Effectiveness and cost-effectiveness of a health systems intervention for latent tuberculosis infection management (ACT4): a cluster-randomised trial

Olivia Oxlade, Andrea Benedetti, Mênonli Adjobimey, Hannah Alsdurf, Severin Anagonou, Victoria J Cook, Dina Fisher, Greg J Fox, Federica Fregonese, Panji Hadisoemarto, Philip C Hill, James Johnston, Faiz Ahmad Khan, Richard Long, Nhung V Nguyen, Thu Anh Nguyen, Joseph Obeng, Rovina Ruslami, Kevin Schwartzman, Anete Trajman, Chantal Valiquette, Dick Menzies

Summary

Background Reaching the UN General Assembly High-Level Meeting on Tuberculosis target of providing tuberculosis preventive treatment to at least 30 million people by 2022, including 4 million children under the age of 5 years and 20 million other household contacts, will require major efforts to strengthen health systems. The aim of this study was to evaluate the effectiveness and cost-effectiveness of a health systems intervention to strengthen management for latent tuberculosis infection (LTBI) in household contacts of confirmed tuberculosis cases.

Methods ACT4 was a cluster-randomised, open-label trial involving 24 health facilities in Benin, Canada, Ghana, Indonesia, and Vietnam randomly assigned to either a three-phase intervention (LTBI programme evaluation, local decision making, and strengthening activities) or control (standard LTBI care). Tuberculin and isoniazid were provided to control and intervention sites if not routinely available. Randomisation was stratified by country and restricted to ensure balance of index patients with tuberculosis by arm and country. The primary outcome was the number of household contacts who initiated tuberculosis preventive treatment at each health facility within 4 months of the diagnosis of the index case, recorded in the first or last 6 months of our 20-month study. To ease interpretation, this number was standardised per 100 newly diagnosed index patients with tuberculosis. Analysis was by intention to treat. Masking of staff at the coordinating centre and sites was not possible; however, those analysing data were masked to assignment of intervention or control. An economic analysis of the intervention was done in parallel with the trial. ACT4 is registered at ClinicalTrials.gov, NCT02810678.

Findings The study was done between Aug 1, 2016, and March 31, 2019. During the first 6 months of the study the crude overall proportion of household contacts initiating tuberculosis preventive treatment out of those eligible at intervention sites was 0·21. After the implementation of programme strengthening activities, the proportion initiating tuberculosis preventive treatment increased to 0·35. Overall, the number of household contacts initiating tuberculosis preventive treatment per 100 index patients with tuberculosis increased between study phases in intervention sites (adjusted rate difference 60, 95% CI 4 to 116), while control sites showed no statistically significant change (–12, –33 to 10). There was a difference in rate differences of 72 (95% CI 10 to 134) contacts per 100 index patients with tuberculosis initiating preventive treatment associated with the intervention. The total cost for the intervention, plus LTBI clinical care per additional contact initiating treatment was estimated to be CA$1348 (range 724 to 9708).

Interpretation A strategy of standardised evaluation, local decision making, and implementation of health systems strengthening activities can provide a mechanism for scale-up of tuberculosis prevention, particularly in low-income and middle-income countries.

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McGill International TB Centre, Research Institute of the McGill University Health Centre, McGill University, Montreal, QC, Canada (O Oxlade PhD, A Benedetti PhD, H Alsdurf PhD, F Fregonese MD, F A Khan MD, Prof K Schwartzman MD, Prof A Trajman MD, C Valiquette, Prof D Menzies MD); **Centre National Hospitalier Universitaire de Pneumo-Phtisiologie de Cotonou, Cotonou, Benin** (M Adjobimey MD); **National Tuberculosis Program, Cotonou, Benin** (Prof S Anagonou PhD); **Provincial TB Services, BC Centre for Disease Control, Vancouver, BC, Canada** (V J Cook MD, J Johnston MD); **Division of Respiratory Medicine, Department of Medicine, University of British Columbia, Vancouver, BC, Canada** (V J Cook, J Johnston); **University of Calgary, Calgary, AB, Canada** (D Fisher MD); **The Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia** (G J Fox PhD, T A Nguyen PhD); **TB-HIV Research Center** (P Hadisoemarto MD, Prof R Ruslami PhD) **and Department of Public Health** (P Hadisoemarto, Prof R Ruslami), **Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia; Centre for International Health, Faculty of Medicine, University of Otago, Otago, New Zealand** (Prof P C Hill MD); **Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB, Canada** (R Long MD); **The National Lung Hospital, Hanoi, Vietnam**

Introduction

Tuberculosis is responsible for an ongoing global public health crisis, causing 1·5 million deaths in 2018.[1] Modelling studies estimate that 24% of the world's population is infected with *Mycobacterium tuberculosis* and thus might be at risk of developing the disease, especially soon after infection.[2] Important reductions in global tuberculosis rates will require very substantial increases in the number of people treated for latent tuberculosis infection (LTBI).[3]

At the 2018 UN General Assembly High-Level Meeting on Tuberculosis, the global community committed to offer tuberculosis preventive treatment to at least 30 million people by 2022.[4] This included 20 million household contacts older than 5 years, a group that only recently was added to WHO recommendations for tuberculosis preventive treatment.[5] In 2018, just 2% (of 20 million) of these household contacts were reported to have been treated with tuberculosis preventive treatment.[1]

(N V Nguyen MD); **The Woolcock Institute of Medical Research in Vietnam, Hanoi, Vietnam** (T A Nguyen); **Ministry of Health, Accra, Ghana** (J Obeng MD); **Federal University of Rio de Janeiro, Rio de Janeiro, Brazil** (Prof A Trajman)

Correspondence to: Prof Dick Menzies, Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, QC H4A 3S5, Canada **dick.menzies@mcgill.ca**

Research in context

Evidence before this study

Most of the literature about the cascade of care for latent tuberculosis infection (LTBI) relates to the efficacy and safety of different regimens for tuberculosis preventive treatment. Different approaches to improve tuberculosis preventive treatment completion have also been extensively studied, especially in high-income settings where preventive treatment has been a part of routine care in tuberculosis programmes for several decades. Although a systematic review on retention in the LTBI cascade of care showed that only 30% of those who are eligible for tuberculosis preventive treatment actually initiate treatment, very little research has been done on how to reduce losses in the LTBI cascade before treatment initiation.

