Sustainability and impact of an intervention to improve initiation of tuberculosis preventive treatment: results from a follow-up study of the ACT4 randomized trial

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Summary

Background In a cluster randomized trial (clinicaltrials.gov: NCT02810678) a flexible but comprehensive health system intervention significantly increased the number of household contacts (HHC) identified and started on tuberculosis preventive treatment (TPT). A follow-up study was conducted one year later to test the hypotheses that these effects were sustained, and were reproducible with a simplified intervention.

Methods We conducted a follow-up study from May 1, 2018 until April 30, 2019, as part of a multinational cluster randomized trial. Eight sites in 4 countries that had received the intervention in the original trial received no further intervention; eight other sites in the same countries that had not received the intervention (control sites in the original trial) now received a simplified version of the intervention. This consisted of repeated local evaluation of the Cascade of care for TB infection, and stakeholder decision making. The number of HHC identified and starting TPT were repeatedly measured at all 16 sites and expressed as rates per 100 newly diagnosed index TB patients. The sustained effect of the original intervention was estimated by comparing these rates after the intervention in the original trial with the last 6 months of the follow-up study. The reproducibility was estimated by comparing the pre-post intervention changes in rates at sites receiving the original intervention with the pre-post changes in rates at sites receiving the later, simplified intervention.

Findings With regard to the sustained impact of the original intervention, compared to the original post-intervention period, the number of HHC identified and treated per 100 newly diagnosed TB patients was 10 more (95% confidence interval: 84 fewer to 105 more), and 1 fewer (95% CI: 22 fewer to 20 more) respectively up to 14 months after the end of the original intervention. With regard to the reproducibility of the simplified intervention, at sites that had initially served as control sites, the number of HHC identified and treated per 100 TB patients increased by 33 (95% CI: −32, 97), and 16 (−69, 100) from 3 months before, to up to 6 months after receiving a streamlined intervention, although differences were larger, and significant if the post-intervention results were compared to all pre-intervention periods.

Interpretation Up to one year after it ended, a health system intervention resulted in sustained increases in the number of HHC identified and starting TPT. A simplified version of the intervention was associated with non-significant increases in the identification and treatment of HHC. Inferences are limited by potential bias due to other temporal effects, and the small number of study sites.

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Research in context

Evidence before this study

We searched PubMed from January 1st, 1980, to September 20, 2023 for randomized trials using the following broad search terms "prevention" and "treatment", and "tuberculosis". We identified only three completed, and one ongoing trial that evaluated health system interventions to enhance management of household contacts, of which only two trials assessed tuberculosis preventive treatment (TPT) initiation using individual-level standardized interventions. Two earlier systematic reviews of interventions to strengthen the tuberculosis (TB) infection cascade of care identified many observational studies of specific interventions such as media campaigns, home visits or digital aids for healthcare workers, but no studies that included multi-faceted or broad health system interventions that would act across all steps of the cascade. In summary, despite numerous observational studies of approaches to improve TPT completion, especially in high income settings, there are far fewer studies that have examined how to improve TBI management and enhance initiation of TPT of persons who are candidates for TPT, and almost no high-quality evidence on how to improve any aspect of TBI managements other than trials of different TPT regimens.

In 2021 we published results of an international, multi-centre cluster randomized trial of a multi-faceted intervention of cascade of care evaluation, followed by local stakeholder decision making to solve the locally identified problems, and then implementation of locally selected, and affordable solutions. The intervention resulted in significant increased number of household contacts identified and started on TPT, but was lengthy and complex, raising concerns about sustainability and reproducibility in other settings.

Added value of this study

The earlier ACT4 randomized trial and this follow-up study tested a health systems approach to TBI program strengthening in which a standardized evaluation was combined with flexible local decision making. The increases in household contacts identified and starting TPT at intervention sites during the trial were unchanged up to one year after the intervention ended. As well, a similar approach, delivered in less time, and using simpler tools resulted in increased numbers of HHC identified and initiating TPT, although no changes were statistically significant. This approach was most useful in low and middle-income settings where household contact and TB infection management had been weak before the study and was particularly impactful if household contacts of all ages were identified, tested and provided TPT.

Implications of all the available evidence

Without major efforts to strengthen the capacity of TB programs globally to manage TB infection, especially among household contacts, it will be impossible to reach the new United Nations High Level Meeting targets set in September 2023- to offer TPT to at least 30 million household contacts. A flexible but comprehensive health system approach to strengthen management of TB infection can result in substantial improvement in TPT uptake. However, this approach needs to be further evaluated, before expansion to other Low and middle-income settings so that TB prevention will have an important epidemiological impact.

