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N Salazar-Austin; S Cohn; B Nonyane; C Mulder; Gavin Churchyard ...

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Clinical Infectious Diseases

MAJOR ARTICLE

Effectiveness of a Home-based Approach to Child Contact Investigation and Tuberculosis Preventive Treatment Management by Community Health Workers in Ethiopia: A Pragmatic Cluster-randomized Trial

Nicole Salazar-Austin,[1,2] Silvia Cohn,[3] Bareng A. S. Nonyane,[2] Christiaan Mulder,[4,5] Fiseha Mulatu,[6] Samuel Bayu,[6] Moges Bizuayehu,[6] Gidea Conradie,[7] Akash Malhotra,[8,9] Paul Phan,[3] Natalia Hernandez Morfin,[1] Stephanie Borsboom,[4] Petros Mitiku,[6] Demissu Fulas,[10] Mulunesh Tulema,[10] Jonathan E. Golub,[3] Richard E. Chaisson,[3] Gavin Churchyard,[7,11,12] and Ahmed Bedru[6]

[1]Department of Pediatrics, Johns Hopkins School of Medicine, Baltimore, Maryland, USA; [2]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [3]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, USA; [4]Tuberculosis Elimination and Health Systems Innovations, KNCV Tuberculosis Foundation, The Hague, The Netherlands; [5]Amsterdam Institute for Global Health and Development, Amsterdam University Medical Centres, Amsterdam, The Netherlands; [6]KNCV Ethiopia, Addis Ababa, Ethiopia; [7]The Aurum Institute, Johannesburg, South Africa; [8]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA; [9]Department of Global Health, University of Washington, Seattle, Washington, USA; [10]Oromia Regional Health Office, Oromia, Ethiopia; [11]School of Public Health, University of Witwatersrand, Johannesburg, South Africa; and [12]Department of Medicine, Vanderbilt University, Nashville, Tennessee, USA

Background. Tuberculosis preventive treatment (TPT) is highly effective at preventing tuberculosis (TB) disease but is poorly implemented. We aimed to determine whether home-based contact management improves TPT uptake among close child contacts compared to the facility-based standard of care.

Methods. We conducted a pragmatic cluster-randomized trial among close contacts of TB clients aged <15 years in 18 primary health facilities in Oromia, Ethiopia. Facilities were randomized 1:1 to home-based or facility-based contact management. The intervention was conducted by community health workers (CHWs) and task-shared with TB focal persons. The primary endpoint was the cluster-level ratio of the number of contacts aged <15 years initiated on TPT per TB client.

Results. The cluster-level mean number of child contacts initiated on TPT per TB client was 40% higher in the home-based (1.7 contacts per TB client) versus facility-based arm (1.3 contacts per TB client; rate ratio 1.4, 95% confidence interval [CI]: .7–2.7). In the care continuum, assuming 2.1 children <15 years per household, 73% and 63% of children completed TPT in the 2 arms, respectively. One child failed TPT and 2 children discontinued TPT due to drug-related adverse reactions in the home-based and facility-based arms, respectively.

Conclusions. Home-based contact management by CHWs increased the number of children initiated on TPT by 40% without negative effects on treatment outcomes. Though not statistically significant, on a larger scale, the increased number of children identified and initiated on TPT has the potential to substantially reduce the burden of pediatric TB in Ethiopia and elsewhere.

Clinical Trials Registration. NCT04369326.

Keywords. tuberculosis prevention; TPT; child contact; community health workers; decentralized trial.

Each year, an estimated 7.5 million children <15 years of age are infected with *Mycobacterium tuberculosis* and 1.3 million develop tuberculosis (TB) disease resulting in 160 000 child deaths [1, 2]. Ethiopia remains 1 of the 30 TB high-burden countries with an incidence rate of 146 cases per 100 000 persons in 2023. TB preventive treatment (TPT) is an effective and cost-effective intervention to prevent TB disease [3–6]. The World Health Organization (WHO) recommends TPT for all close contacts of TB clients, although implementation remains poor [7, 8]. The first United Nations High-level Meeting on TB set ambitious targets, committing TPT to 4 million children aged <5 years and 20 million persons aged ≥5 years between 2018 and 2022 [9]. During this time, only 55% of that target was reached for contacts <5 years and only 10% for those ≥5 years [8]. In Ethiopia, only a quarter of contacts <5 years received TPT in 2018 [10]. Historically, in high burden settings, child contact evaluation has relied on passive referral of contacts to the TB clinic [11, 12]. This has remained unsuccessful in practice; evidence shows most contacts are not identified or not linked to facility-based care [13].

