Enhancing the public health impact of latent TB infection diagnosis and treatment: A pragmatic cluster randomized trial

Late at night a man comes upon another man looking for something on the ground under a street light.
"What are you looking for?"
"My keys"
"Where did you lose them?"
"Over there" (pointing across the street to a dark area)
"Why are you looking here?"
"Because the light is better" *Anonymous*

PREAMBLE

Research into the factors limiting the public health impact of latent TB infection (LTBI) treatment has focused almost exclusively on adherence to treatment once it has been initiated. However there are many steps prior to treatment initiation – including the initial identification of those at risk, screening them, completing the diagnostic testing and medical evaluation, and acceptance of therapy - by providers and patients. Drop-outs during these steps account for greater reduction of the public health impact of LTBI treatment than failure to complete therapy once it is initiated. Patients who initiate treatment are already "in the system", so they are easy to study. The other patient groups are more difficult to study, so we remain in the dark about who they are, why they drop out, and what to do about them.

On a global scale, in the past 20 years, the predominant focus of LTBI treatment research has been the evaluation of shorter regimens in order to improve treatment completion. As part of that effort, we are conducting a large scale multi-center international randomized trial to compare the efficacy and effectiveness of 4 months Rifampin (4RIF) versus 9 months Isoniazid (9INH) for LTBI. Our trial (which has completed recruitment and treatment of 6840 adults and children, and will complete final follow-up in late 2016) addresses the issue of improving adherence to treatment once it is started, but not all the pre-treatment processes. The current proposal addresses the pre-treatment problems; results from the combination of trials should address all problems – from screening and diagnosis to treatment of LTBI.

We are planning a pragmatic cluster randomized trial to assess a new rapid and standardized approach to improving TB prevention. We have identified sites in Canada, Benin, Brazil, Ghana, Indonesia and Vietnam to conduct this study, with the objective of expanding this approach through-out these countries, if successful. This protocol describes the trial.

BACKGROUND - THE NEED FOR A TRIAL

Importance of tuberculosis globally (why study TB?)

As a disease, tuberculosis (TB) is unique in that it is wholly preventable and treatable, yet on a global scale, incidence and mortality rose from 1990 until 2005 [1], and the total number of cases is still increasing [2]. The World Health Organization (WHO) has estimated that there are between 8 and 9 million new cases each year [2], and that 30 million will die from TB over the next decade [2] – close to the total population of Canada!! As well, WHO has estimated that close to **two billion people** have LTBI [2,3], of whom approximately 10% – or 200 million persons alive today - will develop active TB during their lifetime [2]. Despite these remarkable facts, many consider this disease to be of little current significance or importance [3]. In many high income countries, after decades of decline, incidence of tuberculosis increased in the 1980's. In most, with greater investment in TB control, rates have since levelled off or declined somewhat [4,5,6].

Importance of TB in Canada (why study TB in Canada?):

Incidence of active TB in Canada declined steadily from the beginning of the 20th century, although this decline has slowed

since the mid 1980's. In 2012, overall incidence was 4.6 new active cases per 100,000 population[7], but rates were substantially higher in certain populations and regions, because TB remains a disease of poor and marginalised populations [8-10]. Incidence among aboriginals ranges from 25 to 100 per 100,000 compared to less than 2 per 100,000 among non-aboriginal Canadian-born [7]. Rates among the foreign-born are three times higher than the national average [7 11-14 15-17].

Strategies to prevent TB – theory, problems and potential solutions:

Pathogenesis - Transmission of TB and development of latent TB infection: TB is transmitted by the airborne route from persons with active contagious and untreated pulmonary TB to persons without prior infection. In more than 95 % of healthy persons this new infection does not result in disease, but rather the TB bacilli enter a latent or dormant state; this may last only six months or lifelong. Latent TB infection (LTBI) causes no symptoms, and is not contagious. Usually the only detectable abnormality, and the only means of diagnosis is a positive tuberculin skin test (TST) or an interferon gamma release assay (IGRA) [18]. Of persons with LTBI between 5% and 10% will reactivate to active disease over their lifetime. The risk is highest in the first 2 years but other medical illnesses or therapies that suppress the immune system will increase the risk of reactivation at any time [19]. Treatment can be given to those with LTBI which will reduce the risk of reactivation by 60-90% depending on the drug given, and the number of doses taken [20].

Preventing TB through active case finding: The most fundamental method of TB prevention is to prevent transmission. One approach to reduce transmission is earlier diagnosis of active TB through active case finding, as this will reduce the duration of the contagiousness. Mass x-ray screening was an important method of TB control in many high income countries between 1930 and 1960, but was abandoned as yield diminished [21, 22]. In low and middle income countries there is limited evidence of a role for active case finding. Community-based active case finding had no impact on long term epidemiologic trends in Zambia and South Africa [23], but was associated with reduced TB prevalence in Zimbabwe[24].

Preventing TB through Contact investigation: Contact investigation refers to the investigation of persons who have recently been exposed to a person with untreated active contagious TB. Active TB is found in 2-5% of contacts [25, 26]; yield is greater if the source case is more contagious or the contact was closer or longer [26]. In two systematic reviews of yield of contact investigations, the prevalence of active TB detected ranged from 1% to 5%, depending on contagiousness of index cases, and duration and type of contact [25, 26]. Pooled prevalence of LTBI was 51.5% in LMIC [25, 26], and 28.1% in high income countries [25]. The detection of large numbers of contacts with active TB, or with LTBI at high risk of TB who will benefit from LTBI treatment, are the two reasons why contact investigation is strongly recommended for TB control in high income [18, 20, 27] and low and middle income countries [28]. A single study has demonstrated that routine household contact investigation resulted in long term reduction in TB prevalence in two sub-Saharan African countries [23].

Preventing TB through BCG Vaccination: The role of BCG vaccination in TB prevention and control remains controversial, primarily because of the vaccine's uncertain efficacy. BCG vaccination of infants has prevented meningitis and miliary forms of TB consistently in trials [29]. However trials of vaccination of adolescents and adults have provided inconsistent results [29], possibly because of genetic variability in the vaccine itself [30, 31]. BCG vaccine has no impact on long term TB epidemiologic trends [21].

Preventing TB through diagnosis and treatment of LTBI **– in theory:**

LTBI can be diagnosed with immune based tests such as the TST or IGRA's. If treatment is given with one or more anti TB drugs to those with a positive test the risk of active TB is reduced [32-35]. In a recently completed survey, we found that more than $25 million is spent annually in Canada for the diagnosis and treatment of approximately 20,000 persons with latent TB infection [36]. One survey of 110 US health departments found that 127,996 persons initiated LTBI therapy between 2000-2002 [37]. It has been estimated

that 290,000-433,000 persons are treated annually for LTBI in the US [38] [39]. Other reports [40-42] indicate that LTBI therapy is a major component of TB control in many other high income countries. In low and middle income countries the World Health Organization has recommended LTBI therapy for close contacts of patients with smear positive pulmonary TB [28], and HIV infected persons with LTBI[43].

Preventing TB through diagnosis and treatment of contacts with LTBI – ***in reality***: As shown in Figure 1, there are multiple stages involved in contact investigation – termed the Cascade of Care in Latent TB. At each stage of this cascade, there are drop-outs – due to failure to identify individuals who should be screened, screening test positive individuals who did not complete medical evaluation, providers not recommending therapy, or patients refusing to accept or complete recommended therapy. As seen in Table 1, several published evaluations of large scale LTBI treatment programs in the US and Canada have documented dropouts and losses at every stage[47-57]. Importantly, the problems at each pre-treatment stage resulted in greater cumulative loss of program effectiveness than non-completion of LTBI therapy, once it was started. There are few studies of this cascade of care in LTBI in low and middle income countries. In Thailand [44] and Malawi[45] less than 10% of contacts of active cases were seen for initial screening; in Uganda only 11% of HIV infected persons completed TST screening[46].

There have been several extensive reviews, and meta-analyses of trials of LTBI treatment regimens. [32-34, 47], but only one systematic review of adherence to LTBI therapy (once started) [64]; completion rates ranged from 20% to 80%. One systematic review of counselling found three trials in which counselling improved LTBI completion [65]. There have been no systematic reviews of the completion of the different stages of the entire LTBI screening process (ie no reviews of the entire Cascade).

Background to study methods

We propose a pragmatic cluster randomized trial, of a public health intervention. These methods have been used successfully in other settings to address many different questions.