Introduction

Tuberculosis (TB) is one the leading causes of death worldwide, with an estimated 1.6 million deaths in 2021,[1] and TB preventive treatment (TPT) is a key component of global TB elimination plans.[2,3] Expansion of TPT was one of the goals established at the first UN high-level meeting on TB, in 2018,[4] with targets set for household contacts (HHC), and people living with HIV (PLHIV). Although the target coverage of TPT was reached for PLHIV, only 40% of the target for HHC under five, and only 3% of the target for older HHC initiating was achieved by the end of 2021.[1] Barriers to TPT occur at different steps of the cascade of care.[5] There is a need for effective and feasible interventions that target different steps of this cascade, from identification and entry into care, to initiating, and completing TPT. These interventions must be feasible to implement at a large scale in low resource settings and have sustained effect.

The ACT4 trial was a pragmatic, cluster randomized trial, testing a strategy to improve TPT initiation in HHC of people with pulmonary TB.[6] The trial took place in 24 clinic sites in 5 countries (Benin, Canada, Ghana, Indonesia, and Vietnam) between August 2016 and March 2019. Half of the sites (control) were randomized to receive no intervention but continue the standard

care, and half to receive an intervention of five major activities: i) using existing clinic records, to evaluate the cascade of care of HHC management to quantify losses at each step; ii) administer questionnaires to index TB patients, HHC, parents of child contacts, and health care providers; iii) feedback of results to local stakeholders who selected solutions for identified problems; iv) implementation of selected solutions; and v) repeated cascade assessments and further local feedback. Solutions designed to strengthen care varied widely between sites and ranged from patient and provider educational tools, opening clinics during evening hours, text messaging appointment reminders, toys as incentives for children's visits, reimbursement of HHC travel costs, and community meetings to reduce TB-related stigma. Our aim was to develop an approach that would not require continued external funding, but rather drew upon local resources with the intent of being sustainable. The intervention resulted in an increase in the crude overall proportion of household contacts initiating TPT out of those eligible from 0.21 to 0.35, and in 72 more household contacts initiating TPT per 100 index patients with tuberculosis (95% CI: 10–134).[7]

Although judged to be both effective and cost-effective,[7] the intervention was complex and time consuming to deliver, making reproducibility and sustainability uncertain. Therefore, we undertook a follow-up study with two main objectives: first, to measure the sustained effect, up to one year after the end of the intervention, at study sites that received the intervention in the original ACT4 trial but received no further support. Secondly to evaluate the effect of a simplified version of the intervention used in the trial, at sites that had not received the intervention during the trial (i.e., control sites) and compare this to the effect of the intervention in the ACT4 trial.

Methods

Study design and participants

The main ACT4 trial started in sites in Canada, Benin, Ghana and Indonesia on August 1, 2016 and was completed March 31, 2018. The trial was registered with clinicaltrials.gov (NCT02810678), and is described in detail elsewhere.[7] The follow-up study was planned to start as soon as possible after the conclusion of the main trial, so was started in these 4 countries on May 1, 2018, and was completed April 30, 2019. Unfortunately, due to unforeseen problems, start-up was very delayed in Vietnam, such that the main trial was initiated at these sites only August 1, 2017 and completed March 31, 2019. Due to funding limitations, the follow-up study could not be conducted in Vietnam. The sixteen study sites participating in the follow-up study are described in Supplement 1: Table S1. Each 'site' included one to three health facilities and was the unit of randomization. As depicted in Fig. 1, at all sites that received the intervention in the main ACT4 trial, research staff continued to monitor all steps of HHC management but did not provide further support (i.e., no materials, supplies, training, nor other resources), nor did they initiate new study-related activities. The other eight sites which had not received any intervention during the ACT4 trial (i.e., control sites) received a streamlined/simplified version of the trial intervention in this follow-up study. Given the noted complexity and time taken to deliver the intervention in the ACT4 trial, we simplified the trial intervention by shortening the questionnaires used to identify the reasons for the losses in the cascade were reduced from 29 to 6 items (see Supplement 2 for original and simplified questionnaires), and by reducing the time frame. The initial evaluation phase was reduced to 3 months from 6 months, the stakeholder decision phase was reduced to 3 months from 4 months, and the time to implement and evaluate the locally selected solutions was reduced to 6 months from 10 months. As a result, all study activities, from baseline evaluations to implementing and evaluating local solutions, in this follow-up study were completed in 12 months, compared to 20 months in the ACT4 trial.

Ethics

Approval to conduct the study was obtained by McGill University Health Centre (MUHC) ethics review board (15-291-MUHC) and by ethics committees at all study sites. Only aggregate and non-nominal data was collected on outcomes (i.e., only the number of contacts identified and starting TPT in each site each 3 months). Written informed consent was obtained from participants who completed interviewer-administered questionnaires.