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Correspondence: N. Salazar-Austin, Department of Pediatrics, Johns Hopkins School of Medicine, 200 N. Wolfe St Room 3147, Baltimore, MD 21217 (nsalaza1@jhmi.edu).

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Community-based services have improved access to TB care. Home-based TPT initiation in the Gambia and Eswatini demonstrated high TPT acceptability and completion [14, 15]. The CONTACT trial showed children in Cameroon and Uganda receiving home-based care by nurses had three times higher odds of completing TPT than those receiving facility-based care [16]. In Ethiopia, the health extension program was designed to promote and deliver preventive health services at the community level and is focused on reducing maternal and child morbidity and mortality. This programming is provided by community health workers (CHWs) who receive up to 2 years of training to recognize, refer and treat serious childhood illnesses including pneumonia, malaria and neonatal sepsis [17–21]. Services may be provided at the household or a community-based health post. In conjunction with the Oromia Regional Health Bureau, TB partners, healthcare workers and caregivers, we developed home-based TB prevention services where contact management, including contact investigation, TPT initiation and follow-up were task-shared between CHWs and facility-based TB focal persons (nurse or public health officer) to improve access and reduce delays in TB diagnosis, treatment and prevention among children aged <15 years [22].

To our knowledge, no trial has used CHWs to evaluate, initiate and follow children on TPT in the community. We performed a cluster randomized trial of home-based versus facility-based contact management in Oromia, Ethiopia. Our primary hypothesis was that home-based contact management by CHWs would increase the number of children initiating TPT. We also hypothesized that home-based contact tracing would identify more children and would have similar TPT outcomes as those initiated by facility-based providers.

METHODS

Study Population

The CHIP-TB trial was a pragmatic, two-arm, parallel, cluster randomized controlled trial comparing home-based child contact management to the facility-based standard of care in 18 primary health centres (facilities) in the East Shoa Zone of Oromia, Ethiopia. Cluster randomization was used for logistical convenience given practical difficulties in organizing individual randomization at health facilities and to promote equity between neighbors.

Inclusion criteria for facilities included primary health center status, TPT provision, CHW existence, TB client volume ≥10 notifications in the previous year, and geographic location. TB clients who were ≥18 years receiving a diagnosis of pulmonary TB, residing in the facility catchment area, were willing to have a home visit, and were willing to provide informed consent were enrolled. This included clients with both clinically diagnosed and bacteriologically confirmed TB for the first 6 months and clients with bacteriologically-confirmed TB for the last 6 months of the study, aligning with guideline updates. Exclusion criteria for TB clients included evidence of rifampicin and/or isoniazid resistance on Xpert MTB/RIF® and/or drug susceptibility testing (late exclusion) or previous enrollment of that household. Allocation was based on the facility the TB client attended. All close child contact aged <15 years of an enrolled TB client [23, 24] were screened for eligibility. Exclusion criteria included refusal of written informed consent and/or assent.

Procedures

Eligible TB clients provided consent at treatment initiation or shortly thereafter. Standard of care procedures were performed at the facility, for both arms, including enumerating all close contacts. In intervention facilities, a CHW visited each TB clients' household, irrespective of reported contacts. CHWs enumerated close contacts aged <15 years using a study-specific form (Supplementary Figure 1). For those who consented, and where relevant, assented, trained CHWs conducted symptom screening (Supplementary Figure 2). CHWs referred symptomatic children with at least 1 positive symptom to the facility for evaluation. CHWs counseled asymptomatic children and their caregivers on TPT importance. The CHW returned to the facility and determined the TPT regimen and dosing with a TB focal person based on the CHW's clinical assessment. The CHW initiated TPT at a second home visit. CHWs conducted monthly household visits for at least 3 months to either (1) establish contact, (2) provide TPT refills and/or, (3) ensure TB evaluation (symptomatic children only). Household visits were integrated into existing home-based services for the child, TB client, and/or other household members. Therefore, additional visits may have occurred for some children. In control facilities, children were assessed and treated by a TB focal person at the facility.