Pragmatic trials:

In many randomized trials, particularly of new therapies, patients are carefully selected to exclude those at risk of non-adherence or adverse events, and then followed very closely to ensure high completion rates, and minimal sequelae of adverse events. These explanatory trials may be justified to assess safety and efficacy of new therapies, but will over-estimate effectiveness and safety [53]. Pragmatic trials are designed to simulate patient selection and follow-up conditions of usual practice to provide realistic estimates of the intervention's effect and safety [53]. Hence in a pragmatic trial, patients at risk of non-completion, and/or adverse events are included[53]. The ongoing 4RIF versus 9INH trials in adults and children are pragmatic trials, in that patients who are candidates for LTBI therapy are excluded only if they have absolute contra-indications to 4RIF or 9INH, and the follow-up of trial participants during treatment simulates usual practice as much as possible. (For safety and determination of end points, follow up and investigation is much more intensive, if patients are suspected to have adverse events or active TB).

Cluster randomization**:**

When the study intervention must be given at a group level then the unit of randomization must be at a group level [53]. Examples of group-level interventions include fluoridation of a town water supply, public education campaigns, or implementation of new diagnostic or treatment methods at a health facility. With this study design, outcomes may be measured at the level of the individual, but because of the correlation of outcomes among individuals in the same group, statistical power will be reduced, sample size must be increased accordingly, and the statistical approach must account for this correlation [53, 54].

Table 2 provides a few examples of recent cluster randomized trials[24,25,66-68].

Summary of current evidence:

Investigation of contacts of newly diagnosed active pulmonary TB is important for TB control in all countries, as has recently been emphasized by WHO[28]. This detects active TB, as well as persons with LTBI who are at high risk of active disease. The numbers of contacts investigated in the US and Canada is not known, although more than 20,000 persons in Canada [36], and 300,000 persons in the US [55] initiate LTBI therapy each year, mostly with 9INH [39], which is considered the standard of care [20,27], but has very poor completion rates[56-63]. These poor completion rates have spurred substantial investigation into solutions – particularly shorter regimens. However, a largely ignored problem, demonstrated in several studies of large-scale LTBI diagnosis and treatment programmes, is that even before patients initiate LTBI therapy, far greater numbers have already dropped out or been lost during the pre-treatment phase of these programmes. These pre-treatment problems cause greater reduction of the public health impact of LTBI treatment, than non-completion of treatment. However, there have been very few studies exploring the reasons for these pre-treatment losses, and no intervention studies.

Prior relevant work by the investigators:

In the past 20 years, the major focus of efforts to improve LTBI treatment completion has been the development and testing of shorter LTBI regimens. As a result, there are now three alternatives to INH. The combination of 3 or 4 months of INH and Rifampin (3INH-RIF) has similar efficacy, completion and toxicity as 6 months of INH (6INH)[47]. A regimen of 12 doses of INH and Rifapentine (a long acting Rifamycin) given once a week and directly observed had superior completion, similar toxicity and equivalent efficacy to 9INH [48]. Another recommended [27 20] alternative is 4 months of Rifampin (4RIF). In mouse studies 2RIF [49], and among older Chinese men with silicosis and LTBI, 3RIF [35] were as effective as 6INH.

Randomized trials of shorter regimens for LTBI:

Since 2001 we have embarked on a series of randomized trials to compare 4RIF to 9INH. The first trial demonstrated significantly superior completion and somewhat fewer adverse events with 4RIF [50]. In the second trial completion was significantly superior [51], costs were significantly lower [52], and serious adverse events, particular grade 3-4 hepatotoxicity, significantly less with 4RIF [51]. We are currently nearing completion of two large-scale international multi-center randomized trials – to compare safety, efficacy and effectiveness in 6040 adults, and safety and tolerability in 824 children, of 4RIF or 9INH (see Appendix 6: Results from 4RIF v 9INH Phase 1, 2 and 3 trials). The pediatric trial completed enrolment in October 2014, and all follow-up will be completed in January 2016. Enrolment in the adult trial was completed in December 2014, the last patients are finishing treatment in September 2015, and will complete post-treatment follow-up in early 2017. The proposed trial will be conducted at many of the same sites – enhancing feasibility and cost-effectiveness, and facilitating expansion of LTBI treatment there.

Pilot study in Brazil:

In 2014 funding was awarded by the Brazilian government for the conduct of a pilot study in 3 cities – Rio de Janeiro, Manaus, and Recife - in Brazil (PI Dr Anete Trajman). This experience will allow us to make extensive revisions to all study tools to be used in other sites during the main study and cross over. Specific objectives of the pilot study are:

1. To assess feasibility of the public health intervention itself – ie Phase 1 evaluation, then transition, and Phase 2 - implementation of solution.
2. To assess the utility of the questionnaires, cascade analysis, time and motion study as well as health facility questionnaires i.e. all instruments used in Phase 1.
3. To assess the cross-over design, with shortened phase 1 and Transition.
4. Further revise the questionnaires – which will later be used by all other sites in their cross-over phase.

Pilot study Site: In Brazil, since 2010 the NTP has recommended that all (regardless of age) close contacts of newly diagnosed pulmonary TB cases are investigated and treated for LTBI free of charge. Community health agents visit contacts at home, and refer them to a nearby clinic for TST. Those with a positive TST have a CXR. Physicians prescribe self-administered LTBI treatment. Contact investigation and LTBI management are recorded and should be reported to the NTP. Brazil has traditional polyclinics with physicians and nurses, and diagnostic facilities, and Family Health Team clinics. The adult and pediatric 4RIF vs 9INH trial is being conducted at 3 polyclinics, and one Family Health Clinic in Rio de Janeiro. The pilot study will be conducted in Brazil alone with 4 health facilities in Rio de Janeiro which will be intervention and control sites and an additional 2 health facilities in Recife and 2 health facilities in Manaus.

How will the results of the trial be used?

LTBI diagnosis and treatment is a key element of TB control through-out the world, and is now being promoted by WHO [28], particularly in high risk groups such as HIV infected and close contacts. However, there are substantial limitations to this approach – particularly in low and middle income countries. We are nearing completion of two large scale trials of LTBI therapy in Canada and six LMIC, as summarized above. These trials have demonstrated that LTBI diagnosis and therapy is well accepted, feasible and safe in all settings. But experience to date is limited to a few centres within the LMIC, where there are well trained and experienced staff. To scale up LTBI diagnosis and treatment in these countries is a major challenge as there are many barriers. This trial will be the first to systematically introduce and evaluate affordable, simple and feasible interventions to address these problems.

The proposed study will test a complex intervention – a programmatic public health package. This package will consist of standardized public health evaluations to identify problems limiting LTBI diagnosis and treatment among close contacts of active TB cases. This will be based on a framework for analysis and resolution of the problems, based upon the Cascade of Care in Latent TB framework. We will develop procedures for analysis and evidence-based decision making to select solutions to resolve the problems identified. This will include a system of initial training, followed by on-site in-service training during regular visits to consolidate the new interventions. This combination of evaluations linked directly to action should be readily applicable by public health practitioners. We will limit the resources used for these solutions to be equivalent to the costs, in the same setting, of treating patients with active TB. This should ensure the interventions evaluated are affordable and cost-effective (if not cost saving) in the settings where they are needed.

We will develop and use standardized tools – teaching aids for providers, patients with active TB, and with LTBI, as well registries and other methods for recording and reporting. These tools will facilitate subsequent programmatic scale up of enhanced LTBI diagnosis and treatment in low and middle income countries. The findings from Canada should be applicable to other high income countries. Trial results will be disseminated within each country readily as the investigators in all countries have close links to the leadership of their national TB programmes. The Contact Management Registries and reporting procedures are designed for easy uptake by NTP programmes and staff, and will be given to these programme leaders, plus posted on Websites. In addition several of the investigators have worked extensively with WHO, PAHO (Pan-American Health Organization), the International Union Against TB and Lung Disease, Health Canada, Centres for Disease Control (US) and USAID – and have a strong track record of knowledge translation with these organizations. These contacts will be used to enhance dissemination (eg endorsement and publication of these tools by WHO).

THE PROPOSED TRIAL – HYPOTHESIS, OBJECTIVES AND DESIGN

Study Hypothesis:

An intervention package of a standardized public health evaluation and needs assessment, followed by targeted solutions for problems identified will enhance the proportion of household contacts of patients with newly diagnosed active pulmonary TB who initiate treatment for LTBI.

Study Objectives:

Primary: To evaluate the effectiveness of a standardized public health evaluation followed by targeted solutions for problems identified to increase the proportion starting LTBI treatment among household contacts of patients with active pulmonary TB, during the last 6 months, of an 18 month cluster randomized trial;

Secondary:

1) To evaluate the effectiveness of the standardized public health evaluation and solution packages at improving: the proportion completing LTBI treatment, of those who start.

2) To evaluate the health system costs associated with current management of active TB, contact investigation, and latent TB diagnosis and treatment as well as the costs associated with the evaluation and implementation of appropriate solutions – including staff time and other resources used – in order to assess their feasibility, and cost-effectiveness.