Randomization and blinding

Sites participating in this study were randomized for the ACT4 main study, as described in detail elsewhere.[7] It was not possible to blind study personnel, nor site staff to the intervention, but statistical analyses for the ACT4 trial, and this follow-up study were conducted without knowledge of study arm. To limit potential contamination, intervention and control sites were selected that were geographically separated, and staff from these two groups of sites did not meet together during the ACT4 trial.

Outcomes

For the original trial, and the follow-up study, the primary outcome was the number of HHC who initiated TPT, and the secondary outcome was the number of HHC identified at each site. TPT completion was not a study outcome as the TPT regimen routinely used by providers and TB programmes at different sites varied (i.e., was not determined by study investigators) and this was felt likely to be an important determinant of this outcome. Both outcomes were standardized to the number of persons diagnosed with TB at that site

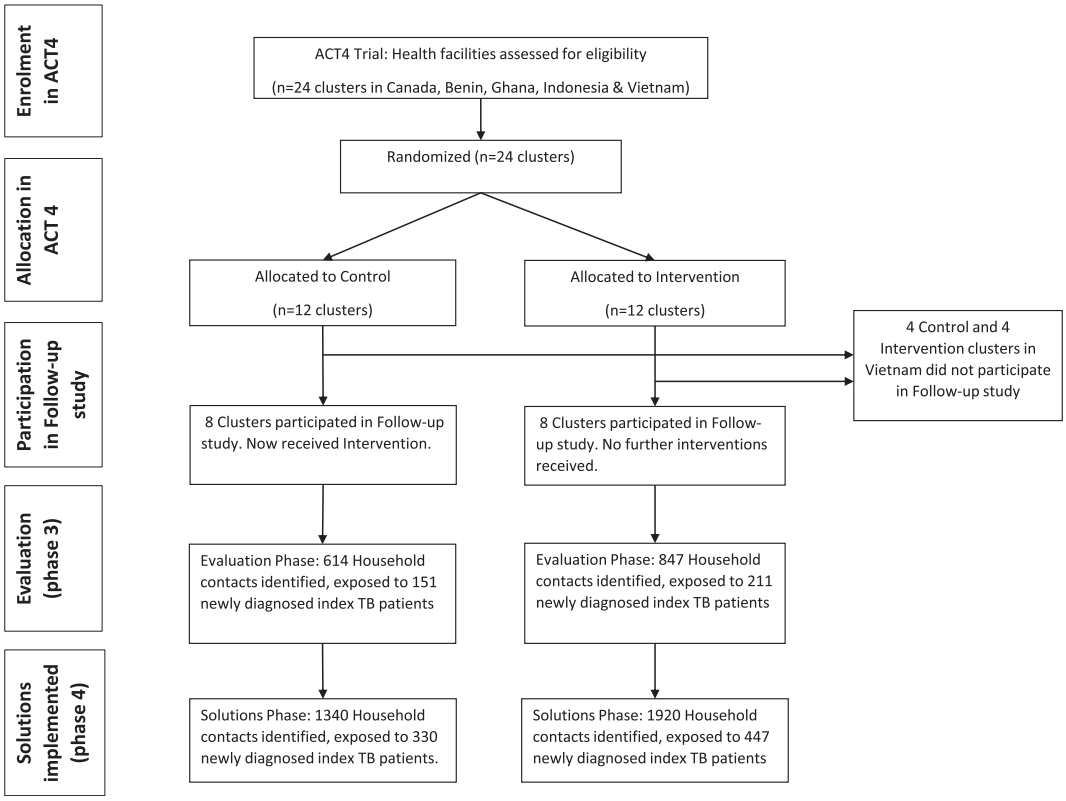

Fig. 1: Consort diagram for follow-up study of ACT 4 trial.

during the study period and expressed per 100 index TB patients. Household contacts were defined as people spending at least one night per week in the same house or spending at least 1 h per day at least 5 days per week, on average, over the preceding 3 months. Initiating TPT was defined as receiving a prescription for TPT, within 3 months after the diagnosis of pulmonary TB disease in the index patients. Identified was defined as a HHC listed by the TB service of a newly diagnosed index TB patient. Index TB patients were persons aged 12 years or older, and newly diagnosed with microbiologically confirmed pulmonary TB.

The number of persons newly diagnosed with pulmonary TB disease, as well as the number of HHC identified and initiating TPT was extracted from TB registries or patients' medical records at each health facility. As depicted in Fig. 1, there were four periods when these outcomes were measured at all sites. The first two phases (phase 1 and 2 in Fig. 1) each lasted 6 months and corresponded to the intervals when pre- and post-intervention evaluations were conducted at intervention sites in the ACT4 trial. These outcomes were ascertained at control sites at the same time. The third and fourth periods of outcome ascertainment (phase 3 and 4 in Fig. 1) at all sites occurred at the same time as the pre- and post-implementation evaluations when the former control sites received the streamlined intervention in this follow-up study.