TPT was provided in accordance with Ethiopian guidelines and included three months of weekly rifapentine and isoniazid (3HP; children aged ≥2 years), 3 months of daily rifampicin and isoniazid (3RH; children aged <2 years and with 3HP stockout) or 6 months of daily isoniazid (6H; children with human immunodeficiency virus [HIV]). A contact management record was introduced to complement the existing contact register to collect data needed for all primary and secondary outcomes (Supplementary Figure 2). Data were recorded by healthcare workers, maintained at the health post (intervention) or facility (control), and abstracted by study staff.

Outcomes and Ascertainment

The primary outcome was the cluster-level ratio of the number of child contacts aged <15 years initiated on TPT per TB client. The prespecified secondary outcomes included the cluster-level ratio of the number of child contacts aged <15 years identified per TB client, the cluster-level proportions of estimated child

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contacts aged <15 years progressing through the TB prevention continuum of care [12, 25], and the proportion of children who initiated and completed TPT, who were lost to follow-up, who developed incident TB (treatment failure), who died, and who discontinued TPT due to toxicity, drug-drug interaction, severe illness, pregnancy, or family preference. For all cluster-level outcomes, data were summarized by cluster/facility and then averaged by arm. The number of estimated contacts was calculated using country-level data in the 2016 Ethiopian Demographic and Health Survey [26]. Adherence was measured by pill count. Treatment completion for 3HP was defined as completing 11 doses in 16 weeks and for 3RH as completing 68 doses in 120 days [25]. Side effects, including gastrointestinal upset, hepatotoxicity, hypersensitivity reaction, and peripheral neuropathy were actively assessed at monthly follow-up visits using a checklist. Acceptability was assessed as the proportion of households whose family agreed to the intervention. Feasibility of the home visits for CHWs was assessed as the proportion of households that require one, two and three visits to complete TPT initiations for all child contacts in the household. Fidelity to the intervention was assessed as the proportion of children initiated on the correct TPT regimen and dose. The continuum of care was also assessed using a per-protocol analysis using the total number of contacts identified through either home-based or facility-based contact enumeration in the 2 arms, respectively.

Power Considerations and Randomization

The study was powered based on anticipated enrollment of 26 pulmonary TB clients per facility, which accounted for a potential 20% reduction in evaluable TB clients due to nonparticipation. Prior data suggest that there are 2.1 children per household [26] and that 30% of eligible children would initiate TPT under facility-based care [10, 27], hence an expected ratio of 0.63 (=2.1 × 0.3) child contacts per TB client. Without reliable data to inform a CV in the intervention arm, we assumed a moderate coefficient of variation (CV) of 0.35. We estimated that 18 clusters (9 per arm) were required to detect a doubling of the number of children initiated on TPT per TB client (from 0.6 to 1.2) in the home-based arm versus the facility-based arm with 80% at a 5% type 1 error rate (Supplementary Table 1).

We conducted covariate constrained cluster-randomization based on the facility's previous years' TB notifications and geographical location (Central, East, and South) using STATA's *cvcrand* function [28]. Study staff and participants were not masked to arm allocation.

Statistical Analysis

Characteristics of facilities, TB clients and child contacts at enrollment were summarized by arm. We used a modified intention-to-treat (mITT) analysis for the primary outcome; child contacts of TB clients who had rifamycin and/or isoniazid resistance identified on culture were included in the analysis through the time when their resistance became known. Using the mITT population, we calculated the ratio of child contacts who initiated TPT per enrolled TB client for each cluster, and these were compared between arms using an unpaired *t* test. Considering the large variation in the outcome and cluster sizes we further analyzed the number of children initiating TPT using a Poisson regression analysis with an overdispersion parameter, taking the number of TB clients per facility as the offset. For the secondary outcomes, cluster-level ratios and proportions (continuum of care) were compared between arms using an unpaired *t* test. WHO-defined TPT outcomes (treatment completion, loss to follow-up, TPT failure, death, not evaluated and other) were summarized [25]. Analyses were conducted using STATA, version 18.

Ethical Considerations

This study was approved by the Oromia Regional Health Bureau: Public Health Emergency Management and Health Research Directorate, the WHO Ethics Review Committee, and the Johns Hopkins School of Medicine Institutional Review Board. Informed consent was obtained from TB clients and the contact's parent/guardian. Assent was obtained from contacts aged 12–14 years, as per Ethiopian guidelines.