3) To evaluate the sustained effect of this complex intervention for one year after the end of the randomized trial

4) To evaluate the costs, and impact of a stream-lined Phase 1 and 2 – administered to control sites, after the 18 month trial.

Study design:

We propose a cluster randomized trial at 36 sites in 6 countries. Sites randomized to the intervention group will receive a complex two-phase intervention lasting 18 months. Control sites will receive a stream-lined version of this 2-phase intervention after 18 months, while outcomes are continued to be measured at all sites for an added 12 months.

Randomization will be stratified by country, and restricted to ensure equal number of participants receiving or not receiving the intervention within each country. Following randomization, in **Phase 1,** a standardized public health evaluation will be conducted at all intervention sites to identify barriers to LTBI diagnosis and treatment initiation, in order to select the solutions to be used in Phase 2. This will include measurement of the key study outcomes (see below). To ensure standardization of data gathering we will use (i) current indicators of the LTBI cascade of care in the participating units (number of contacts per index case registered, investigated, started on treatment and completing treatment) and (ii) interviewer-administered standardized questionnaires – for patients with newly diagnosed active pulmonary TB, household contacts of these patients, clinic staff and administrators. These questionnaires will assess management of contacts, LTBI diagnosis and therapy, as well as TB-related knowledge, attitudes and beliefs from the perspective of these different participants. Results from this phase will be analysed, and used by the investigators, together with local public health officials, to decide on appropriate corrective solutions. In control sites we will gather data on study outcomes only (see below).

In Phase 2, solutions will be selected, and implemented at the intervention sites. Preparations and training of staff at each site will be conducted before the intervention begins, as soon as each site (clinic) is judged ready to begin. Study outcomes will continue to be measured at all sites through-out Phase 2.

Rationale for study design

The study is designed as a pragmatic public health intervention study in that the intervention package will be tailored to the problems identified from the standardized public health evaluation in that country.

The specific problems and changes required will not be exactly the same in all sites, raising potential concerns over generalizability. **However the intervention being tested is the approach – a standardized public health evaluation and analysis, with identification of problems (barriers), and appropriate solutions. T**he initial evaluation will utilize standardized questionnaires, and data gathering to facilitate replication in other settings. We have reduced the variability of the final solutions package by limiting the budget allocated for these solutions. This type of public health intervention has been used successfully in other cluster randomized trials - training hospital staff in Senegal and Mali to conduct maternal mortality review resulted in reduced maternal mortality[66], and facilitation of women's group meetings in Nepal lead to improved birth outcomes[67]. In both studies the actual solutions that were implemented were site-specific; it was the process to identify problems that was standardized.

The choice of LTBI treatment regimen by the primary providers will follow local treatment guidelines. This for several reasons: i) The primary objective of the trial is to evaluate interventions up to treatment initiation – which will not be affected by the treatment selected; ii) The current standard in most countries remains INH for 6 or 9 months; iii) The 4RIF vs 9INH trial will only be finished in early 2017, so findings from that RCT will not affect practise until close to the end of this study.

We are not planning solutions aimed at enhancing treatment completion (once it has been initiated). Patients will be followed in the usual fashion by their usual providers, until treatment completion. This reflects our belief that the problems encountered in the different pre-treatment evaluation steps have not been adequately studied; hence very few effective interventions have been identified. However, it is evident that LTBI treatment completion is necessary in order for LTBI investigation and treatment to achieve long term individual and public health benefits. Therefore treatment completion will be documented, and analyzed. If treatment completion is less than 50%, this will be a focus of in-service training and other solutions.

In this study blinding of patients with active TB, their contacts, and the health workers to the public health interventions will not be possible. This is similar to many other cluster randomized trials [66, 67], including many published large scale trials in TB [23, 24, 68-70]. Given this, the outcomes, and their ascertainment must be as objective as possible. Outcomes will be ascertained from written Contact Registries, and are objective (persons either are identified, complete testing, come to health facilities, etc, or they do not).

DETAILS OF PHASE 1: STANDARDISED PUBLIC HEALTH EVALUATION

During Phase 1, data will be obtained from administrative records, health clinic staff, active TB patients and their household contacts.

STUDY POPULATION:

Participants:

Potential participants are all index patients with newly diagnosed microbiologically confirmed active pulmonary TB (smear and/or culture positive active pulmonary TB) and their household contacts. Household contacts of all ages will be considered eligible. A household contact will be defined as someone who, in the preceding 3 months, slept in the same house at least one night per week, or spent more than 1 hour per day in the house for at least 5 days per week. The house will be defined as the dwelling, or buildings, which the family unit occupies and uses regularly.

Selection of sites:

Most of the involved countries, and investigators in this trial are participating in the ongoing pediatric and adult 4RIF v 9INH RCT for LTBI treatment trials. Research staff at these sites are well trained in clinical trials, enhancing feasibility of the proposed trial. In Vietnam, Dr Marks and Dr Fox of the University of Sydney have recently completed two large scale studies of contact investigations, and are initiating a randomized trial of LTBI treatment for contacts of patients with MDR-TB. Hence this group, and their Vietnamese collaborators have substantial experience in clinical research, particularly in contact investigations.

Table 1: Anticipated number of active TB cases, and their house-hold contacts at the sites

Country	Number of Patients with PTB		Close Contacts		Randomization Units**
	Annually	In 18 months	Identified #	With LTBI ## (TST pos.)	
*Canada	250	375	1575	450	4
*Benin	500	750	3150	1600	2
*Ghana	300	450	1900	975	2
*Indonesia	300	450	1900	975	8
Vietnam	300	450	1900	975	8
Total	1650	2475	10,425	4975	24

* RCT sites that are participating in the 4RIF/9INH trial and will participate in this study

** Randomization units - These are health facility-based units for which all of the interventions can be implemented, independent of other units in the same country.

Estimated based on 4.2 contacts identified per active TB case - from systematic review [26]

Estimated based on prevalence of LTBI among contacts screened: of 51.5% in LMIC [25, 26], and 28.1% in Canada [25].

We anticipate that our study objectives can be met with this number of sites or clinics (which will be the units of randomization) in each country. This number of sites is considered optimal for several reasons: i) ensures variation in clinic staff, setting and population; ii) avoids experience overly skewed by one or two high performing (or poorly performing) clinics;

Each site should have an adequate number of contacts – but this may be unknown before Phase 1 begins. Hence each unit of randomization (ie each clinic), should have diagnosed an annual average of at least 40 patients with active pulmonary TB in each of the preceding 3 years - in order to have enough contacts to study (from prior systematic reviews, on average 4.2 household contacts are identified per active PTB patient in LMIC).

A narrative description of the functioning of the TB programme, particularly contact investigation, at each site will be written by the research staff, with the input of a member of the site's administrative staff. This narrative will also describe how active TB is diagnosed and treated, how LTBI prophylaxis and contacts are presently managed, plus the diagnostic capacity of the facility (eg whether Chest X-rays are done on site).

Planned recruitment rate:

The number of participants needed for Phase 1 is small, relative to the large numbers of patients with disease, and their contacts seen at each site. So we do not anticipate problems in recruitment of adequate numbers in Phase 1.

Specific Sites:

Montreal: The Montreal Chest Institute houses the largest adult TB clinic in Montreal, and is now adjacent to the TB clinic of the Montreal Children's Hospital. Household contacts are identified by the nurses of the TB clinic, and the Montreal public health unit, during interviews with patients who are newly diagnosed with active PTB. Home visits are made for some newly diagnosed TB patients. TST administration and reading is performed at the TB clinics or at community clinics; those with positive TST are referred for medical evaluation to the hospital-based TB clinics. There is no follow-up for contacts who fail to complete TST, or to present for evaluation. LTBI therapy is individualized.

Vancouver: In Vancouver, household contacts are identified by the public health nurses during an interview with each patient with newly diagnosed active PTB. Household contacts undergo symptom inquiry, TST, and reading at their local public health unit or during a home visit. If symptomatic or a positive TST, the contact is referred to the TB Clinic, for evaluation. The Vancouver BCCDC TB Clinic works with the Vancouver Coastal Health Authority, and is involved in the 4RIF vs 9INH trial. The New Westminster TB Clinic serves the Fraser Health Authority, has separate staffing, and will be the second site.

Edmonton: In Edmonton, newly diagnosed patients with active pulmonary TB are assigned a public health nurse who is based at the Edmonton Public Health TB Clinic, the proposed trial site. The nurse interviews the patient and family in the clinic, or if this cannot be arranged, the nurse will make a home visit. All screening investigations and clinical evaluations are performed at the TB clinic. Identified contacts that do not come to the clinic for assessment are telephoned (twice) by the clinic nurse, and if unsuccessful, a letter is sent. This clinic will be matched with the Calgary site for randomization.