Costs

Costs of the intervention were carefully measured in the main ACT4 trial, as described in the paper and supplement describing these results.[7] To estimate costs in the follow-up study we used those published average monthly costs in each of the three phases of the intervention in each country multiplied by the duration of each phase of the streamlined intervention in this study. To this we added the total amount of external funding allocated to each site for solutions in the follow-up study (these are detailed in Supplement Table S4), and expressed these costs per index TB patient to give an approximate idea of the costs for the intervention in each country.

Statistics

We did not establish an *a priori* statistical analysis plan. For our first objective, to assess the sustainability of the ACT4 trial intervention, we analyzed the results only at the original intervention sites. We compared the number of HHCs identified per 100 index cases between the entire follow-up time (phases 3 and 4 combined) with phase 2. We used the same approach to compare the number of HHC starting TPT in phases 3 and 4

combined vs phase 2. In a restricted analysis we excluded Canadian sites from the analysis and estimated the effect in low- and middle-income countries (LMIC) sites only.

For our second objective, to estimate the effect of the simplified intervention in former control sites, we compared the number of HHCs initiating TPT (primary outcome) and HHC identified (secondary outcome) per 100 index TB patients between phase 4 (post-intervention) and combined results from phase 1, 2 and 3 (all pre-intervention). In restricted analyses we estimated the effect in LMIC sites only. We also compared the outcomes in Phase 4 (post intervention) to each of the preceding pre-intervention phases separately.

To compare the effect of the original and simplified interventions, we estimated a difference of differences. This meant we compared the differences in the number of HHCs identified and initiating TPT per 100 index TB patients in Phase 4 vs phases 1, 2 and 3 combined at control sites (before and after the simplified intervention) to the differences between phase 1 vs phases 2, 3 and 4 in the original intervention sites (before and after the original intervention in the ACT 4 trial).

All analyses were done using marginal Poisson regression models, estimated via generalized estimating equations (GEE), which account for clustering. For the analysis of the number of HHCs who initiated TPT, we corrected for the small number of clusters in all models, using the method described by Fay and Graubard of a bias-corrected sandwich estimator.[8] However models for analyses of the number of HHCs identified per 100 index cases did not converge using this method, and so are estimated using GEE without correction for few clusters. This may result in estimated confidence intervals that are too narrow, with an over-estimate of statistical significance. All analyses included an offset: log (n index patients), and for all analyses we used the NLESTIMATE macro in SAS to estimate differences rather than relative measures.[9]

All analyses were conducted using SAS v 9.4 (SAS Institute, Cary, NC, USA).

Role of the funding source

This study was funded by the Canadian Institutes of Health Research (Grant number 143350). The funding agency had no role in study design, data collection, data analysis, data interpretation, or writing of this paper.

Results

The follow-up study took place between May 1, 2018 and April 30, 2019, as planned. In the 16 participating sites, the number of persons who were newly diagnosed with pulmonary TB disease each month was similar in all phases of the ACT4 trial and the follow-up study, as seen in Table 1 (Note that in the follow-up study, the baseline evaluation phase was only 3 months, vs 6 months duration of all other phases). The rate of HHC identified and starting TPT in all 4 study phases at original intervention and control sites is depicted in Fig. 2.

	Study phases (duration)			
	Main study		Follow-up study	
	Phase 1 (6mos)	Phase 2 (6mos)	Phase 3 (3mos)	Phase 4 (6mos)
Patients with pulmonary TB (total)	682	777	362	777
Intervention sites	305	353	151	330
Control sites	377	424	211	447
HHC identified (total)	1474	2067	1461	3260
Intervention sites	788	1400	614	1340
Control sites	686	667	847	1920
HHC starting TPT (total)	346	424	238	634
Intervention sites	120	277	86	252
Control sites	226	147	152	382
HHC identified per 100 TB patients, estimates (95% CI)[a]				
Intervention sites	257 (148, 448)	395 (333, 468)	408 (277, 601)	404 (347, 472)
Control sites	180 (96, 339)	158 (61, 407)	395 (352, 444)	428 (375, 489)
HHC starting TPT per 100 TB patients, estimates (95% CI)[b]				
Intervention sites	38 (18, 81)	73 (28, 191)	65 (25, 173)	76 (32, 177)
Control sites	58 (19, 180)	40 (19, 86)	72 (33, 158)	88 (23, 333)

Numbers and rates per 100 index TB patients of HHC that were identified and started TPT per arm and phase. [a]Estimated with marginal model with log link using NLESTIMATE, corrected for clustering. [b]Estimated with marginal model with log link using NLESTIMATE, corrected for clustering, and small clusters.