RESULTS

Out of 61 facilities assessed for eligibility, 18 were randomized (Figure 1). Their baseline characteristics are shown in Supplementary Table 2. From 6 September 2021, through 30 September 2022, 853 TB clients were assessed for eligibility, 354 were enrolled. Primary reasons for exclusion of TB clients were age <18 years (n = 123), not having pulmonary TB (n = 323), not living in the facility catchment area (n = 33), or unwillingness to have a home visit (n = 8). Contact tracing identified 588 child contacts of which 534 were assessed for eligibility and 527 were enrolled. Primary reasons for child contact exclusion were lack of consent (n = 4) and age ≥15 years (n = 2). TB clients and child contacts in facilities randomized to home-based versus facility-based care had similar baseline characteristics (Table 1).

The home-based intervention identified 309 children from 168 TB clients and the facility-based standard of care identified 279 children from 186 TB clients. The cluster-level mean number of child contacts identified per TB client was 50% higher in the home-based (1.9 contacts per TB client) versus facility-based arm (1.5 contacts per TB client; RR 1.5, 95% confidence interval [CI]: .7–3.3; $P = .3$; Table 2 and Supplementary Table 3).

TPT initiation occurred in 272 and 244 children in the home-based and facility-based arms, respectively. The cluster-

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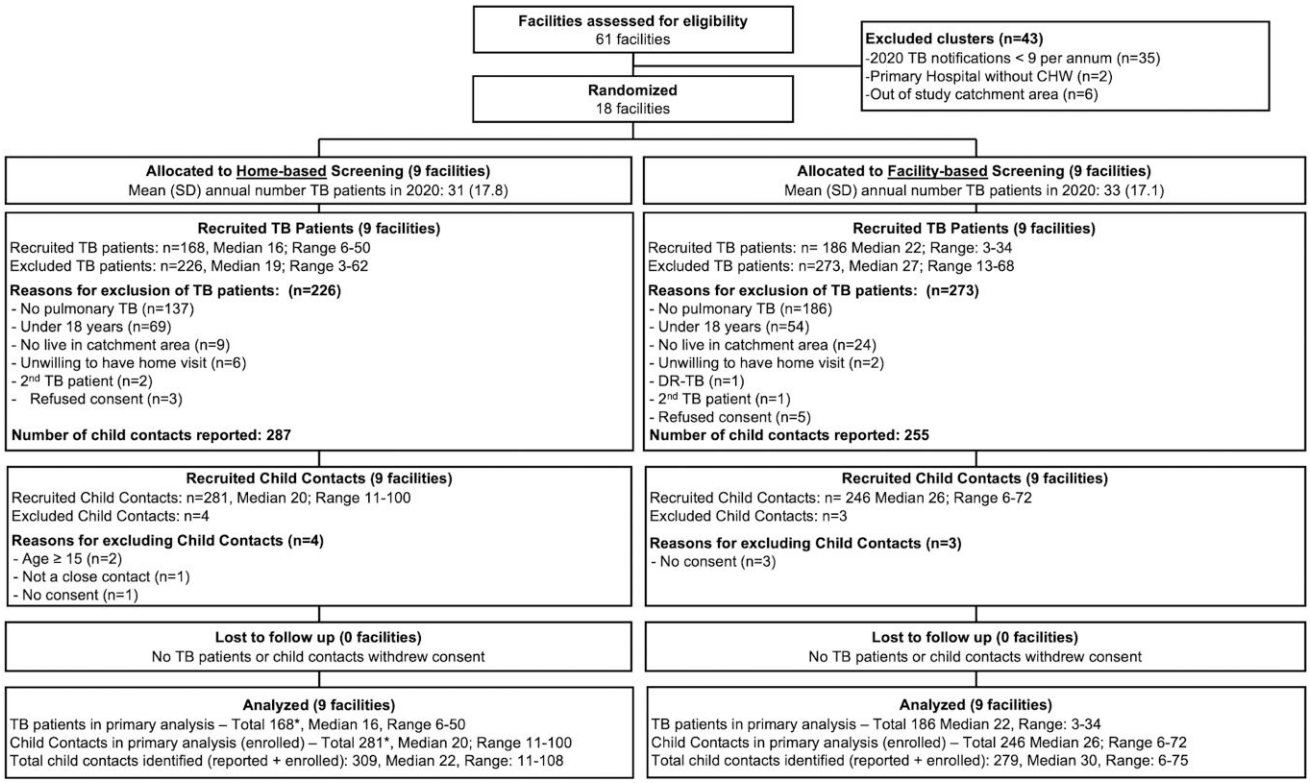