Calgary: In Calgary, all patients newly diagnosed with active PTB are assigned a public health nurse who is based at the Calgary Public Health TB Clinic. This nurse interviews the family in the clinic, or if this cannot be arranged, the nurse will make a home visit. Identified contacts that do not come to clinic are contacted via telephone twice and if unsuccessful, a letter is sent on two occasions. Contacts that live in the city of Calgary are referred to the Foothills hospital TB clinic for evaluation. If they do not come the public health nurse will call them twice. If LTBI is diagnosed, LTBI therapy is individualized. Individuals who drop out during LTBI therapy are called by clinic staff.

Benin: The Benin NTP policy is to ask all newly diagnosed active pulmonary TB cases to bring all children aged under 5 living in the same household to the nearest TB treatment facility for evaluation. The patient is also asked to advise all symptomatic household contacts to visit diagnostic centres for evaluation. Home visits are not done to identify or screen contacts. The adult and pediatric 4RIF vs 9INH trials are being conducted at the Centre National de Pneumo-Phthisiology (CNPP) in Cotonou. The randomization units for the proposed trial will be two independently staffed treatment centres in Cotonou – the CNPP, and the Centre de Akron a Portonovo.

Ghana: In Kumasi, Ghana, all patients newly diagnosed with active pulmonary TB are interviewed, and screened for symptoms of active PTB. Contacts that do not have symptoms are not assessed further except for children under the age of 5 and known HIV infected persons – who are referred to the hospital TB clinic, where they receive 6 months INH. Individuals who drop out during LTBI therapy are contacted by telephone.

Indonesia: In Indonesia, the National TB Programme (NTP) has recognized the high risk of disease in contacts and adopted symptom screening of contacts, but this is rarely implemented, and is not recorded nor reported. Bandung city in West Java, Indonesia has a population of approximately 2.5 million. The greater Bandung area, however, has a population of over 7 million. The incidence of new smear positive TB is approximately 100 per 100,000 population for a total case load of approximately 2000 new cases each year. Both the city and the area is served by a network of community based primary care clinics. The adult and pediatric trials comparing 4RIF and 9INH recruited patients from community clinics in the central Bandung area, in conjunction with a clinic at the University of Padjadjaran. We propose to conduct the study in 8 of these community clinics - where the current LTBI trial was well received, and well executed.

Vietnam: At the Vietnam site, household contacts are identified by clinical officers working at District Tuberculosis Units (DTU). The clinical officers interview newly diagnosed patients with active TB, and make a list of household contacts that are eligible for screening. These contacts attend the DTU for clinical assessment and chest X-ray. TST is not routinely performed. Despite national policies recommending 6INH for contacts who are children or with known HIV infection, few are treated.

DATA GATHERING:

Study Outcomes:

Based on the primary study objective, the key data to be collected prospectively after the trial begins is the number of patients diagnosed with microbiologically confirmed Pulmonary TB (index cases) (also will collect number of not confirmed pulmonary and not pulmonary), the number of identified household contacts of these index cases with confirmed pulmonary TB, and the number of household contacts who started LTBI therapy Note that the number who actually complete therapy is not required as this is a secondary outcome that occurs later and data will be collected retrospectively. The primary study outcomes of number of index cases, number of household contacts identified and the number of household contacts starting LTBI therapy must be measured every month at all health facilities (Intervention and Control) throughout the trial. Outcomes will be recorded using a standardized form. More detail on data sources and how to ascertain study outcomes is provided below.

Ascertainment of study outcomes - at all sites:

Ultimately, in the intervention sites we will be able to use the newly developed and introduced Contact Management Registries (see below) to extract all necessary information and outcomes – including number of pulmonary TB cases (Index cases), number of contacts identified, and number who initiate LTBI therapy. However, these detailed contact registries are considered an integral part of the public health intervention, since considerable training in recording and reporting as well as the procedures of contact management will be needed for these to be completed accurately and completely. Introduction of these registries at control sites would be difficult without extensive training; if such training was given at the control sites, this would constitute a partial intervention, and reduce potential differences between intervention and control sites.

Hence recording of outcomes at control and intervention sites must rely on simple measures that can be implemented with minimal training, prior to the start of the trial at all sites. It is important that the procedures to ascertain (measure) these outcomes be established at the beginning of Phase 1, and continue **unchanged** at all health facilities (both intervention and control facilities) through-out the 18 months of the study.

Identification of contacts may not be performed, or not clearly recorded at all health facilities – especially the control facilities. This is why we must carefully document the number of index patients with active pulmonary TB diagnosed at each site. When the study is completed, the coordinating centre may use the number of index cases to estimate the number of household contacts that likely could have been identified (see Analysis section) Data sources will vary by site, depending what methods of documentation are already being used. We will collect information on the number of newly diagnosed index cases from lab or other sources that report active cases. The number of household contacts indentified will come from different sources depending on what is available the site. Finally, we will estimate the number of contacts who start LTBI treatment from hospital and or clinic records using a standard data collection form in all sites. The number of contacts completing LTBI therapy will be estimated retrospectively from clinic records.

Cascade indicators:

We will gather quantitative information from existing patient records (retrospectively) regarding the current functioning of contact investigation and LTBI management in all intervention health facilities in all countries.

Whose records are reviewed: Our objective is to collect data on 100 to 150 household contacts identified at each participating site. This is the expected number of contacts for approximately 30-35 index cases (may be more for Canadian sites. This data collection will start with consecutive patients, or a representative sample across the observation period, diagnosed with confirmed active Pulmonary TB during an interval ending 6 months ago. This interval is selected so that all screening and diagnostic procedures will have been completed by the time of review, yet is recent enough that problems identified in questionnaires and interviews are likely to accurately reflect the current situation.

Information to be gathered: Key information to extract will include the following: 1) The number of patients diagnosed with microbiologically confirmed active Pulmonary TB (index cases), 2) The number of their household contacts who are identified as eligible for symptom screening and LTBI testing, 3) The number who are questioned about symptoms only, and the number who complete LTBI testing procedures - using Tuberculin Skin Test (TST) or Interferon Gamma Release Assays (IGRA), 4) The number who are LTBI test positive, 5) The number of contacts with positive LTBI tests who have a medical evaluation to exclude active TB (e.g. medical examination, chest X-ray and sputum test if applicable), 6) The number of contacts with positive LTBI tests who complete medical evaluation and start LTBI therapy. The number of household contacts of index cases and the identification, investigation and treatment of household contacts of index cases will be abstracted from different sources. Sources may include the index case registry, treatment cards and other sources described below.

A standardized form will be used to record this information.

Sources of information: In most clinics in DOTS programs (the acronym for the WHO recommended approach to diagnosis, treatment and follow-up of patients with active TB), all patients with newly diagnosed PTB are registered in the TB Patient Treatment Registry (In Brazil – this is the "Green Book"). Their identified close/household contacts may be listed on the DOTS treatment cards of their index cases (in most DOTS programs). The investigation and management of these contacts may be summarized on the same treatment cards, or in the medical records of these same patients. In a few programmes this will be summarized in Latent TB registries, or Contact registries, but in most sites this information will be gathered from several sources.

Interviewer administered Questionnaires: At the same time we will gather information about the problems and barriers that impede TB contact management. These will be mapped onto the Cascade of care in Latent TB.

Who is interviewed: At each Intervention health facility, 5 groups of persons are to be interviewed: 1) Patients with active PTB (Index cases); 2) Household contacts who did come to be seen at the clinics; 3)

Household contacts who did not come to clinics; 4) Community health workers; 5) Nurses and doctors. Of the household contacts interviewed, an equal number should be adults in families with, and without children. Of the doctors and nurses the priority is to select those most directly involved in the care of patients with active PTB, and their contacts.
How many will be interviewed: In Vietnam and Indonesia, the aim will be to interview up to 5 persons in each of these categories at each site - giving a minimum of 40 persons in each group. In countries with fewer health facilities, such as Ghana, Benin and Canada - then the number in each group will be increased to 20 per site. This will result in a total of 40 interviewees in each group in Ghana and Benin, and 80 per group in Canada. In many health facilities the number of health workers, especially physicians and nurses, who work in the TB programme, is less than 5, and in Benin, Ghana and Canada - will certainly be less than 20. In all intervention health facilities we will interview all TB nurses and doctors - up to a maximum of 5 each (for Vietnam and Indonesia), and 20 each in the remaining countries

Questionnaires: Three questionnaires will be used:
Health workers: This will investigate their knowledge and attitudes regarding contact management, diagnosis and treatment for LTBI, as well as knowledge and attitudes about TB diagnosis and treatment.
Index cases: This will investigate TB patients' knowledge, attitudes and perceptions about TB and transmission, as well as their health system experiences.
Contacts: This will investigate household contacts' knowledge, attitudes and perceptions regarding TB and transmission, and their health system experiences with contact investigation.

