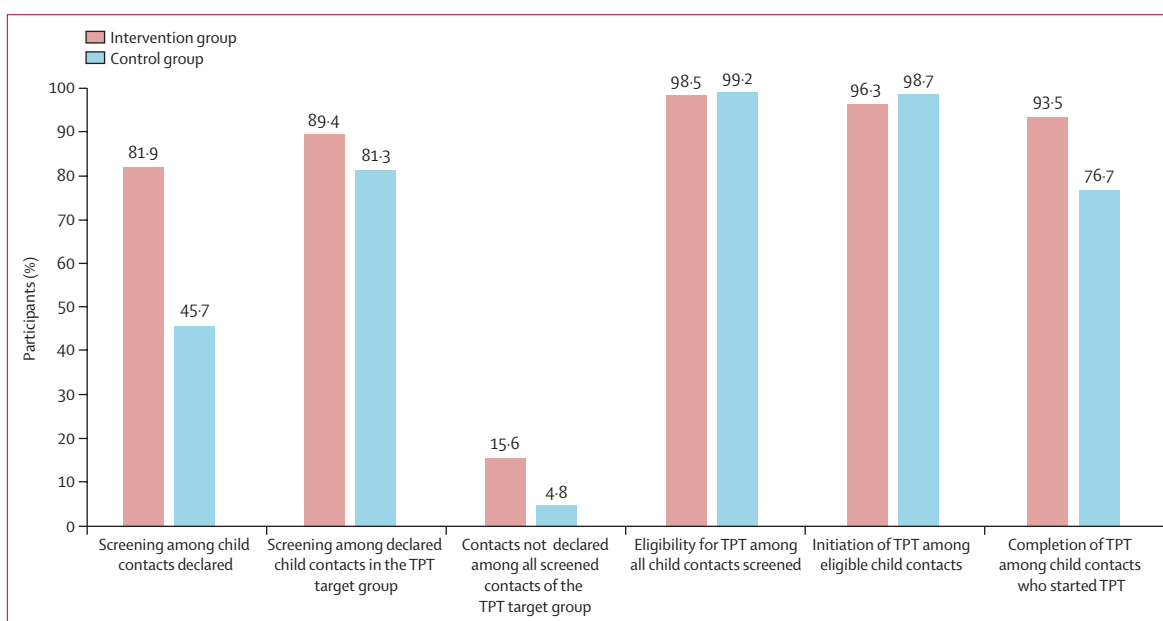


Figure 3: Cascade of care for all child contact investigations and management of TPT in the intervention and control groups
 TPT=tuberculosis-preventive treatment.

community-based programme in Eswatini (0.5%),²⁷ but lower than that reported in systematic reviews for child and adolescent household contacts (1–3%)^{21,28} and by operational research projects in Cameroon (2.8%) and Uganda (2.4%).^{29–31} The lower proportion of symptomatic children investigated for tuberculosis in the intervention group compared with the control group was mainly due to losses during the referral from households. Transport of children to the health facility after screening was not supported by the study. This potential limitation of community-based contact investigation is, however,

outweighed by the increased coverage achieved through this approach, and could be mitigated by implementing close monitoring of referrals and by financial schemes to reduce family costs. Most children had specimens collected for Xpert MTB/RIF testing, but few underwent chest x-ray. Access to x-ray is a challenge in resource-limited countries and the emergence of mobile technology and computer aided x-ray interpretation might facilitate community-based investigation.

The main causes of TPT interruption in the control group were related to a lack of transport or no time for

parents to come to the facility, supporting the community-based approach. In the intervention, the main reason for interruption was parents' refusal, but we were not able to further investigate this. Medical reasons for TPT discontinuation were few. Our findings are consistent with results of the Vikela Ekhaya programme in Eswatini, which reported 93% completion of TPT (either a 3-month course of rifampicin–isoniazid [77% of patients] or a 6-month course of isoniazid [23% of patients]), with follow-up done by nurses.²⁷ In the CONTACT study, follow-up by community health workers ensured acceptability of the family-centred intervention by household members, reduced the intervention cost,²⁰ and increased feasibility.⁹ The use of a 3-month course of daily rifampicin–isoniazid is likely to have enhanced feasibility of the intervention. Completion of the 6-month isoniazid regimen was 50% (27 of 54) before the start of the CaP-TB project at the same sites as the current study's control sites (unpublished data)—lower than the 76% in the control group in this study.