We searched PubMed from Jan 1, 1980, to June 15, 2020, using the following search terms: "preventive treatment", "latent tuberculosis", "treatment initiation", "cascade-of-care", "contact management", and "household contacts". This search revealed that few studies have considered ways to increase tuberculosis preventive treatment initiation by focusing on health system strengthening. The CRESPIT study was one study that we found that was a randomised controlled trial that aimed to increase treatment initiation through conditional cash transfers, community meetings, and household visits, but in this study the intervention was targeted at the household level rather than focusing on improving training and deployment of tools aimed to strengthen the LTBI programmes at health facilities. In addition, as part of our study, we did a systematic review on interventions designed to strengthen the LTBI cascade. Although we found many studies that targeted specific steps of the cascade using interventions such as media campaigns, home visits, or digital aids for health-care workers, we found no studies where the intervention was targeted at the health system and designed to act across all steps of the cascade.

Added value of this study

To our knowledge, this study is the first randomised trial that tests a health systems approach to LTBI programme strengthening and combines standardised evaluations with flexible local decision making based on the information gathered. We found that in low-income and middle-income countries (LMICs) a three-phased approach of programme evaluation, local decision making, and strengthening improved tuberculosis preventive treatment initiation rates in health facilities in four LMICs, at relatively low cost. Improvements were greatest, and cost per contact initiating tuberculosis preventive treatment lowest, in LMICs where household contacts of all ages were identified, tested, and provided with tuberculosis preventive treatment.

Implications of all the available evidence

Without major efforts to strengthen LTBI programmes globally it will be impossible to reach the UN High-Level Meeting targets set in 2018—to offer tuberculosis preventive treatment to at least 24 million household contacts, who are considered a priority group for this type of treatment as they are at high risk of developing tuberculosis—by 2022. Tuberculosis preventive drug regimens that are shorter and safer with superior completion rates are available, but uptake of these regimens is poor. Strengthening LTBI programmes in LMICs is essential to ensure that individuals at greatest risk of developing tuberculosis reach the starting line for initiation of preventive treatment.

Household contacts of patients with infectious tuberculosis have a high risk of recent infection and are considered likely to benefit from tuberculosis preventive treatment. The pathway from identification to treatment of high-risk contacts can be presented as a cascade of care: from identification of contacts, through initial testing for latent tuberculosis and further medical evaluation to exclude active tuberculosis, and to provider recommendation for tuberculosis preventive treatment and initiation of such treatment. A systematic review of the cascade of care found that only 30% of all of those who should have been treated initiated tuberculosis preventive treatment,[6] even though these studies were based at centres with well established programmes of LTBI management. Multiple factors related to different steps in the cascade contribute to losses before treatment initiation.[6–8]

To maximise the impact on tuberculosis prevention, LTBI programmes in low-income and middle-income countries (LMICs) must be strengthened so that individuals will at least reach the point of treatment initiation. The aim of this cluster-randomised trial was to test the effectiveness and cost-effectiveness of a health systems strengthening intervention, delivered at the level of the health facility, to increase initiation of tuberculosis preventive treatment among household contacts.

Methods

Study design

This open-label, cluster-randomised controlled trial was done in four health facilities in the low tuberculosis incidence setting of Canada (cities of Calgary [AB], Edmonton [AB], Montreal [QC], and Vancouver [BC]), plus 20 health facilities in four countries with intermediate to high tuberculosis incidence rates: Benin, Ghana, Indonesia, and Vietnam.

A cluster was defined as a health facility that was randomly assigned to receive the intervention or not (controls). The central coordinating team consisted of the principal investigator, a project manager, and two senior research staff who worked to develop materials and tools and to liaise with sites. As summarised in figure 1, at intervention sites during an initial evaluation phase the proportion of eligible contacts progressing through each step of the LTBI cascade of care in the 6 months preceding

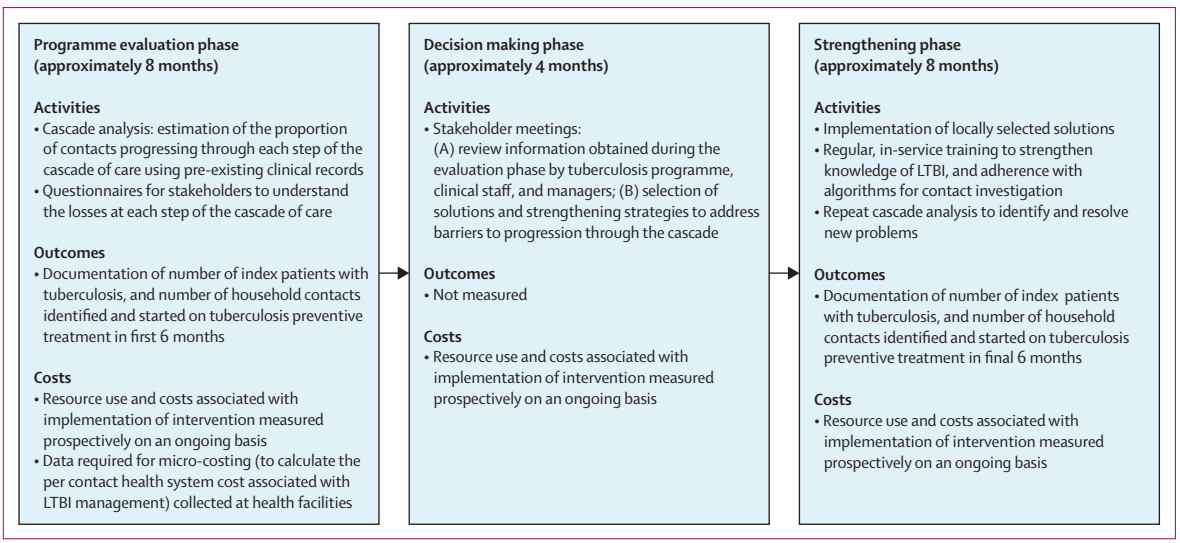

Figure 1: **Summary of intervention phases**
LTBI=latent tuberculosis infection.