These questionnaires are attached in the Appendix. These were originally developed and used in an earlier study in Bandung, then revised and used in a pilot study in Brazil. These have been revised again based on this experience, and further revised based on pre-testing in Montreal. Certain questions are site-specific; these will be adapted to the local situation. All questionnaires will be pre-tested for understanding and adequacy of responses in each country, then revised for final versions. These final versions will be translated into local languages as needed.

Questionnaire administration: All questionnaires will be administered by trained interviewers. The interviewers will explain each section, reading the script printed in the questionnaires at the start of each section. For some questions they read all responses and ask for a single response, and others are open-ended. For some of these open questions the most common responses are listed, allowing the interviewer to simply tick if these responses are given. Other responses will be written down as free text.

Measuring Costs:
At each participating site, we will estimate costs, from the perspective of the health system, particularly the TB programme, of the following three major activities:

1. *TB related health care activities* including contact investigation, and diagnosis and treatment of active and latent TB. To estimate these health system expenditures at the participating sites, we will use bottom up micro-costing methods. This means that, as much as possible, we will directly measure resources used and staff time for each specific TB related activity, at each site. Staff time will be measured using Time And Motion (TAM) measurement where all clinical staff involved in TB related activities will be shadowed for a complete work day. The amount of time spent on active TB vs. LTBI will be carefully quantified The research staff who will shadow the clinical staff will record stop and start times for each type of clinical activity (eg., clinical encounter, administrative activity, training etc) and type patient (eg active TB, LTBI or non TB)). Research staff will be trained to ensure that they do not interfere with the work performed by clinical staff being shadowed and to ensure that they

respect the privacy of the staff being observed as well as the patient. The research staff will remain outside the consultation room at all times so that patient confidentiality is not compromised. A script describing what the TAM measurements are and how they will be done will be read to the health care worker by the research staff before the exercise begins. Measurements will be conducted at 3 different times in Intervention facilities and twice in control facilities.

Costs associated with building facilities will be tabulated using a questionnaire and apportioned based on staff/space allocations for the TB program. Other resources such as consumables and overhead will also be quantified. These costs will be quantified twice –at the start of Phase 1 (before any study-related interventions), and near the end of Phase 2 after full implementation of contact investigation and LTBI management.

2. *The public health intervention* itself - including research costs and costs for health care staff and administrators to participate in the research. Research costs will include time of research staff and investigators in Phase 1 and Phase 2. In Phase 1 this will include , data extraction for cascade indicators, measurement of outcomes, conducting interviews, measuring costs, data analysis and assistance in the selection of appropriate solutions. In Phase 2 this will include initial and in-service training of health care staff at participating sites (and retraining as needed for staff turnover) for LTBI diagnosis and management, implementation of full contact registry, implementation and training for solutions following identification of problems. This information will be useful to understand the "learning curve" at the clinics – how long does it take to get the contact investigations running well, with few missed cases, complete Contact Registries, and resolution of all administrative problems. How much time is required for monitoring and supervision? How frequent do in-service training visits need to be? To measure the time spent by research staff on ACT4 trial activities, time and motion self report activity logs will be completed monthly by all research staff involved in ACT4 throughout the study. For staff time, all activities will also be tabulated for health care personnel who contribute time in the research study, including meetings, interviews and training sessions. Logs specifying time spent on different research activities will be submitted to the central coordinating centre who will calculate the total amount of time spent on each discrete activity.

3. *The costs of the solutions* - A fixed amount of money will be given to sites for solutions (See page 18 for more detail). Sites will be asked to provide a detailed breakdown of how funds allocated for solutions were spent as well as details of any additional human resource requirements while solutions were in place.

Data analysis;

The number of household contacts **expected** will be calculated as the number of index cases times the average number of household contacts identified in the same countries, or countries with similar resource levels (based on World Bank classification of national income level), from two recent systematic reviews (Fox and Morrison). This will be compared to the number actually identified.
We will match the problems identified with each step in the Cascade associated with more than 10% losses/drop-outs, based on the Indicator review. For example if a large number of identified contacts are not initially screened (in the systematic review, we found that 30% of identified contacts were lost at this stage), then we will identify problems associated with that step in the Cascade and prioritize identifying interventions to address these (See Figure 3 for schematic). The problems to be addressed may have been identified from questionnaires completed by patients with active TB, their contacts, or the health care

providers. Simple proportions will be estimated at each centre, corrected for clustering at the household level via generalized estimating equations.

Reporting findings:

The final step of Phase 1, and really the transition to Phase 2, is the presentation of the findings to TB control authorities in each jurisdiction (ie at municipal, state or provincial levels), and to local health authorities, who will be involved in the selection, and implementation of corrective interventions.

TIMETABLE FOR PHASE 1:

Months 0-3: Cascade indicators & Interviewer administered questionnaires at each clinic/facility.
Months 4-5: Data analysis, preparation of reports, identification of potential solutions with options analysis.
Months 5-6: Presentations/discussions with TB control officials at national/state/municipal levels and responsible officials at Health facilities.

ETHICAL CONSIDERATIONS – PHASE 1

This protocol will be submitted for review by ethics review committees at the coordinating centre, and the coordinating centres in each country.

Informed consent will be obtained for all workers, index cases, and contacts before they complete questionnaires or participate in interviews. For the Cascade indicators, only non-nominal data will be abstracted, so consent from patients included in the registries or other information sources will not be sought. However approval from the responsible health officials at participating facilities will be obtained.

Mechanisms to protect confidentiality are the following. Only non-nominal data will be extracted from index case registries, and treatment cards, and from other sources of information for Cascade indicators. Nominal information of participants in questionnaires and interviews will be kept in separate files, under lock and key in the offices of the coordinating centres in each country. This information will not be entered into electronic files - only a unique study ID assigned to each participant. In public presentations no individual identities will be revealed.

DETAILS OF METHODS OF PHASE 2 OF THE STUDY:

STUDY POPULATION:

The participants are the household contacts of newly diagnosed patients with microbiologically confirmed active PTB. The intervention and control sites are also the same as in Phase 1.

Sample size considerations:

As seen in Table 1 above (Study population), we estimate that during the 18 months of the study, 2475 active TB cases will be diagnosed at the participating sites, and 10,425 contacts will be identified, of whom 4975 will be diagnosed with LTBI. We wish to detect a 15% increase in the proportion of contacts that initiate therapy, with a level of statistical significance of 0.05 (alpha error). The intra-class correlation coefficient (ICC) which describes the inter-cluster heterogeneity, (or analogously the correlation amongst subjects in the same cluster) has less effect, but to be conservative we will assume this to be 0.05 to 0.1– which is high. In data from the 9INH vs 4RIF trial (comprising 6031 adults treated for latent TB in 12 centres), the ICC for the centre effect was low – just 0.01-0.02, depending on the method used to estimate it, for treatment completion. We will have 24 clusters in 5 countries. Our power calculations are based on the number of close contacts identified per randomization unit (from Table 1).

Table 2: Detectable differences with all sites in all countries (alpha=.05, and Power = 80%

Proportion starting LTBI therapy in Control Arms	N Contacts per clinic	Design Effect	Total sample size per arm	Intra-Class Correlation	Detectable difference
0.10	100	2.0	1222	0.01	0.05
0.10	100	6.0	1214	0.05	0.10
0.10	**100**	**10.9**	**1199**	**0.10**	**0.14**
0.30	100	2.0	1236	0.01	0.08
0.30	**100**	**6.0**	**1261**	**0.05**	**0.13**
0.30	100	10.9	1221	0.10	0.18

Therefore, given 24 clusters in 5 countries, with at least 100 contacts per site every 6 months (based on minimum 40 active cases every year, and estimated 4.2 contacts per index case), and assuming that at baseline only 10% of contacts are started on Latent TB therapy, plus an ICC of 5%, we would have 80% power to detect a 10% increase in proportion of contacts starting therapy. If the number of contacts per site is higher this will actually have a modest effect on the detectable difference. If the proportion starting therapy is much higher (30%), then the detectable difference would be near 13%.

The resources and prior staff experience in LTBI care at the Canadian sites are very different from that of the sites in the LMIC. This makes it likely there will be better pre-intervention outcomes in Canada, potentially limiting the need for, and impact of certain interventions. The other 5 countries are also different – with regard to resources, availability of trained health workers, and patient populations. This may result in large differences in the baseline situation, and intervention effect size. Hence secondary analysis is planned to estimate the intervention effect within each country. Since Canada has the smallest numbers we estimated the power to detect differences in Canada alone, as shown in Table 3.