Figure 1. Study population. *One TB client with 2 child contacts was diagnosed with DR-TB after TPT completion. The TB client and both contacts therefore remained in all analyses. Abbreviations: CHW, community health worker; DR-TB, drug-resistant tuberculosis; SD, standard deviation; TB, tuberculosis.

level mean number of child contacts initiated on TPT per TB client was 40% higher in the home-based (1.7 contacts per TB client) versus facility-based arm (1.3 contacts per TB client; rate ratio (RR) 1.4, 95% CI: .7–2.7; $P = .3$; Table 2). Significant heterogeneity was observed across facilities (Supplementary Table 4), the CV for the primary analysis was 0.44 overall, 0.37 for the home-based arm and 0.52 for the facility-based arm. Poisson regression demonstrated similar results with an incidence rate ratio of 1.2 (95% CI: .8–1.9; $P = .3$).

Assuming 2.1 children per household, the cluster-level mean proportion of children identified in the home-based and facility-based arms were 91% (95% CI: 64, 100) and 73% (95% CI: 46, 100), respectively ($P = .28$; Figure 2 and Supplementary Table 5). The cluster-level mean proportion of children initiating TPT per arm was 78% (95% CI: 56, 100) and 64% (95% CI: 38, 90), respectively ($P = .35$). The cluster-level mean proportion of children completing TPT per arm were 73% (95% CI: 54, 92) and 63% (95% CI: 38, 87), respectively ($P = .46$). Additional continuum of care using a per protocol analysis is presented in Supplementary Figure 3.

All enrolled children had documented TB symptom screening. In the 2 arms, 12/281 (4%) and 2/246 (1%) children were symptomatic, respectively and all were evaluated. Of those initially screened by a CHW and TB focal person, 25% (2/12) and 100% (2/2) had Xpert-confirmed pulmonary TB, respectively. No children were empirically started on TB treatment.

TPT regimens initiated and reasons for non-initiation are described in Supplementary Tables 6 and 7. Of the 272 and 244 children initiated on TPT in the intervention and control arms, 259 (95%) and 238 (98%) were initiated on the correct TPT regimen and dose.

Among those children who initiated TPT, 14 (5%) and 9 (4%) children in the home-based and facility-based arms did not complete TPT, respectively (Table 3).

In the intervention arm, children were identified in 103 (62%) households; 102 of these households received an initial home visit. No caregivers refused a home visit. CHWs were able to reach all contacts within the first visit in 89% of households, within the first and second visits in 7% of households, and within 3 visits in 4% of households (Supplementary Table 8). Two households (2%) with close proximity to the facility had a mix of home-based and facility-based visits for some children at multiple visits.

DISCUSSION

In this cluster randomized trial, home-based contact management conducted by CHWs in Ethiopia increased the number

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Table 1. Baseline Characteristics of Participants

Characteristic of TB Clients	Home-based n = 168	Facility-based n = 186	Total N = 354
Demographics			
Mean age (SD)	39 (15)	37 (15)	38 (15)
18–35 y	80 (48%)	105 (56%)	185 (52%)
36–55 y	62 (37%)	53 (29%)	115 (33%)
>55 y	26 (15%)	28 (15%)	54 (15%)
Male	112 (67%)	109 (59%)	221 (62%)
TB disease type			
Bacteriologically confirmed pulmonary TB[a]	145 (86%)	152 (82%)	297 (84%)
Clinically diagnosed pulmonary TB	23 (14%)	34 (18%)	57 (16%)
Smear status			
Smear positive	115 (68%)	95 (51%)	210 (59%)
Smear negative	16 (10%)	23 (12%)	39 (11%)
Smear not done or not recorded	37 (22%)	68 (37%)	105 (30%)
HIV status			
HIV positive	18 (11%)	8 (4%)	26 (7%)
HIV negative	149 (88.4%)	175 (94%)	324 (92%)
HIV status not recorded	1 (0.6%)	3 (2%)	4 (1%)
Characteristic of child contact	Home-based n = 281	Facility-based n = 246	Total N = 527
Age /age groups			
<2 y	30 (11%)	39 (16%)	69 (1%3)
2 to < 5 y	64 (23%)	60 (24%)	124 (24%)
5 to < 10 y	102 (36%)	83 (34%)	185 (35%)
10 to < 15 y	85 (30%)	64 (26%)	149 (28%)
Sex			
Male	143 (51%)	136 (55%)	279 (53%)
Relationship to TB client			
Son/daughter	235 (84%)	166 (68%)	401 (76%)
Grandchild	23 (8%)	35 (14%)	58 (11%)
Niece/nephew	6 (2%)	10 (4%)	16 (3%)
Sibling	15 (5%)	27 (11%)	42 (8%)
Other	1 (0.5%)	8 (3%)	9 (2%)
Not recorded	1 (0.5%)	0 (0%)	1 (0.2%)
HIV positive	1 (0.5%)	0 (0%)	1 (0.2%)