the start of the study was measured, and interviewer-administered questionnaires identified local barriers to LTBI diagnosis and treatment initiation. In the decision-making phase, results from the baseline evaluation were analysed, and presented at stakeholder meetings with site investigators, tuberculosis programme officials, and staff and management of the participating health facilities and solutions to identified barriers were selected. The final phase of the intervention (the strengthening phase) included training related to LTBI management, implementation of solutions and, in some sites, implementation of LTBI registries. Funds were provided for the solutions selected.

Health facilities in the control arm received neither evaluation nor programmatic strengthening activities; however, current LTBI activities continued as usual. Tuberculin (for diagnosis of latent tuberculosis infection) and isoniazid were provided to control and intervention sites if not routinely available. Outcomes were collected during the first 6 and last 6 months of the 20-month study period and were analysed at the level of the health facility. Measured outcomes included the number of household contacts identified and started on tuberculosis preventive treatment, as well as costs associated with the intervention. Due to unforeseen problems, all sites in one country started the trial approximately 12 months after sites in other countries. This had no effect on overall balance as the trial design had accounted for such potential problems by stratifying initial randomisation by country.

The published study protocol provides full details of the study design and intervention.[9] For primary outcome data collection, consent was not sought from individuals attending health facilities as no data was collected at the individual level; individual baseline characteristics are not presented as we did not obtain permission to collect individual-level data. Written informed consent was obtained from individuals who agreed to participate in questionnaires during the programme evaluation phase. Ethical approval was first obtained at the coordinating centre (McGill University Health Centre ethics review board [15-291-MUHC]) and subsequently at each of the sites.

Health facilities

Countries were chosen to ensure global representation, and a range of resources available as well as varied tuberculosis incidence rates. Within these countries, facilities were selected that had a minimum number of patients with tuberculosis diagnosed in the year preceding the trial onset. Participating sites also had experience with clinical research to ensure that the research study could be successfully integrated into the health system. For countries that had multiple intervention sites, facilities were selected to ensure balance of rural to urban location, and regional socioeconomic status (appendix p 2). In addition, sites had to be sufficiently distanced to minimise contamination. Local study coinvestigators enrolled health facilities and informed them of their randomisation status.

See Online for appendix

Randomisation and masking

Randomisation took place at the level of the health facility. The randomisation sequence was generated by the study biostatistician (AB) and stratified by country and restricted to ensure balance of index patients with tuberculosis by arm and country to address country-level differences, such as tuberculosis preventive treatment policy. To achieve balance of index patients with tuberculosis, the study biostatistician did a simulation in Excel, in which 100 000 randomisations were done; from this we selected the 12 709 sequences that achieved balance (between 48% and 52% in the two arms). From these 12 709 sequences,

one was then randomly selected for the study. Because the intervention was delivered at the level of the health facility, blinding of study staff at the coordinating centre and sites was not possible. However, the principal investigator (DM), project manager (OO), and study biostatistician (AB) were not involved in outcome measurement. For data analysis site names and intervention status were removed from data and replaced with arm A or B.

Procedures

For collection of data on the primary study outcome, at each intervention and control health facility, the number of identified household contacts of newly diagnosed index patients with tuberculosis and the number of household contacts initiating tuberculosis preventive treatment during the first 6 months of the first study phase and the last 6 months of the final study phase was abstracted from routine clinic records by research staff. Summary data at the health facility level were collected from all index patients with tuberculosis diagnosed at the health facility during those 6-month periods. Although data sources varied in different health facilities (eg, electronic medical record or paper charts), the procedures followed to measure study outcomes remained the same at each facility throughout the study.

During the programme evaluation phase, an LTBI cascade analysis was done retrospectively at intervention sites using pre-existing registries and individual treatment records for patients with tuberculosis, and their household contacts. Consecutive index patients were identified and summary data at the health facility level were collected on 100–150 household contacts who should have been identified before the date on which data collection began. This procedure differed from the primary outcome data collection procedure as data were collected for every step of the LTBI cascade from the time period before study onset. For each index patient with tuberculosis we documented information about their contacts: number identified, number screened, number who required medical evaluation, number completing medical evaluation, and number starting tuberculosis preventive treatment. Next, standardised open-ended questionnaires—designed to provide information from different perspectives about cascade of care barriers—were administered to: index patients with tuberculosis, household contacts of index patients with tuberculosis, parents of child household contacts, and health-care workers involved in tuberculosis care. Questionnaires were based on those used in a previous study.[10] Responses provided by participants were classified by interviewers at the data entry stage using pre-coded categories relating to different types of barriers.

In the decision-making phase, research staff at the central coordinating centre assisted site investigators to identify the steps in the LTBI cascade with greatest losses at their sites, and to understand these cascade losses using the responses on the questionnaires from those sites. The key barriers were matched to a specific cascade step, and the target population for solutions was identified. Sites were then asked to consult the systematic review of potential interventions[11] that was done as part of the study, to identify a short list of potential solutions. Stakeholder meetings were then held at each health facility to review the findings from the LTBI cascade of care, the questionnaires from that facility, the potential solutions identified in the review, and the estimated cost-effectiveness of those solutions. On the basis of this evaluation, local stakeholders selected solutions with evidence of efficacy and cost-effectiveness, that they believed would be feasible at their site.