Table 3: Detectable differences in Canada alone (alpha=.05, and Power = 80% [84])

Proportion starting LTBI therapy in Control Arms	N Contacts per clinic	Design Effect	Total sample size per arm	Intra-Class Correlation	Detectable difference
0.30	50	1.5	150	0.01	0.19
0.30	50	3.5	150	0.05	0.29
0.30	50	5.9	150	0.10	0.37
0.30	100	2.0	300	0.01	0.16
0.30	**100**	**6.0**	**300**	**0.05**	**0.27**
0.30	100	10.9	300	0.10	0.36

Therefore in Canada, we should have sufficient power to detect a 27% increase in proportion of infected contacts starting LTBI therapy, if 30% now start therapy. Increasing the number of contacts per cluster (clinic) to 300 would only decrease the detectable difference to 25%.

Planned recruitment rate:
In Phase 2, subjects are not recruited directly, but receive all diagnostic and treatment services from routine clinical staff. For the trial the evaluations and results are recorded. The estimated number of contacts is based on the number of active TB cases seen annually at these sites over the past 3-5 years; it seems unlikely there will be major changes in these numbers.

RANDOMIZATION:
As described earlier in the Study Design section, the sites which receive the intervention of Phase 1 followed by Phase 2 will be selected randomly. Randomization will be stratified by country (See again Figure 3). As much as possible, within each country, the randomization of sites must result in reasonable balance in the number of contacts managed with and without the intervention. Because the number of patients with newly diagnosed pulmonary TB is not the same at all sites, a special procedure to ensure optimal balance will be undertaken. A total of 1000 randomization sequences will be generated (using a computer programme developed by Dr A Benedetti – biostatistician for this project). Each sequence will then be examined to verify the resultant balance in contacts who will and won't receive the interventions. Randomizations that result in reasonable balance will be selected. (In other studies this has meant approximately 200 of the 1000 randomization are selected). In the final step, one sequence is randomly selected from this sub-group of balanced randomization sequences.

SELECTING THE SOLUTIONS FOR PHASE 2:

As part of the intervention, during Phase 2 health facilities will implement initial and in-service training, a standardized system for recording, reporting and monitoring, and additional site-specific solutions selected based on the analysis of Phase 1 results at that site. Potential site-specific solutions include conditional cash transfers, staff or patient incentives, and "one-stop shopping" (organization of services to deliver TST reading, medical evaluation, Chest X-ray, blood tests and initiation of LTBI therapy - all in one day and at the same clinic). The specific training/educational messages will be identified from Phase 1 results and incorporated into scripts prepared for teaching. If other organizational issues are identified as major barriers for index cases or contacts, then other potential service delivery improvements can be suggested.

The Phase 1 findings will be reviewed by the investigators from each country coordinating centre with the International Coordinating Centre (McGill) to identify the major problems and discuss potential solutions. Then the in-country investigators will meet TB program officials at the appropriate jurisdictional level (ie this may be at national or provincial/state, or at municipal level – depending on the organization of TB services within each country). At these meetings, the results of the Cascade analysis and the questionnaires/interviews from Phase 1 will be presented and used to pre-select a package of possible interventions to be 'pre-approved' by TB programme officials. Each of the possible options will be evaluated using an options analysis and simulation modelling exercise. With the collaboration of investigators at Liverpool School of Tropical Medicine we have developed a simple model, using discrete event simulation software, which uses site specific Phase 1 cascade data on LTBI cases seen, together with associated health system costs at each step in the LTBI cascade. This model also allows integration of cost and potential effect of proposed solutions to strengthen the cascade and thus provides real time cost effectiveness analysis for different solutions proposed. The effectiveness of solutions is based on systematic reviews of the published literature for each solution. The costs are based upon information from each site gathered by the site investigators during Phase 1. This tool was developed using Witness software with an arrangement from the company that the software will be provided to sites at no cost, as it is intended for use by site investigators and their Local TB Control Programs for future assessments, and decisions regarding further solutions to newly identified problems.

Next, the investigators from the country coordinating centres will meet administrators from the participating health facilities - to present the Phase 1 findings, and select the Phase 2 solutions. They will also explain the initial, and in-service training and recording/reporting methods, as well as review general aspect of the diagnosis and treatment of LTBI. The regimen to be used, selected as above by the responsible TB programme, will be reviewed. Note that within each country health facilities fall within one to four municipal or provincial jurisdictions. Therefore in Vietnam (2 provinces with 4 health centres each), and Canada (4 cities with one clinic each) results will be analyzed and presented and interventions selected, using the same options analysis approach described above, at the level of the city or province. On the other hand, all health facilities fall within one city in each of Ghana, Indonesia and Benin – hence Phase 1 results from all health facilities within each country will be used to select country-specific set of solutions. If there are substantial differences in Phase 1 findings between sites within each of these jurisdictions, then some solutions will be site-specific.

[As examples: In Site A, the indicator data reveals that the step when most contacts are missed is the identification of contacts by newly diagnosed pulmonary TB patients. Responses from the questionnaires and interviews at this same site suggests that this occurs because health workers do not explain, and the patients do not understand the reasons for contact investigation. Therefore one cadre of health workers will be assigned this task (by health officials), and training around a scripted set of messages provided (by research staff) to that cadre of workers. In Site B, indicator data reveals that many contacts with positive TST fail to complete diagnostic evaluation. Questionnaire and interview information suggests this is because contacts must come at least 3 times to complete this – once for TST reading, a second time to see a physician, then a 3rd time to have a chest X-ray done. The intervention suggested will be to organize the service delivery so that all three activities can be completed on the same day – "one stop shopping".]

Financing of Solutions and LTBI expansion in Phase 2:

Minimal funds will be provided by the study to sites to finance site specific solutions and cover any start up costs related to LTBI expansion (including initial and in-service training, including training materials, plus the development and implementation of new methods of recording, reporting and monitoring). Any ongoing, or recurrent costs must be borne by the public health system in each country. 100,000 CAN$ will be budgeted for solutions and funds will be divided across sites based on the number of active cases at each site as well as the per capita GDP. Below are the amounts (CAD$) that will be made available to each site:

Vancouver	$17,449
Calgary	$17,449
Benin	$16,778
Ghana	$16,778
Indonesia	$20,134
Vietnam	$11,409

The way in which the funds for solutions are spent is left up to each site (ie. all for one solution, or across several different ones). Additional funds are also provided to sites to purchase INH and Tuberculin.

DESCRIPTION OF THE *POTENTIAL SOLUTIONS*: *(Below are examples - to be selected and modified based on findings of Phase 1)*

Training:

Solutions to enhance the education of workers, PTB patients and their contacts seems almost inevitable. These educational materials will be selected from a host of materials already developed and available freely (for examples, see the CDC website: https://findtbresources.cdc.gov/), but their content will be modified

based on country specific findings from Phase 1. It is possible that in some sites more targeted solutions are necessary to overcome certain beliefs and attitudes (eg health workers who believe INH therapy of LTBI is useless, or will create drug resistance).

Education of patients with active TB: This will be done with a prepared script of key messages, identified from the questionnaires in Phase 1. Study staff will prepare the scripts and train clinic workers to deliver the teaching using these scripts.

Education of health care workers (physicians, nurses, and community health workers): Research staff will provide training to the different cadres of health workers at the participating sites – during the initial workshops and in-service site visits as described above. The key messages will be based on the findings in Phase 1. Lectures and other training materials that are prepared and delivered by research staff will also be given to TB program staff to assist in scale up activities later.

Education of contacts starting LTBI therapy: Scripts of key messages will be prepared, based on the questionnaires completed by contacts in Phase 1. Study staff will train clinic staff to educate contacts using these scripts.

Delivering the Initial Training:

Prior to the start of Phase 2 – all health workers involved in the TB program from each site will receive training in the new system of recording and reporting of TB contact management. They will also receive training in contact management including Latent TB diagnosis and treatment. The LTBI regimen currently recommended by the National TB programme to be used through-out Phase 2 will also be reviewed.

About two weeks before Phase 2, a half-day training workshop will be held at each site (randomization unit). At this workshop the new methods of recording and reporting, plus basics of contact management will be reviewed, and problems encountered discussed. The major emphasis will be to present and discuss findings from Phase 1 at that site. These findings will be used to demonstrate the need for various solutions which will then be reviewed and discussed. A consensus will be reached about the solutions to be implemented, including any site-specific interventions, in that facility will be reached before closing the initial training workshops.

During the intervening weeks, research staff and investigators will make final preparations for any site specific solutions. A few days before the start of Phase 2, a final training meeting of 1-2 hours will be held at each site. During this session the site staff will receive any training needed for site-specific solutions (if any were selected for the site), plus a quick refresher about the procedures of contact investigation and treatment, as well as recording and reporting.

Delivering In-service training (site visits):

Once the solutions are initiated at a site, research staff will come to the site weekly for 2 months, then every other week for 2 months, then monthly - for in-service training. During these visits the staff will review the new contact registries, and all other relevant records (such as the TB patient registries) to ascertain if new contacts have been identified and investigated. They will discuss with site staff any problems encountered, and reinforce the initial training - in terms of procedures for contact identification investigation and treatment, as well as recording and reporting. They will also train any new health workers assigned to contact management. In addition, once a month in the first 3 months, an investigator from the country coordinating centre will accompany the research staff - to discuss the contact management program with site staff, and reinforce messages and training.