Table 1: **People with pulmonary TB and households contacts (HHC).**

Objective 1, sustainability

The rate of HHC identified and started on TPT seen in Phase 2 at the original intervention sites in the main trial (Table 1 and Fig. 2), was similar during Phases 3 and 4 of the follow-up study (Fig. 3). As seen in Table 2, in the analysis of all countries, on average, there were 10 more (95% CI: −84, 105) HHC identified and one fewer (95% CI: −22, 20) HHC starting TPT per 100 index TB patients throughout Phases 3 and 4 of the follow-up study, compared to Phase 2, the post-intervention phase, in the ACT4 trial. The difference in the rate of HHC identified, and started on TPT between Phases 3 & 4 vs Phase 1 was 148 and 35 per 100 index TB patients respectively; these point estimates of differences are similar in magnitude to the point estimates from the trial, but confidence intervals were very broad, so none of these differences were significant. These findings were consistent when restricting the analysis to sites in LMIC (Benin, Ghana and Indonesia), although confidence intervals are even larger for all estimates. Results in each of the participating countries are shown in Supplement 1: Tables S2 and S3a.

Objective 2, effect of simplified intervention

In control sites, at the start of the main ACT4 trial, the number of HHCs identified per 100 index TB patients

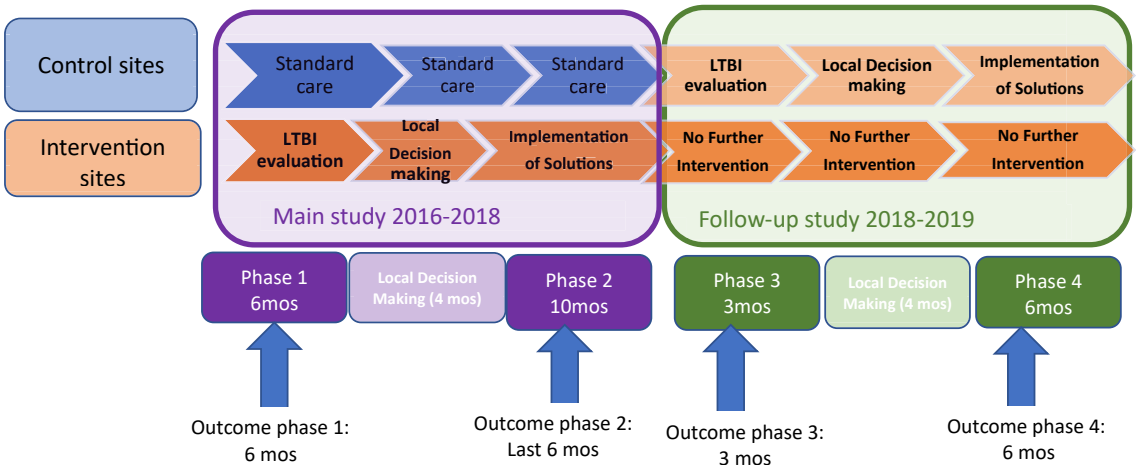

Fig. 2: Schematic of study design and phases of outcome ascertainment.

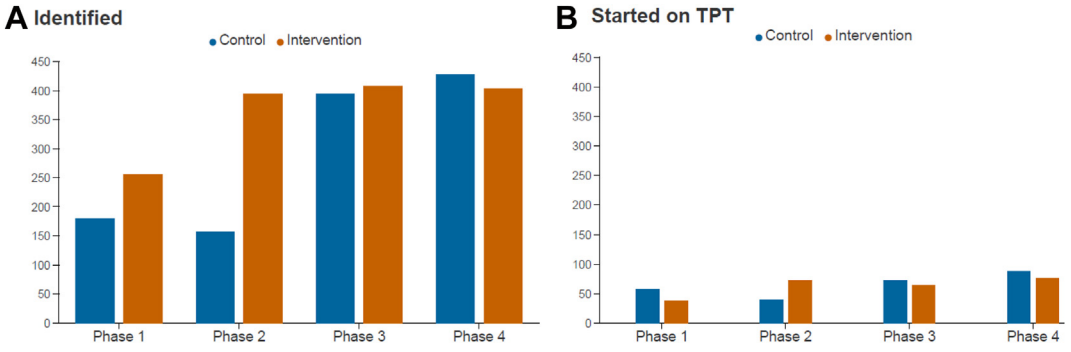

Fig. 3: HHC who were identified and started on TPT per 100 index TB patients in the 4 phases of the studies, by original allocation. A. Identified; B. Started on TPT. Blue columns: Control; Red columns: Intervention.