During the strengthening phase, programme strengthening was achieved through the following activities: (1) initial clinical training for all health-care workers providing tuberculosis care services at the health facility (topics included household contacts identification and investigation, initial assessment, medical evaluation and LTBI diagnosis); (2) in LMICs, introduction of a new clinic registry for the management of contacts; (3) ongoing in-service training to reinforce clinical skills, answer questions, and help with documentation such as use of the registries (the frequency of in-service training varied by country, between every 1–2 weeks initially and then decreased to once monthly after 3–4 months); (4) support for implementation of site-specific solutions selected in the decision-making phase and; (5) review of information about repeat cascade-of-care performance (appendix p 3). Information obtained from repeat cascade evaluations were fed back to clinic staff to motivate and inform them of outstanding issues. Further details of each of the strengthening activities are provided in the published study protocol.[9]

During the trial, approaches to management of household contacts varied in different countries. In Indonesia and Benin, national guidelines specified that household contacts of all ages should be investigated to rule out active tuberculosis, but only children younger than 5 years should be offered tuberculosis preventive treatment. In Ghana, Vietnam, and Canada, household contacts of all ages were investigated with the tuberculin skin test or interferon γ release assay, and chest x-ray if necessary, and those deemed eligible were offered tuberculosis preventive treatment (appendix p 4).

Research staff from the coordinating centre visited study sites every 6 months and investigator meetings were held annually to review study procedures, progress, and future plans.

Outcomes

The primary study outcome was the number of household contacts that initiated tuberculosis preventive treatment within up to 4 months of the diagnosis of the index case. For each site the local site principal investigator judged, based on local practice and standards, if a 3-month or 4-month delay was considered acceptable to complete the contacts' screening and evaluation and start tuberculosis

preventive treatment when indicated. We standardised the primary study outcome to the number of index cases diagnosed at each health facility, such that the final number was the number of household contacts initiating tuberculosis preventive treatment per 100 index cases. Index patients with tuberculosis were defined as patients aged 12 years or older with newly diagnosed pulmonary tuberculosis that had been microbiologically confirmed. A household contact was defined as someone who slept in the same house at least one night per week or spent more than 1 h in the house at least 5 days per week, on average, over the preceding 3 months. This definition was based on consensus among the investigators and the scientific advisory committee. Treatment initiation for household contact was defined as clinical or pharmacy records indicating that medications had been dispensed or a prescription had been issued.

The secondary study outcome was the cost-effectiveness of the intervention. Costs at intervention sites included the implementation costs from the tuberculosis programme perspective and the health system costs for LTBI clinical care. These same outcomes were also measured during the crossover period, when health facilities that were originally randomised as control sites received the intervention. These outcomes will be reported in future work.

Measurement of costs

The secondary study outcome—the cost-effectiveness of the intervention—involved costs that were quantified from two different sources: the cost of the intervention itself, and the increased health system costs for clinical LTBI-related care for the increased number of household contacts managed because of the intervention. For the economic analysis, a real-world costing approach was used, meaning that resource use was measured at sites and local supplier costs were used wherever possible.

The implementation cost of the intervention included: (1) the amount of time spent by all personnel on conducting the evaluation, participating in decision-making activities, and LTBI strengthening activities in intervention sites, which were quantified using activity logs completed by all staff involved in these activities. These staffing costs included time spent by research staff, tuberculosis programme staff, and clinical staff involved in running training activities. Hours were converted into costs using standard hourly rates for different types of personnel, obtained from each of the sites; (2) supplies used during the trial; and (3) costs for solutions that were estimated based on the funding allocated to sites to implement locally selected solutions. Each site received funds for these solutions; the amount allocated depended upon the volume of household contacts, gross domestic product per capita, and the needs expressed by the local site investigators (appendix p 29). Costs associated with research aspects of the trial, such as collection of primary outcome data or cost outcome data were not included.

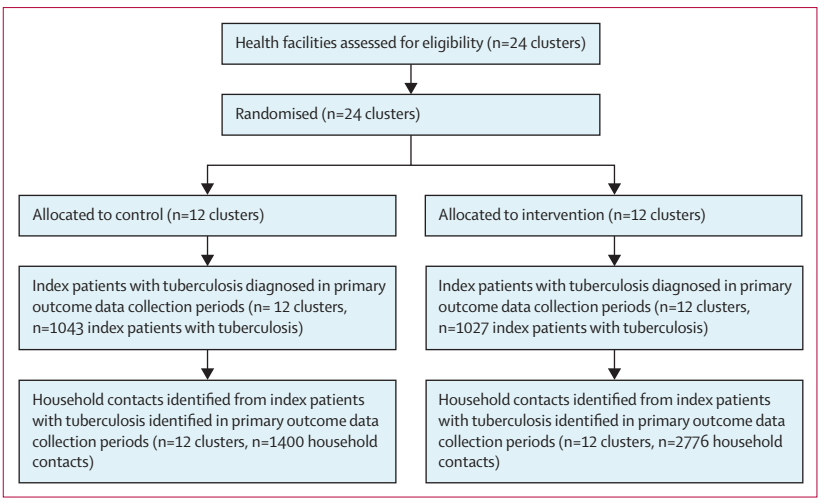

Figure 2: **Trial profile**

The additional health system costs of clinical care for each contact at each step of the LTBI cascade were estimated using a micro-costing approach.[12] The health system costs included were those associated with LTBI or tuberculosis-related diagnosis, screening, and medical evaluation, but not those incurred once tuberculosis preventive treatment was initiated—such as costs for treatment phase follow-up or drug costs—because the primary outcome was tuberculosis preventive treatment initiation, and not completion. The number of contacts receiving clinical care at each cascade step was taken from observed data in the study. Further information on costing is presented in the appendix (pp 26–45).