This study has several limitations. First, in both countries, an unexpectedly high proportion of index patients did not report any household child contact, more frequently in the urban clusters and in the control group. It is possible that people with tuberculosis living in an urban setting have fewer child household contacts because they are more likely to live away from families for professional reasons. A previous study in urban populations in four west African countries, including Cameroon, reported that 54% of people with tuberculosis did not have young household child contacts.³¹ Second, only facilities supported by the CaP-TB project were selected, in order to reduce heterogeneity between sites and ensure access to the 3-month rifampicin–isoniazid regimen at all sites. This restriction might limit the generalisability of findings to other communities that were not part of the CaP-TB project. Third, the number of clusters was low, although statistical analysis was adjusted to account for this. Fourth, despite the use of a covariate-constrained randomisation on the number of bacteriologically confirmed tuberculosis patients per cluster, there was an imbalance of the number of declared child contacts between the two groups, contributing to higher intercluster variability. However, we did not observe any difference in child contact characteristics between the two groups. Finally, we used the WHO household contact definition, which is very inclusive and might not always be well understood by the TFP, which could have contributed to the fact that 13% of enrolled child contacts were not declared by index patients.¹⁹

There are many advantages to using a community-based, family-centred approach. The approach limits the number of visits to the health facility and reduces cost for parents; offers the possibility to assess the entire household, including contacts who might not have been declared; and could facilitate the integration of other health interventions by community health workers, if

human resources are well planned.¹⁹ However, potential barriers and facilitators need consideration before implementation. The feasibility assessment done before the study suggested that stigma would not be a barrier to household visits in either country, and identified key factors including the importance of selection and training of community health workers, the need for a trust-based relationship between the TFP and community health workers, and the use of simplified tools for symptom screening, TPT adherence, and tolerability assessment.⁹ The motivation of community health workers is crucial to the success of the intervention and an incentive system to cover at least transport and communication costs is needed.⁹ Referral systems need to be put in place that prevent delayed tuberculosis diagnosis.¹⁹ Some patients might prefer facility-based approaches, such as those who are reluctant to disclose their tuberculosis diagnosis to other family members. Therefore, comprehensive and patient-centred approaches that give patients the possibility to choose the most comfortable approach for themselves and their family are likely to be better accepted. The intervention's cost-effectiveness and effect on patient costs are also key; we have reported these results in separate articles.^{31,32}

In conclusion, community family-centred approaches are effective for improving child contact investigations and could be integrated within other health interventions at the community level that involve community health workers. A community-based approach is likely to increase the uptake of investigation of household tuberculosis contacts and reduce the burden of tuberculosis in households and health facilities.

Contributors

MB and AV designed the study with input from MC, SMG, BKT, DA, and JC. AV and MB oversaw and coordinated the multicentre study. DA, BKT, BTY, and BS supervised the study implementation in the study sites. LS, PT, AKK, ST, GT, and RFO provided support to the study implementation in the study sites. SMG, JC, MC, and KF provided scientific support. BC did the statistical analysis with support from KF. MB wrote the manuscript draft. AV, MC, and SMG provided substantial input to the manuscript. MB, AV, and BC accessed and verified the data. All authors contributed to the interpretation of data and the revision of the article, approved the final version of the manuscript, and had final responsibility for the decision to submit for publication.

Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 3). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of *The Lancet Global Health's* broader goal to decolonise global health.

Declaration of interests

MB has received grants (paid to her institution) from Unitaid and Expertise France for the TB-Speed project on childhood tuberculosis diagnosis, from ANRS for a COVID-19 prevalence study in children with presumptive tuberculosis, and from EDCTP-2 for two therapeutic trials for the treatment of adults with tuberculosis meningitis (INTENSE-TBM) and adults with advanced HIV-TB co-infection (DATURA). All other authors declare no competing interests.

Data sharing

Data collected for the study will be made available upon request after publication of the Article. Data will include individual de-identified

See Online for appendix 3

participant data and the data dictionary. Requests can be addressed to the corresponding author. Requests will be examined by a committee of relevant people involved in the study. The scientific aspects of the proposal and the ethical and legal implications of data sharing will be considered. Data will be shared after approval of the proposal and after signing a data sharing agreement by all parties involved.

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