Abbreviations: HIV, human immunodeficiency virus; SD, standard deviation; TB, tuberculosis.

[a]Bacteriologic confirmation includes smear, culture and/or Xpert MTB/RIF positivity.

Table 2. Primary and Key Secondary Outcomes

	Home-based (95% CI)	Facility-based (95% CI)	RR (95% CI)	*P* Value
Primary outcome				
Mean number of child contacts < 15 y old INITIATED on TPT per TB patient	1.7 (1.2, 2.1)	1.3 (.8, 1.9)	1.4 (.7, 2.7)	.3
Secondary outcome				
Mean number of child contacts < 15 y old IDENTIFIED[a] per TB client	1.9 (1.3, 2.5)	1.5 (1.0, 2.1)	1.5 (.7, 3.3)	.3

Abbreviations: CI, confidence interval; RR, risk ratio; TB, tuberculosis.

[a]Identified child contacts includes close contacts <15 y of age reported by the TB client during facility-based contact tracing in both arms and also any additional children reported by a caregiver and/or found during the home visit (home-based arm) or any additional children who presented to the clinic for evaluation that may not have been initially reported (facility-based arm).

of child contacts initiated on TPT per TB client by 40% compared with facility-based standard of care. Though these differences were not statistically significant, the increased number of child contacts identified and initiated on TPT is important from a public health perspective and has the potential to substantially reduce the burden of pediatric TB in Ethiopia and elsewhere. This intervention was acceptable to TB clients and caregivers and was feasible for CHWs and TB focal persons. Previous randomized controlled trials have evaluated home-based TPT management and TPT initiation by a nurse

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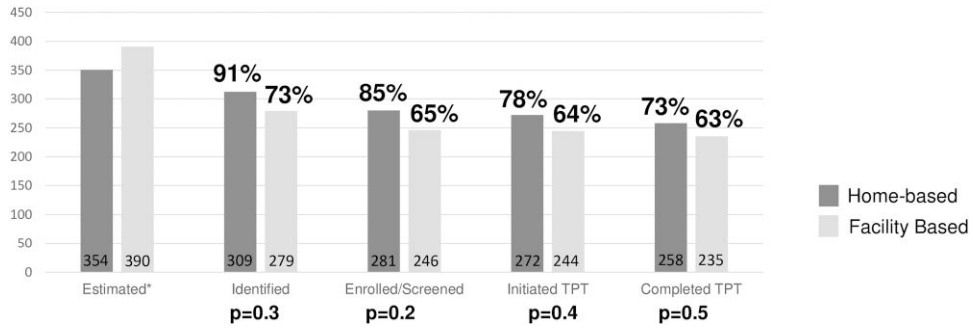


Figure 2. TPT prevention continuum of care. Proportions reflect the estimated number of child contacts (based on DHS data) completing each step of the care continuum by arm. *Assumes 2.1 HHC <15 per household (from DHS data). Abbreviations: DHS, Department of Human Services; HHC, household contact; TPT, tuberculosis preventive treatment.

Table 3. TPT Outcomes by Arm and by Regimen

TPT Outcome	Home-based n = 272			Facility-based n = 244			Total N = 516		
Treatment completed	258			235			493		
3HP completed	141			163			304		
3RH completed	117			72			189		
6H completed	0			0			0		
Treatment not completed	14			9			23		
	3HP	3RH	6H	3HP	3RH	6H	3HP	3RH	6H
Treatment discontinued or changed									
Due to child/family preference	1	7	0	3	4	0	4	11	0
Due to toxicity	0	0	0	2[a]	0	0	2	0	0
Due to drug-drug interaction	0	0	0	0	0	0	0	0	0
Due to severe illness	0	0	0	0	0	0	0	0	0
Lost to follow-up	0	2	0	0	0	0	0	2	0
Treatment failure	1	0	0	0	0	0	1	0	0
Died	0	0	0	0	0	0	0	0	0
Other	2[b]	0	1[c]	0	0	0	2	0	1
Not evaluated	0	0	0	0	0	0	0	0	0

Abbreviations: 3HP, 3 months of weekly rifapentine and isoniazid; 3RH, 3 months of daily rifampicin and isoniazid; 6H, 6 months of isoniazid; TPT, tuberculosis preventive treatment.