<u>Health services delivery</u>:

Solutions decided at this level will affect policy and budget. Hence the problems are likely to affect all sites within this jurisdiction, and any solutions will need to be approved by administrators for all sites. **Home visits to teach and screen contacts**: Site staff (not research staff) will visit homes of patients with active TB to identify their household contacts, and initiate symptom screening (for active TB) and screen, or refer for screening the eligible contacts. In many programmes in many LMIC community workers visit homes of patients with active TB to supervise treatment (ie they provide DOT). These workers could easily incorporate contact identification and education into their routine activities at little added cost. This intervention would be entirely under the control of, and hence at the discretion of, local health officials.

Incentives for health workers:

In jurisdictions where contact investigation is not mandated, it is likely that some incentives will be necessary in order to get programme staff to take on these added responsibilities. Compensation can be made for teaching sessions, (such as teaching patients with PTB or their contacts about the need for screening, teaching persons about to start LTBI therapy), or for each medication renewal visit. Incentives would have to be commensurate with usual salaries for the cadre of health workers involved. These incentives may be continued by TB programs after the study ends – several of the participating TB programmes already have similar incentives for detection and complete treatment of active TB. In other jurisdictions, (based on discussions with TB program managers there) we understand the TB programmes will add contact investigations to routine TB program activities, and adjust staffing accordingly.

Coordinating service delivery ("One stop shopping"): This would involve organizing services so that TST reading, medical evaluation, chest x-ray, any other necessary investigations and the decision to start LTBI therapy are all completed in the same place and on the same day. The research staff and investigators will invest the time for the administrative work required to create the service delivery models, including a check list of items to be arranged to ensure that the providers, support staff, and lab services are all present, and there is smooth flow of patients and information between services. However the sites will have to undertake responsibility for changes in staffing or other resources – again for sustainability reasons.

Patient incentives and enablers:

Conditional cash transfers: Another method to enhance completion of screening and diagnostic procedures is to offer to pay costs so that the contacts can visit the clinics, for administration and reading of TST, symptom screening, and further evaluation if needed, or to reimburse costs for Chest X-rays. This implies that this type of transfer payment programme is available within the country, and at that site – which is the case in some, but not all countries..

PHASE 2 ENHANCED REPORTING:

Contact Management Registries

A new registry book will be developed to record the key diagnostic and treatment steps in contact management. To facilitate their later adoption by health facilities as part of routine TB control activities, these contact registries will be modeled after the Active TB Treatment Registries of national TB programs that are currently used in all DOTS programmes and recommended by WHO [73].

The Contact Registry will include identifying information for each new patient with active pulmonary TB, as well as identifying, and demographic information for all identified contacts. The results of screening tests, plus Chest X-ray and medical evaluation for the TST (or IGRA) positive contacts will be included, as well as initiation and completion of LTBI treatment. Information on LTBI treatment starts from these registries will be compared to the other methods of ascertainment of the primary outcome – in the final 6 months – in secondary analysis

Reporting:
The Contact Management registries will be used to generate quarterly reports of diagnoses of contacts, and cohort reports of treatment outcomes in TST positive contacts. These quarterly reports will be modeled after the quarterly reports of case finding, and treatment outcomes that are recommended by WHO [73], and used by the National TB control programmes in almost all LMIC.
The quarterly reports will be based on data abstracted from the Registries (they are designed to be abstracted very easily), and initially prepared by study staff. These reports will include the number of new pulmonary TB patients, household contacts identified, investigated with symptom screening and TST, had TST reading, TST positive who underwent medical evaluation, and initiated LTBI medication.

LTBI related activities at Control sites:
At the control sites, investigators will work with local TB programmes to ensure that staff have access to materials (PPD and INH), as well as possess the skills necessary for basic management of latent TB. These skills will include tuberculin skin test techniques as well as understanding of the current local standard for treatment of latent TB (usually 6-months INH as recommended by WHO.) Note that investigators will facilitate this work, but the primary responsibility will remain with the local TB control programs to ensure that the control sites have LTBI management policies and procedures in place.

DATA ANALYSIS FOR PHASE 2

Contact investigation outcomes:
Among the household contacts, the following outcomes will be measured

1. Contacts identified.
2. Started LTBI therapy (primary outcome)
3. Completed LTBI therapy (secondary outcome)

The primary outcome will be the proportion of identified contacts who start LTBI therapy – in the final 6 months of the trial (to account for delayed impact of this complex intervention). If we find that more than 20% of contacts are diagnosed to have active TB, which would be far in excess of published experience, then we would investigate if this reflected over-diagnosis.

Our analysis will be performed at the level of the individual, but will account for correlation between subjects from the same centre. Population averaged logistic regression with an identity link estimated via generalized estimating equations (GEE) and using a jack-knife estimate of the variance will be used to assess the effect of the intervention on the primary and secondary outcomes above, depending on the type of outcome (e.g. count or proportion). This approach will account for the correlation between subjects in the same cluster, and for varying cluster sizes. Using an identity link (rather than a logit link) will allow us to estimate risk differences for binary outcomes.
Population averaged models estimated via GEE are robust to mis-specification of the correlation structure. While our data will surely have clustering at the household level as well, we need only account for the top-level cluster (here centre) and use the empirical standard errors to ensure that our inferences are conservative.
For count type outcomes, we will use a similar approach as described above, but using a Poisson distribution.
In secondary analyses, we will use logistic regression with a logit link estimated via GEE and also adjust for additional confounders (country, age, sex and smear status of index case). In sensitivity analyses we will analyze at the level of the cluster. Missing data will be dealt with via multiple imputation using chained equations which will allow us to impute binary as well as continuous variables [85].

Estimation of costs, and cost-effectiveness:

We will estimate the total Investigator, research staff, and clinic staff time involved in data gathering in Phase 1, and for training, implementation, supervision, and for each type of solution delivered to patients in Phase 2. This will be based on the time spent on different study related activities, recorded by research and clinic staff in their time logs. The total effort for public health evaluation and intervention implementation for health facility staff and research staff will be estimated from these total times. The average salaries of the different cadres of health facility workers will be used to valuate these activities. From this we will estimate total costs for each activity, and from the numbers of index cases and contacts derive an average cost per index case, or per contact. The primary cost-effectiveness measure will be the total cost of all Phase 2 activities ***per additional contact who starts LTBI therapy***. Additional will be calculated based on the difference in proportion starting LTBI therapy between the pre- and post-intervention periods.

As well we will tabulate all diagnostic tests, visits and drugs related to contact management. Costs for these health care activities will be estimated using the WHO cost indices as described above. Patient costs will be ascertained in a sample of patients based upon a short interviewer-administered questionnaire regarding time taken for the various steps of the contact investigation and management as well as their out of pocket expenses related to travel, food etc. Incremental health system costs will be expressed per additional contact initiating LTBI (primary outcome), and per additional active TB case detected, and per contact completing LTBI therapy (secondary outcomes) as measures of cost-effectiveness.

TIME-TABLE OF PHASE 2:

The chronology can be summarized as:

Months 6-8: Selection/confirmation of solutions, and methods for contact identification, diagnosis, treatment and reporting. Training, then introduction of solutions at the sites (as soon as each site is prepared). Continued outcome measurement at all sites.

Months 9-12: All intervention sites have started, and are 'scaling up' to fully implement all planned solutions.

Months 13-18: Full implementation of all solutions at all Intervention sites

Data analysis – we anticipate this will be finished quickly as it is very simple – involving simple counts of outcomes from the contact diagnosis and Contact treatment quarterly reports, with verification from the source documents – the Contact Registries

ETHICAL CONSIDERATIONS FOR PHASE 2:

Individual consent will not be sought for Phase 2. The interventions themselves pose no risks to trial participants, and indeed represent best clinical practice. All procedures that directly impact patient care will be approved by health officials, and by the site staff themselves. These procedures will be implemented as part of routine practice – that we hope will continue long after the trial is completed. As part of that routine health care, the agreement of patients and their contacts will be necessary – particularly for things that patients may consider more intrusive such as providing information on their household contacts, or allowing home visits by site staff. However this should not require consent as it will be part of standard care and is not part of a direct research intervention.

An important ethical issue is that of withholding a potentially effective intervention in some sites while it is introduced in others. However, we will not withdraw any programs or practices that are part of current or standard practice at the sites. More importantly, there is equipoise, as we are not certain that this complex intervention (or the specific solutions) will work.