Statistical analysis

We did a simulation study to assess power. We identified and randomly assigned 24 health facilities or clusters of similar sizes anticipating that each health facility would see at least 20 index patients with tuberculosis and 80 household contacts over a 6-month period. For each health facility, the number of household contacts expected to initiate treatment per index patient was generated from a Poisson distribution with a rate that depended on the effect of the intervention, the effect of time, and a normally distributed random effect for each randomisation unit such that the intra-class correlation coefficients ranged from 0·16 to 0·40. Using this approach, we estimated that we had 96% power to detect a significant (α=0·05) effect of the intervention if the true increase in the number of household contacts initiating tuberculosis preventive treatment (between study phases, and controlling for any temporal effects in the control sites) was at least 15 per 100 index patients with tuberculosis.

In descriptive analysis the number of household contacts identified, the number estimated to be eligible for tuberculosis preventive treatment, and the number and proportion initiating treatment were reported for control and intervention sites for each study phase. For

	Household contacts identified (from index patients with tuberculosis) in the evaluation phase		Household contacts estimated to be eligible to initiate tuberculosis preventive treatment*		Number of household contacts initiating treatment		Proportion of household contacts initiating tuberculosis preventive treatment out of those eligible	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Overall (24 sites)								
Total	702	807	553	576	226	122	0·41	0·21
Age <5 years	239	155	239	155	194	82	0·81	0·53
Age ≥5 years	463	652	314	421	32	40	0·10	0·10
Canada (4 sites)								
Total	99	296	59	179	38	57	0·64	0·32
Age <5 years	11	36	11	36	8	18	0·73	0·50
Age ≥5 years	88	260	48	143	30	39	0·63	0·27
LMICs only (20 sites)								
Total	603	511	494	397	188	65	0·38	0·16
Age <5 years	228	119	228	119	186	64	0·82	0·54
Age ≥5 years	375	392	266	278	2	1	0·01	0
LMICs with national policies to identify and give tuberculosis preventive treatment to household contacts of all ages (10 sites)								
Total	130	142	97	109	11	2	0·11	0·02
Age <5 years	17	31	17	31	9	1	0·53	0·03
Age ≥5 years	113	111	80	78	2	1	0·03	0·01
LMICs with national policies to identify and screen for active tuberculosis in all ages, but give tuberculosis preventive treatment only to children younger than 5 years (10 sites)								
Total	473	369	397	288	177	63	0·45	0·22
Age <5 years	211	88	211	88	177	63	0·84	0·72
Age ≥5 years	262	281	186	200	0	0	0	0

LMICs=low-income and middle-income countries. *The number of household contacts that are estimated to be eligible for tuberculosis preventive treatment include all children younger than 5 years, and household contacts older than 5 years who are expected to test positive in the tuberculin skin test based on prevalence data collected at sites[16] and published data[17] (average for Canada 0·55, average for all other countries 0·70).

Table 1: **Household contacts identified and initiating treatment during the first 6 months of the study (evaluation phase) in control and intervention sites**

countries that treated only household contacts younger than 5 years in the trial, all the household contacts of those younger than 5 years identified were considered eligible to receive tuberculosis preventive treatment. For countries that treated household contacts of all ages, the number eligible to receive tuberculosis preventive treatment was calculated by adding all the household contacts of those younger than 5 years, and a proportion of the household contacts aged 5 years and older. This proportion was based on the estimated LTBI prevalence in that country.

For the main intention-to-treat analysis, we estimated a marginal Poisson regression model via generalised estimating equations with an exchangeable correlation structure at the level of the unit of randomisation, using robust standard errors, and correcting for few clusters.[13] The dependent variable was the number of household contacts who initiated tuberculosis preventive treatment per index patient with tuberculosis. When possible, we used an identity link[14] and estimated the difference between the intervention and control arms in the change between evaluation and strengthening phases in intervention sites (in control sites the equivalent time period was considered as there were no defined study phases), in the number of household contacts starting tuberculosis preventive treatment per index patient (ie, a rate difference). Otherwise, we used a log link and included the log of the number of patients with tuberculosis as an offset, with other details listed here, and estimated rate differences. In prespecified secondary analyses, we assessed LMIC and Canadian sites separately and also investigated potential mechanisms of action of the intervention. Finally, we assessed the effect of the intervention separately in countries that treated household contacts of all ages, or countries that only treated children younger than 5 years. All statistical analyses were done using SAS version 9.4.

Costing data were collected in local currency and then inflated using local inflation indices to 2017.[15] These calculations were then exchanged to Canadian currency using either direct exchange rates (for tradable items) or purchasing power parity exchange (for salary and non-tradable items).[16] The total cost of the intervention in each country was calculated by combining the implementation costs and the additional LTBI-associated health system costs in each country. Incremental cost-effectiveness ratios (defined as the health system costs per additional contact initiating treatment) were used to assess the cost-effectiveness of the intervention versus the current standard of care for LTBI. We also estimated a range for the incremental cost-effectiveness ratios using