[a]Toxicity: peripheral neuropathy (3HP) and GI upset (3HP)—both from same family.

[b]Two children were stopped on therapy due to security concerns and resulting lack of home visit.

[c]One child with human immunodeficiency virus (HIV) who started 6H at the end of trial remained on isoniazid at study closure.

[16]. We showed that CHWs successfully and safely initiated TPT when task-shared with a TB focal person.

Home-based contact enumeration identified 1.9 child contacts <15 years per TB client, compared with an average of 2.1 children <15 years per household [26]. Facility-based contact enumeration identified only 1.5 child contacts <15 years per TB client. The difference between home-based and facility-based contact tracing has been noted in high and low TB burden settings previously and may be due to limited staffing, TB client disease severity at diagnosis, poor understanding of household definition, and stigma [16, 27, 29].

Overall, TPT initiation was 78% in the home-based arm and 64% in the facility-based arm. This is higher than the global average of 37% for children <5 and the Ethiopian national average of 28% in 2022 [13, 30]. Among those initiated on TPT, completion was high and >90% in both arms. High initiation and completion rates have also been seen in prior home-based TPT studies in Uganda, Cameroon, Eswatini, Gambia, and Ethiopia [14–16, 31, 32]. The relatively high initiation and completion observed in the standard of care arm was unanticipated. The study occurred concurrently with Ethiopia's roll-out of short-course TPT and their National TPT Acceleration Plan that may have improved TPT

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acceptability and completion in control facilities. Additionally, being monitored in the clinical trial setting may have motivated control facilities to enhance contact tracing and TPT management.

Overall, when considering estimated contacts who may not have engaged in care, TPT coverage was estimated to be 73% in the home-based arm and 63% in the facility-based arm. The distinction between identified and estimated contacts is important because although the facility-based care arm performed well, home-based contact tracing identified more children and, on a larger scale, would likely have a significant public health impact on reducing TB-related child morbidity and mortality.

The intervention was highly acceptable with less than 1% of TB clients and 0% of caregivers refusing a home visit, similar to other studies evaluating home-based care models [14–16]. Acceptability was further characterized with post-trial qualitative research.

CHWs were able to symptom screen, initiate TPT among asymptomatic children and refer sick children for evaluation. Previous studies show up to 1% of children initiated on TPT by a nurse develop TB disease [27, 33]; CHWs were comparable at 0.3%. This may not reflect a missed diagnosis, but asymptomatic hilar adenopathy that may progress to TB disease despite adequate symptom screening and TPT.

This study has several limitations. First, fewer TB clients enrolled per cluster, thereby reducing the effective sample size by 2 clusters. Although this may be explained by hindered care-seeking behaviors during a global pandemic, the lower-than-expected (40% vs 100%) increase in effect, and the higher-than-expected coefficient of variation in our outcome were likely more impactful. Second, facilities in urban or pastoral communities were not assessed. The intervention may be less effective in these communities due to closeness of households to facilities or populations who move between catchment areas of various facilities. Finally, this pragmatic trial may have been affected by CHW shortages, competing CHW programming (campaigns for vaccination, bed nets, etc.), and regional conflict that sometimes-limited timely home visits. Moreover, while fidelity to the location of visits was high, the frequency of CHW engagement may have varied in the home-based arm. A post-trial qualitative assessment will further explore the potential effect on intervention efficacy.

In summary, home-based contact management task-shared by CHWs and TB focal persons is a feasible, acceptable and family-centered alternative care model for TB prevention among child contacts. Although not found to improve TPT uptake compared with facility-based care, TPT outcomes were similar between arms. The intervention was found to be cost-saving for households with only marginally increased health system costs [34]. These data have informed Ethiopia's National Strategic Plan (2023–2030) that now endorses integrating contact management into community-based care through the health extension program [35]. In communities with trained CHWs with high incidence of TB disease, this may be an important family-centered care model that may reduce time and cost for clients.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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