SECONDARY STUDY - CROSS OVER STUDY (PROVIDING THE INTERVENTION TO CONTROL SITES):

Objectives:
1) To evaluate the sustained effect of this complex intervention for one year after the end of the randomized trial – at original intervention sites.
2) To evaluate the costs, and impact of a stream-lined Phase 1 and 2 – administered to control sites, after the 18 month trial.

Design:
In the cross-over study the intervention sites now become control sites, and the control sites now receive the intervention. In the cross-over study the entire intervention of evaluation, decision making and implementation of solutions (i.e. Phase 1, transition, and Phase 2) should take a total of 12 months. Hence all activities must be streamlined. Outcomes will be measured as before – monthly – at all sites.

Phase 1: Phase 1 is shortened to 3 months. During Phase 1, questionnaires are administered to health care workers, contacts, and index cases as in the main study. However, these questionnaires are much shorter - 10 to 15 items which are mostly open-ended questions. These questionnaires are also virtually identical to each other, facilitating analysis. In Brazil, we will assess whether these can be self-administered or must remain interviewer administered. This means the time taken to complete the questionnaires, and enter the data will be measured, as well as the information collected will be compared descriptively.

The cascade analysis is not changed. Data on all seven Cascade steps will be abstracted for approximately 100 identified contacts – meaning for about 30-50 index cases (depending on number of contacts identified per index case.) We will review consecutive index cases, with the last reviewed diagnosed 6 months earlier (meaning we go back in time from 6 months to 7, then 8 and then 9, etc, until the required number of contacts are available). This 6 months limit is imposed because it can take several months for identified contacts to be reached, screened, evaluated, and therapy proposed and refused/started.

For costs – labour costs for personnel will be estimated using the time and motion studies as in the main study. These will be streamlined in that most of the general questions are eliminated. Facility costs, and hourly wages will be collected using the health facility questionnaire – most sites will complete this while control sites (before the cross-over), but if this was not completed, this will be done in Phase 1 of the cross-over. In Phase 2 of the cross-over, all sites will complete a brief update of the health facility questionnaire – which will ascertain if there have major changes in the staffing and other costs related to the TB program at that facility if this has not been completed before at the participating sites (most sites will have done this).

Transition: There are 3 months between Phase 1 and Phase 2. The first month will be used for data analysis – which will be primarily descriptive. In the second month we will present the questionnaires and cascade analysis findings to the local TB program managers as well as clinic managers and discuss potential solutions. In the 3rd month we will prepare materials and supplies for Phase 2, and conduct all necessary training – for LTBI management, registry use and analysis.

Phase 2: Phase 2 will last 6 months. The (new) intervention sites will receive in-service visits weekly for the first month, then twice a month for months 2&3, then monthly for Months 4-6. All sites will now use the new registries; no further changes will be made to these registries, once the site specific registries were developed in the Main trial. Interim Cascade analysis will be done at end of Month 3 in the Cross-over

intervention clinics; these results will be shared with the staff and administration of these clinics, to identify remaining/unresolved problems, and generate new solutions to correct these problems.

Outcomes will be continued to be measured as before and will also continue to be measured in former intervention sites. Clinical TAMs will be measured twice at all sites Research. TAMs will be measured monthly as before.

Data Analysis:
There are three main comparisons:
First, we will compare the results at the original intervention clinics, from the last 6 months of the Primary study with the last 6 months of the secondary study - to assess whether any benefits found are sustained over time.
Second, we will assess the increase in contacts seen, investigated, started and completing LTBI treatment at the former control sites by comparing these numbers in the last 6 months of the Primary study with the last 6 months of the Secondary study.
As before, our analysis will be performed at the level of the individual, but will account for correlation between subjects from the same centre. Population averaged logistic regression with an identity link estimated via generalized estimating equations (GEE) and using a jack-knife estimate of the variance will be used to assess the effect of the intervention on the primary and secondary outcomes above, depending on the type of outcome (e.g. count or proportion). This approach will account for the correlation between subjects in the same cluster, and for varying cluster sizes. Using an identity link (rather than a logit link) will allow us to estimate risk differences for binary outcomes.
Population averaged models estimated via GEE are robust to mis-specification of the correlation structure. While our data will surely have clustering at the household level as well, we need only account for the top-level cluster (here centre) and use the empirical standard errors to ensure that our inferences are conservative.
For count type outcomes, we will use a similar approach as described above, but using a Poisson distribution.
In secondary analyses, we will use logistic regression with a logit link estimated via GEE and also adjust for additional confounders (country, age, sex and smear status of index case). In sensitivity analyses we will analyze at the level of the cluster. Missing data will be dealt with via multiple imputation using chained equations which will allow us to impute binary as well as continuous variables [85].

Third, we will estimate the cost-effectiveness of the streamlined intervention given to the former control sites in the secondary study. This will be estimated as the total research and health system costs for the Phase 1 and Phase 2 intervention package per added contact who starts LTBI therapy. This can also be compared to the cost-effectiveness (estimated in the same way) of the original intervention given to the original intervention sites.

Ethical Issues:
The ethical concerns over with-holding the intervention at control sites will be addressed by introducing the full intervention package to the control sites at the end of the 18 months primary study. At this time we will take advantage of the experience gained and lessons learned from the primary study to introduce what should be a more streamlined, effective and cost-effective set of interventions - providing enhanced benefit to these populations. Consent will not be sought - for the same reasons explained above, and all measures to protect confidentiality will remain in place.

3. TRIAL OVERSIGHT AND ROLE OF INVESTIGATORS

3.1 Day to Day management:

The study will be managed in each country by the Country Principal Investigators. Randomization will be overseen by the trial biostatistician – Dr Benedetti. Dr. Trajman and Hill will be involved in adapting the questionnaires developed in Brazil to the other countries' settings and populations.

3.2. Roles of Investigators:

Principal investigator – D. Menzies- Supervision of the coordination center staff, Chairing investigators' meetings, and Trial Steering committee. Liason with SAC and DSMB. Participate in refinement and final standardization of the public health evaluation. Review Phase 1 findings from each country, and participle in selection of interventions.

Co-Principal Investigators - P. Hill & A Trajman – Involved in refinement and final standardization of the public health evaluation. Analysis of Phase 1 findings. Selection of interventions. Members of the Trial Steering Committee. Participate in the investigators meetings and training sessions pre-phase 1 and phase 2.

Country Principal Investigators: In each country a country coordinating centre will be established, and one or two investigators will serve as the Country PIs. These persons will be responsible for supervision of site research staff, liaison with local public health (TB) and clinic authorities, coordinate and lead the training at the sites for Phase 1 and 2, plus supervise data gathering in both phases. One investigator from each country will serve as member of trial steering committee.

Trial biostatistician – A Benedetti. Advice on study design, sample size, and analyses of results.

Economic analyses – K Schwartzman and O Oxlade. Advice on data gathering and analysis of cost data

3.3. Trial oversight mechanisms:

3.3.1 Trial steering committee (TSC): The TSC will review all major changes in the protocol and major budgetary changes, and will be comprised of the site investigators, the study coordinator, and the principal and co-principal investigators. The TSC will meet during the investigator meetings, and otherwise by Skype.

3.3.2. Scientific advisory committee (SAC). The SAC will be: Dr. Andrew Vernon (CDC), Dr. Haileyesus Getahun (World Health Organization), Dr. Peter Godfrey-Fausett (London School of Tropical Medicine and Hygiene), and Dr Ben Marais (Univ of Sydney). The SAC will meet regularly to advise on major scientific issues.

3.3.3. Data, safety and monitoring board (DSMB). The ongoing 4RIF-9INH trials have a DSMB comprised of: Dr. Rick O'Brien (FIND, Geneva), Dr. Michael Lauzardo (Florida TB Control) and Dr. Wendy Cronin (Maryland TB control). This DSMB will meet if patient safety or other concerns arise.

4. IMPORTANCE OF THE STUDY AND NEXT STEPS

The proposed study will establish a firm methodological foundation and establish the feasibility of this complex public health approach in Canada and five low or middle income countries. The questionnaires and other instruments including the contact registries, treatment cards and reporting forms will be developed and validated by the end of this study. These instruments can then be adapted and translated for use in many other countries to assess the barriers to successful contact investigation and management. These can be used immediately to scale up this activity through-out the countries involved in the study, and also introduced in other countries to identify key problems and potential solutions in those settings. We will also have developed an important tool for eventual use by National TB programmes within many LMIC – the Contact Management Registries and their related quarterly reporting mechanisms. These registries and reports are modeled after registries and reports used for active TB by NTP in many LMIC.

At the end of Phase 2 we will have established the feasibility, as well as identified all costs related to the implementation of a package of interventions to improve contact investigation. We will also have refined the approach to training and supervision, based on our experience. Given the potential impact of contact investigation and treatment on TB prevention activities, this pragmatic package may offer a blue-print for global action to help meet the World Health Organization's post-2015 targets for TB elimination.

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