	Household contacts identified (from index patients with tuberculosis) in the strengthening phase		Household contacts estimated to be eligible to initiate tuberculosis preventive treatment*		Number of household contacts initiating treatment		Proportion of household contacts initiating tuberculosis preventive treatment out of those eligible	
	Control	Intervention	Control	Intervention	Control	Intervention	Control	Intervention
Overall (24 sites)								
Total	698	1969	525	1402	147	487	0·28	0·35
Age <5 years	167	275	167	275	108	188	0·65	0·68
Age ≥5 years	531	1694	358	1127	39	299	0·11	0·27
Canada (4 sites)								
Total	108	451	60	269	29	82	0·48	0·30
Age <5 years	3	51	3	51	1	20	0·33	0·39
Age ≥5 years	105	400	57	218	28	62	0·49	0·28
LMICs only (20 sites)								
Total	590	1518	465	1133	118	405	0·25	0·36
Age <5 years	164	224	164	224	107	168	0·65	0·75
Age ≥5 years	426	1294	301	909	11	237	0·04	0·26
LMIC sites with policies to identify and give tuberculosis preventive treatment to household contacts of all ages (10 sites)								
Total	129	763	97	554	14	290	0·14	0·52
Age <5 years	23	77	23	77	3	53	0·13	0·69
Age ≥5 years	106	686	74	477	11	237	0·15	0·50
LMIC sites with policies to identify and screen for active tuberculosis in all ages, but give tuberculosis preventive treatment only to children younger than 5 years (10 sites)								
Total	461	755	368	579	104	115	0·28	0·20
Age <5 years	141	147	141	147	104	115	0·74	0·78
Age ≥5 years	320	608	227	432	0	0	0·00	0·00

LMICs=low-income and middle-income countries. *The number of household contacts that are estimated to be eligible for tuberculosis preventive treatment include all children younger than 5 years, and household contacts older than 5 years who are expected to test positive with the tuberculin skin test based on prevalence data collected at sites[16] and published data[17] (average for Canada 0·55, average for all other countries 0·70).

Table 2: **Household contacts identified and initiating treatment during the final 6 months of the study (health strengthening phase) in control and intervention sites**

the lower and upper limit of the 95% CI around the estimate of effect. More details on the methods used for costing are provided in the appendix (pp 26–45).

In sensitivity analyses for the economic analyses, several alternative scenarios were considered. These included a simplified version of the intervention (where only strengthening activities were included), an extended time horizon with longer benefit of the intervention (where in-service training and intervention were assumed to continue for a total of 24 months after introduction of the intervention), and, in settings where only children younger than 5 years are now treated, adopting a policy of providing tuberculosis preventive treatment to household contacts of all ages instead.

A data safety monitoring board was not required for this health systems trial which did not have any anticipated safety issues. The trial was registered with ClinicalTrials.gov, NCT02810678.

Role of the funding source

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

Results

The study was done between Aug 1, 2016, and March 31, 2019. During the 12 months in which primary outcome data were collected, 1043 index patients with tuberculosis were seen in the 12 control sites and 1400 household contacts were initiated on tuberculosis preventive treatment. In the 12 intervention sites 1027 index patients with tuberculosis were seen with 2776 household contacts initiating tuberculosis preventive treatment (figure 2, appendix p 5). During the first 6 months of the study (evaluation phase) the crude overall proportion of household contacts initiating tuberculosis preventive treatment, out of those eligible, at intervention sites was 0·21 and at control sites was 0·41 (table 1). In response to the programme evaluation at intervention sites, health facilities implemented many different low-cost solutions that targeted patients (eg, reminder calls), the health system (eg, improved registries), health-care workers (eg, flip charts), or the community (eg, meetings with community leaders and members). For a full list of all solutions that were implemented at sites, together with key barriers identified through questionnaires, see the appendix (pp 6–7). Repeat cascade analyses during the strengthening

	Control			Intervention			Rate difference between arms
	Time equivalent to evaluation phase in intervention sites	Time equivalent to strengthening phase in intervention sites	Difference between phases	Evaluation phase	Strengthening phase	Difference between phases	
All countries (12 intervention and 12 control sites)							
Total number of confirmed pulmonary patients with tuberculosis (index patients)	494	549	55	494	533	39	..
Total number of identified household contacts	702	698	–4	807	1969	1162	..
Total number of household contacts initiating tuberculosis preventive treatment	226	147	–79	122	487	365	..
Adjusted* rate of household contacts initiating treatment per 100 index patients	30 (11 to 83)	18 (6 to 52)	–12 (–33 to 10)†‡	23 (8 to 65)	83 (43 to 162)	60 (4 to 116)†‡§	72 (10 to 134)‡¶§
Benin, Ghana, Indonesia, and Vietnam (10 intervention and 10 control sites)							
Total number of confirmed pulmonary patients with tuberculosis (index patients)	454	520	66	416	409	–7	..
Total number of identified household contacts	603	590	–13	511	1518	1007	..
Total number of household contacts initiating tuberculosis preventive treatment	188	118	–70	65	405	340	..
Adjusted|| rate of household contacts initiating tuberculosis preventive treatment per 100 index patients	55 (–10 to 121)	35 (10 to 60)	–20 (–61 to 20)†‡	24 (–9 to 57)	107 (61 to 154)	84 (26 to 141)†‡§	104 (31 to 177)‡¶§

Data are n or n (95% CI). *Adjusted for study site clustering, using a marginal Poisson regression model, estimated via generalised estimating equations, and using a log link with an exchangeable correlation structure at the level of the unit of randomisation and using robust standard errors, with a correction for few clusters. †Rate is defined as number of household contacts initiating treatment per 100 index patients. ‡The NLEstimate macro (SAS version 9.4) was used to convert parameters from the model to rate differences. This macro allows to estimate one or more linear or non-linear combinations of parameters from any model for which the model parameters and their variance–covariance matrix can be saved. §Statistically significant difference. ¶Rate difference estimates the difference between the intervention and control arms in the change between evaluation and strengthening phases in intervention sites (in control sites the equivalent time period was considered as there were no defined study phases) in the number of household contacts starting tuberculosis preventive treatment per index patient with tuberculosis (ie, a rate difference). ||Adjusted for study site clustering, using a marginal Poisson regression model, estimated via generalised estimating equations, and using an identity link with an exchangeable correlation structure at the level of the unit of randomisation and using robust standard errors, with a correction for few clusters.