was 180 (95% CI: 96, 339); this declined slightly to 158 (95% CI: 61, 407) in Phase 2 of the main trial (Table 1). Similarly, the number of HHC starting TPT was 58 (95% CI: 19, 180) per 100 index TB patients at the start of the main trial, and declined to 40 (95% CI: 19, 86) in Phase 2 at the control sites. In Phase 3, and before the simplified intervention was implemented, there was an unexpected substantial increase in rate of HHC identified at these control sites (Table 1 and Fig. 2). As shown in Table 3, when results in the final post-intervention phase (phase 4) were compared to all pre-intervention periods (Phases 1, 2 and 3), in sites receiving the simplified intervention in the follow-up study, there was a non-significant increase of 33 (95% CI: –77, 144) HHC starting TPT per 100 index TB patients overall. When restricted to LMIC sites there was a non-significant increase of 26 (95% CI: –27, 80) HHC starting TPT. Results within each country are shown in Supplement 1: Tables S2 and S3b. The estimated costs, expressed per index TB patient, for the simplified intervention were much higher at Canadian sites than LMIC sites. At the latter, total costs for the intervention ranged from $194 to $1064 (CAD) per index TB patient; most of these costs were related to personnel costs. Costs for the solutions accounted for less than 20% of total costs, and ranged from $33 to $178 (CAD) per index TB patient at LMIC sites (Supplement Table S4).

As seen in Table 4, when comparing all pre- and post-intervention periods, the pre-post difference in HHC identified following the simplified intervention in the follow-up study was not significantly different from the pre-post difference following the original intervention applied in the main trial (this is the difference of differences shown in Table 4). When comparing all pre-intervention phases to all post intervention phases, at the two groups of sites, with the simplified intervention 68 more HHC were identified (95% CI: –140, 276), and 2 fewer HHC started TPT per 100 index TB patients (95% CI: –124, 121) than with the original intervention. Findings were similar, with even broader confidence intervals when restricting analyses to LMIC sites.

Discussion

In this follow-up study we found evidence of a sustained effect, with increased numbers of HHC identified, and initiating TPT, up to one year after the end of a health system intervention. This finding suggests that improvements to the latent TB cascade of care for HHC were sustainable. This is important because few studies have assessed the impact of health services optimization on TPT initiation, and even fewer have looked at sustainability of the resulting improvements. We also found that a simplified intervention was associated with a non-significant increase in the number of HHC identified and initiating TPT. The effects of the intervention, in the original trial, and the follow-up study, were less in Canada than in sites in Ghana, Benin and Indonesia.

The intervention delivered in the trial posed minimal risk to participants, required minimal training or technology, and no equipment nor supplies. The initial assessment was based on analysis of the latent TB cascade of care for HHC, using routinely collected data at all sites, plus short questionnaires administered to persons with TB disease, their household contacts, and health care workers. Local decision making required no added resources, except personnel time, although external funding was provided for implementation of solutions (see again Table S4). This intervention was designed to be 'low-tech' and low risk and so should be readily applicable to other settings. In the three participating LMIC, costs for this programme of HHC management were estimated to range from less than 200 (CAD) to slightly over 1000 per index TB patient; these costs were much lower than in the original trial.

An earlier systematic review identified that of persons who could potentially benefit from TPT, more than 70% were lost in the various steps of the cascade of TB infection care, before TPT initiation.[5] A more recent review of interventions to strengthen the TB infection cascade of care identified many observational studies of specific interventions such as media campaigns, home visits or digital aids for healthcare workers,[10] but no studies that included multi-faceted or broad health system interventions that would act across all steps of the cascade. As background to this study, we identified only three completed,[11–13] and one ongoing trial[14] that tested health system interventions to enhance management of household contacts. Of these, only one completed trial,[13] and the ongoing trial[14] assessed TPT initiation; both assessed individual-level standardized interventions—either home based contact investigation,[14] or teaching persons with newly diagnosed TB how to screen their household contacts.[13] The other two trials tested health facility directed interventions,[11,12] but measured TB disease detection and treatment. All these trials tested single interventions that were pre-established by the investigators, and standardized.[11–14] Although such intervention studies may be successful, their applicability in other settings might be limited. On the other hand, the intervention tested in this study was highly flexible and adaptable, because the process of local evaluation, feedback and local decision making was standardized, but the solutions selected varied widely; these were appropriate for the local setting and responded to local problems. One earlier trial that showed a reduction in maternal mortality resulting from regular multi-disciplinary maternal mortality review in obstetric units in Mali is a similar intervention, in that the 'intervention' was a process, with total flexibility in the actual solutions implemented in each unit.[15]

The sustainability of any intervention is crucial. This study tested a complex intervention with many features. One feature that we felt was key to sustainability was the

HHC identified at intervention sites:	Compared to phase 1 (Difference in rates)	Compared to phase 2 (Difference in rates)
All countries (n = 8 sites)[a]		
Phases 3&4 compared to:	148 (−63, 359)	10 (−84, 105)
LMIC only (n = 6 sites)[a]		
Phases 3&4 compared to:	208 (−50, 466)	11 (−142, 164)
HHC starting TPT at intervention sites:		
All countries (n = 8 sites)[b]		
Phases 3&4 compared to:	35 (−10, 80)	−1 (−22, 20)
LMIC only (n = 6 sites)[b]		
Phases 3&4 compared to	44 (−37, 124)	−12 (−92, 69)

Rates per 100 persons with pulmonary TB, in intervention sites (n = 8) and control sites in main trial) All countries (Benin, Canada, Ghana, and Indonesia) and in LMIC only (Benin, Ghana, Indonesia. [a]Estimated with marginal model with log link using NLESTIMATE, corrected for clustering. [b]Estimated with marginal model with log link using NLESTIMATE, corrected for clustering, and small clusters.

Table 2: **Assessment of sustainability: comparison between all of follow-up study with phases in the main trial (95% CI) of HHC identified and starting TPT at original intervention sites.**

HHC identified at control sites:	Estimates (95% CI) of differences in rates between phase 4 and:			
	Phase 1	Phase 2	Phase 3	Phase 1,2,3
All countries (n = 8 sites)[a]				
Phase 4 compared to:	**248 (130, 365)**	**270 (123, 417)**	33 (−32, 97)	**212 (104, 320)**
LMIC only (n = 6 sites)[a]				
Phase 4 compared to:	**260 (143, 378)**	**291 (157, 425)**	48 (−25, 121)	**229 (130, 328)**
HHC starting TPT at control sites:	**Phase 1**	**Phase 2**	**Phase 3**	**Phase 1,2,3**
All countries (n = 8 sites)[b]				
Phase 4 compared to	30 (−117, 176)	47 (−54, 149)	16 (−69, 100)	33 (−77, 144)
LMIC only (n = 6 sites)[b]				
Phase 4 compared to	24 (−41, 89)	42 (−20, 105)	13 (−64, 90)	26 (−27, 80)

Rates per 100 persons with pulmonary TB, in intervention sites (n = 8) and control sites in main trial. Differences that are significant are in bold.) All countries (Benin, Canada, Ghana, and Indonesia) and in LMIC only (Benin, Ghana, Indonesia. [a]Estimated with marginal model with log link using NLESTIMATE, corrected for clustering. [b]Estimated with marginal model with log link using NLESTIMATE, corrected for clustering, and small clusters.

Table 3: **Assessment of the streamlined intervention at original control sites: on HHC identified and starting TPT.**

HHC identified per 100 TB	Estimates of differences in rates (95% CI)	
	Original control sites	Original intervention sites
All phases with vs without intervention	Phase 4 vs 1,2,3	Phase 2,3,4 vs 1
All sites in all countries (n = 16). Difference in rates[a]	**212 (104, 320)**	144 (−34, 322)
Difference of differences (Streamlined vs Original)	68 (−140, 276)	
Sites in LMIC countries (n = 12). Difference in rates[a]	**229 (130, 328)**	**203 (4, 400)**
Difference of differences (Streamlined vs Original)	26 (−196, 248)	
HHC starting TPT per 100 TB	Original control sites	Original intervention sites
All phases with vs without intervention	Phase 4 vs 1,2,3	Phase 2,3,4 vs 1
All sites in countries (n = 16). Difference in rates[b]	33 (−77, 144)	35 (−16, 86)
Difference of differences (Streamlined vs Original)	−2 (−124, 121)	
Sites in LMIC countries (n = 12). Difference in rates[b]	26 (−27, 80)	47 (−24, 119)
Difference of differences (Streamlined vs Original)	−21 (−110, 68)	

Rates and 95% CI per 100 TB index TB patients. Differences that are significant are in bold. [a]Estimated with marginal model with log link using NLESTIMATE, corrected for clustering. [b]Estimated with marginal model with log link using NLESTIMATE, corrected for clustering, and small clusters.

Table 4: **Comparability of effect of intervention on HHC identified and starting TPT in main study and in follow-up study.**

early and continued engagement of local decision makers. Through their engagement, solutions were identified that deployed more sustainable low-cost local resources. Simple data systems were established as well to ensure that routine reporting continued to the TB programs; and we engaged TB programme and site staff for delivery of training. Feedback from sites was that the visual communication tools created for displaying local cascade of care data were invaluable to facilitate local decision making, similar to findings elsewhere.[16] Review of findings, and selection of locally appropriate approaches to strengthen the cascade (termed "solutions") occurred independently at each site, allowing greater flexibility in solutions implemented, and greater stakeholder acceptance of new measures. We found in an earlier study that improvements in the initial steps of the latent TB cascade of care often unmasked problems at later stages of the cascade.[17] Hence, iterative cycles of evaluation, decision making, and intervention, considered fundamental for quality improvement[18] were critical to the long term success of this study.[19,20]