***Table 3*: Rate of household contacts initiating tuberculosis preventive therapy in the intervention versus the control arm**

phase showed ongoing improvement at sites, compared with the initial cascade analysis (appendix pp 19–25).

During the final study phase the crude overall proportion of household contacts initiating tuberculosis preventive treatment out of those eligible was 0·35 in intervention sites and 0·28 at control sites (table 2). In LMICs that had guidelines that recommended identification and treatment of household contacts of all ages, the proportion of household contacts initiating tuberculosis preventive treatment out of those eligible was 0·52 at intervention sites. At intervention sites in LMICs that identified contacts of all ages but only treated children younger than 5 years, the proportion of household contacts who initiated treatment was 0·78 but, when all ages are considered, the proportion was reduced to 0·20.

When adjusted for clustering, the mean number of household contacts initiating treatment per 100 index patients with tuberculosis during the strengthening phase in intervention sites was 83 (95% CI 43 to 162) versus 18 (6 to 52) in control sites (table 3). When the change between strengthening and evaluation phase was considered, the number of household contacts initiating tuberculosis preventive treatment per 100 index patients with tuberculosis significantly increased in intervention sites by 60 (95% CI 4 to 116) and in control sites non-significantly decreased –12 (95% CI –33 to 100). The difference in rate differences between intervention and control sites in the number of contacts initiating tuberculosis preventive treatment per 100 index patients with tuberculosis was 72 (95% CI 10–134). Restricting analysis to LMICs, the number of household contacts initiating tuberculosis preventive treatment increased. This increase was greater than the change at control sites during the corresponding time periods (table 3). In contrast, at Canadian sites, no change was found with the intervention (appendix pp 8–14).

As shown in the appendix (p 15), there was no change in the number of index patients with tuberculosis diagnosed at intervention or control sites, nor the proportion of household contacts identified who were treated. The major change, and so the presumed mechanism of action of the intervention, was that the number of household

	Total cost*	Number of index patients identified in the strengthening phase	Cost per 100 index patients, CA$	Change in number of household contacts initiating tuberculosis preventive treatment per 100 index patients (95% CI)†	Cost per additional household contacts initiating tuberculosis preventive treatment (range), CA$‡
Overall	$517 422	533	$97 077	72 (10 to 134)	$1348 (724 to 9708)
Canada	$201 622	124	$162 599	–11 (–148 to 127)	NA§
LMICs only	$315 799	409	$77 213	104 (31 to 177)	$742 (436 to 2491)
Benin	$68 158	110	$61 961	77 (49 to 104)	$805 (596 to 1265)
Indonesia	$77 713	97	$80 116	11 (0 to 22)	$7283 (3642 to >50 000)
Ghana	$75 346	22	$342 483	332 (247 to 419)	$1032 (817 to 1387)
Vietnam	$94 583	180	$52 546	104 (55 to 154)	$505 (341 to 955)
LMICs that gave tuberculosis preventive treatment to all household contacts during the trial	$169 929	202	$84 123	148 (40 to 256)	$568 (329 to 2103)
LMICs that screened all household contacts for active tuberculosis, but only gave tuberculosis preventive treatment to children aged 5 years or younger	$145 871	207	$70 469	60 (23 to 96)	$1174 (734 to 3064)

All costs in 2017 CA$. LMICs=low-income and middle-income countries. *Total cost includes costs related to the study intervention and costs associated with clinical care. †Additional number of contacts initiating treatment is the main study effect (see table 3 for overall estimate). Estimate is adjusted for clustering. See footnote for table 3. ‡The range represents the incremental cost-effectiveness ratios when the lower and upper limit of the 95% CI around the estimate of effect (rather than the point estimate) are used in calculations for each country. §A value was not calculated for Canada as no effect was found with the intervention.

Table 4: **Overall, LMICs only, and by country cost of the intervention per added household contacts starting tuberculosis preventive treatment**

contacts of these index patients that were identified increased significantly at the intervention sites, compared with no change at control sites.

The total cost estimated for implementation activities at the 12 intervention sites in all five countries was CA$445 765 (appendix p 16). The strengthening phase was the costliest study phase due to the personnel time required for initial and in-service training. The LTBI-related clinical care for all of the additional household contacts identified during the strengthening phase at intervention sites was an additional $71 656 (appendix p 17).

The total cost for evaluation and strengthening activities plus LTBI clinical care per additional contact initiating treatment was $1348 (range 724–9708; table 4). In LMICs, the cost per additional contact initiating treatment was $742 (436–2491). For the subset of sites in LMICs that identified and treated household contacts of all ages (Ghana and Vietnam) the cost per additional contact initiating treatment was $568 (329–2103). The cost per additional contact initiating treatment was not calculated at the Canadian sites as the intervention had no effect.

If we assumed that only strengthening activities were delivered in LMICs, but these resulted in the same overall effect, the cost per additional contact initiating treatment was $435 (255 to 1259; appendix p 18). If we assumed the benefit of the intervention extended for 2 years (rather than the 6 months limit of outcome measurement in this study), the cost per additional contact initiating treatment would be only $263 (155 to 883). If household contacts policy in Benin was changed from treating only children younger than 5 years to providing tuberculosis preventive treatment to household contacts of all ages, the cost per additional contact initiating treatment would drop from $805 (596 to 1265) to $264 (196 to 417). A similar change in Indonesia would reduce the cost per additional contact initiating treatment from $7283 (3642 to 50 000) to $820 (410 to >50 000; appendix p 18).