This follow-up study had a number of limitations. First, only 16 sites participated, in 4 countries, limiting power, particularly in view of the substantial within-site variation in outcomes over the course of the study. This variability was often unexplained, but in some instances was coincident with changes unrelated to the study such as turnover in key clinical or TB program personnel. A second important source of potential bias is the possibility of temporal changes—in policy, programmes, personnel, and study populations. In this follow-up study the primary analysis was a within-site change; hence this bias was not controlled through the original randomization. There were no major changes in TB program policy over the course of the trial (for example age criteria policies for provision of TPT), but other unmeasured changes may have affected our results. In particular, there was evidence of contamination in the control sites, given that the number of HHC identified and treated increased, even before the intervention was started at these sites in the follow-up study. Since the results of the main ACT4 trial were known at the start of the follow-up study to investigators and study staff, as well as local TB programme officials who were heavily engaged in the study for supervision and training at all sites, we speculate this knowledge may have influenced the behaviour of these staff at the control sites. As a result, the differences in outcomes between Phase 3 and 4 (pre- and post-simplified intervention) were relatively modest, although when outcomes in all pre-intervention periods (phases 1–3) were compared to the post-intervention period (Phase 4), the differences in HHC identified and treated were substantial and significant.

The results in each of the participating countries (see again Supplement 1: Tables S2 and S3), underscore the difficulties of health system interventions in multiple sites with differing TPT policies and practices, and numerous other constraints. In Indonesia, where TPT was given only to HHC aged under five, following national policy, the number treated was low but nevertheless was significantly higher post-intervention in all sites. In Ghana, where TPT was given to HHC of all ages, the intervention site achieved the biggest absolute increase in HHC treated in the main ACT4 trial, as did the control site in the follow-up study. However, in Phase 3 there were almost no index TB patients diagnosed at the original intervention site, with associated difficulties in HHC management. This was due to problems external to this study, and, once corrected, this site resumed high rates of HHC identified and starting TPT, although overall the net effect was a drop in outcomes albeit with very wide confidence intervals. In Benin (where TPT is given only to HHC aged <5) and Canada the gains achieved during the main trial and follow-up study were more modest. This is most likely because the programmes for HHC management at the participating sites in these two countries were already functioning reasonably well, so potential gains were more limited. Given the variability in outcomes, these small gains were not significant.

This study also had important strengths. The involvement of multiple sites in settings with very different resources and infrastructure should enhance the generalizability of this approach. The study examined impact of new health system approaches on important and relevant patient outcomes in all eligible HHC seen at the participating sites, rather than only a selected sub-group. The emphasis on engagement with local providers and health care administrators, with local data gathering, decision making, and implementation of

solutions provided a proof of principle that strengthening local health systems using a quality improvement approach can be successful.

We conclude that a health system intervention of repeated cycles of local evaluation, decision making, and implementation was associated with increased number of HHC identified and starting TPT, and this impact appeared to be sustained for more than a year. This low-risk minimal technology intervention could be evaluated as a means to enhance uptake of TPT among HHC in many settings.

Contributors

Authors contributed to this manuscript as follows: Initial conception of the study, including objectives and design by DM, OO, and AB. All authors contributed to the writing and approval of the final study protocol, and also to the enrolment of study participants and all related data gathering. Data analysis was performed by: DM, OO, and AB. DM wrote the initial draft of the manuscript, and all authors made revisions and provided critical input. All authors read and approved the final version of the manuscript. The underlying study data was reviewed and verified by O Oxlade, D Menzies, and A Benedetti.

Data sharing statement

The data collected for this trial in the form of deidentified participant data and data dictionary will be made available one year after publication date. Investigators wishing to access these data will need to have a research proposal approved by their ethics committee and complete a data access agreement. All inquiries should be sent to Dick Menzies (dick.menzies@mcgill.ca).

Declaration of interests

Dr Fox reports receiving peer reviewed grants as PI for operating funds for other TB research projects from the Australian Medical Research Council (paid to institution), and receipt of a $50,000 in-kind donation of Rifapentine from Sanofi Inc, for a study outside of the scope of work of the current trial. Dr Menzies reports receiving peer reviewed grants as PI for operating funds for other TB research projects from the Canadian Institutes of Health Research, and from the TB Trials Consortium of Centres for Disease Control (USA) (paid to institution). Dr TA Nguyen reports receiving peer reviewed grants as PI for operating funds for other TB research projects from the Australian Medical Research Council (paid to institution), Dr Ruslami reports receiving honoraria from the Indonesian Pediatric Society. All other authors declare no competing interests relevant to this study. All other authors declare no relevant Conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102546.

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