Discussion

We found a health systems intervention (of standardised evaluation, and feedback to inform local decision making, followed by training and other LTBI programme strengthening activities) substantially increased the number of household contacts starting tuberculosis preventive treatment in LMICs at a reasonable cost (considering the overall cost of tuberculosis disease management). The approach provides a framework for LTBI programme scale-up that capitalises on local data, and involves key stakeholders and feasible low-cost solutions. The study also suggests that in many LMICs, successful LTBI programme expansion will require substantial initial and recurrent investments for assessment and engagement, hiring additional skilled health-care workers, ongoing in-service training, and quality control.

These findings add to the body of literature on interventions to improve management of household contacts in LMICs. Previous studies have found that interventions such as home visits, vouchers, and health-care worker education have improved treatment initiation; however, most of these studies have focused only on children because of national tuberculosis programme policy.[17–21] The CRESPIT trial[22] also found that treatment initiation increased through socioeconomic support directed at the households of index patients with tuberculosis.

Our study had several limitations. Final outcome data were collected during the last 6 months of the 8-month (approximate) strengthening phase, which limited the

time to fully implement LTBI programme strengthening activities. Thus, the full effect of the strengthening activities might have been underestimated.

An additional limitation was that in settings with very low tuberculosis preventive treatment uptake at baseline, it took more time for barriers further down the cascade to become apparent. These subsequent problems were identified primarily through repeated cascade analyses suggesting that ongoing monitoring, evaluation, and feedback (through frequent in-service training) are essential to identify new barriers and develop solutions.

We can also not be certain that introducing a new registry for tuberculosis preventive treatment did not introduce bias due to improved reporting at study sites.[23] However, the more stringent definition that we used to define household contacts in intervention facilities might have reduced the number of household contacts identified, making the direction of the effect, if any, uncertain. Finally, our cost-effectiveness analysis did not include health system costs incurred during LTBI treatment.

A key strength of this study is that the intervention was tested in diverse epidemiological, demographic, and economic settings. The types of health facilities ranged from small community-based clinics to out-patient departments in large university hospitals. Some programmes focused only on children younger than 5 years, whereas others treated contacts of all ages. Despite this variability, the intervention was found to be effective in all LMIC settings studied.

Health ministries in LMICs face many competing demands from different programmes for health resources. Through a variety of methods, including time logs and diaries, direct observations of health workers, and narratives, we captured all costs associated with the start-up and implementation of enhanced LTBI management of household contacts. We included time spent by all levels of personnel, ranging from initial meetings with senior officials of the national tuberculosis programmes, to initial and in-service training of health facility staff. As a result, the costing information in this study should provide a more accurate reflection of the true costs of starting up and implementing this complex health programme of LTBI management—one that is highly useful for budget planning. Understanding these start-up and implementation costs is key for public health decision making, yet very few economic analyses have accounted for these costs, and even then have not actually measured these costs prospectively.[24] Similar to other studies that considered cost allocation of prevention efforts, we found that personnel were the major driver of cost in all countries during programme strengthening.[25,26] We also found that the costs for initial evaluation, start-up, and initial training accounted for the great majority of costs, and the ongoing running costs for the LTBI programme were much lower.

The population included in this study was household contacts—individuals who are at higher risk of developing active tuberculosis than the general population. In LMIC settings, this population is often already linked to the health system through active case finding efforts following the identification of an index case. We believe that this study provides valuable evidence that the expansion of tuberculosis preventive treatment to this high-risk group can be done relatively easily.

The intervention focused on identifying, quantifying, and addressing barriers throughout the cascade up to the point of treatment initiation, as the number of individuals lost before treatment initiation is substantially greater than the number lost during tuberculosis preventive treatment.[6] Many randomised trials have evaluated shorter tuberculosis preventive treatment regimens, and have consistently shown high completion rates.[27] There is also some evidence from programmatic settings.[28,29] However, the potential public health benefits of improved treatment completion will only be gained if at-risk populations actually start these short regimens—a problem that has been largely ignored until now.

In Canada, the intervention did not increase the number of household contacts initiating treatment. Household contacts are already considered a high priority in most high-income settings and our study highlights the challenge of improving a programme that is already well established, within a short timeframe.[30,31] In settings like these, it might take more time to make programmatic changes, and to change provider or patient behaviour.

In LMICs not all study sites were able to obtain high rates of treatment initiation. To optimise the approach, all household contacts who are eligible should be able to initiate tuberculosis preventive treatment. In settings where household contacts of all ages were able to begin treatment, and there was strong support from key stakeholders, initiation rates approached those seen in established tuberculosis preventive treatment programmes. However, in sites where contacts of all ages were identified, but only children younger than 5 years could begin tuberculosis preventive treatment, the overall proportion of household contacts who initiated treatment was much lower. In these settings, additional interventions will probably be required, together with policy change, to have an impact on tuberculosis prevention.

Our findings have relevant implications for tuberculosis prevention globally as programmes aim to address the UN targets. For LTBI scale-up to be successful, an in-depth understanding of the local health system facilitators and barriers, as well as key motivators for health-care workers and health managers is essential. Rather than a one-size-fits-all approach understanding and resolving local barriers with ongoing support and training is needed for LTBI programmes to expand successfully.

Contributors

DM wrote the proposal for the study that was awarded funding. OO, AB, PCH, and AT contributed substantially to the study protocol. All authors contributed to subsequent improvements to the study design and development of study tools. The trial was managed (with input from other coinvestigators) by OO, FF, CV, and DM. MA, SA, VJC, DF, GJF, PH, PCH, JJ, FAK, RL, NVN, TAN, JO, RR,

and AT oversaw the trial at international sites. OO and AB accessed and verified the data and did the analyses. OO wrote the first version of the manuscript. All authors reviewed the manuscript and accepted the final version of the paper. All authors had full access to all the data in the study and the corresponding author takes final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data will be available once results of all planned primary and secondary outcomes have been published, upon written request and provision of a detailed statistical analysis plan to the authors.

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