# Latent Tuberculosis Infection in Iqaluit, Nunavut: an Analysis of the Cascade of Care and Cost-Effectiveness of a Novel Treatment Regimen

**Christopher Pease**

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School of Epidemiology and Public Health

Faculty of Medicine

University of Ottawa

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## Preface

This thesis consists of two related components presented in manuscript format: an analysis of the latent tuberculosis infection cascade of care in Iqaluit, Nunavut and a cost-effectiveness analysis comparing a novel treatment regimen for latent tuberculosis infection to standard therapy in Iqaluit, Nunavut. The second component utilizes data from the first component as well as other sources.

For the first component, a Nunavut Research Institute Research license was obtained. Approval of the Ottawa Health Science Network Research Ethics Board was also obtained for the collection and analysis of the data. Permission to access data was provided by Iqaluit Public Health.

Because the second component utilized previously published data, ethics approval was not required. However, a Nunavut Research Institute Research license was obtained

For the first component, Dr Christopher Pease was involved in the design of the study along with Dr Alice Zwerling, Dr Gonzalo Alvarez and Deborah van Dyk. Dr Pease was not involved in the data collection but did design and perform the statistical analysis with guidance from Dr Zwerling, Dr Alvarez and Dr Ranjeeta Mallick. Dr Pease wrote the manuscript with comments and approval obtained from all co-authors. For the second component, Dr Pease contributed to the study design with Dr Zwerling and Dr Alvarez. Dr Pease performed the data analysis including building the Markov model and determining its component parameters. He also wrote the manuscript with guidance from Dr Zwerling along with Dr Alvarez, Dr Mallick and other co-authors. All co-authors reviewed and approved of the final manuscript. The thesis

manuscript was written by Dr Pease with guidance from his thesis advisory committee (Dr Zwerling, Dr Alvarez, Dr Mallick and Dr Shawn Aaron).

## Abstract

### Background

The incidence of tuberculosis (TB) among Inuit is over 400 times that of Canadian-born non-indigenous people. To address this, more patients will need to complete preventative treatment.

### Methods

First, data were extracted retrospectively for all patients with a tuberculin skin test (TST) implanted in Iqaluit, Nunavut between January 2012 and March 2016 and used to identify sources of loss from the latent TB infection (LTBI) cascade of care. Associations between demographic and clinical factors and treatment non-initiation and treatment non-completion were identified using regression models. Second, using a slightly expanded version of the retrospective dataset plus other sources, a Markov model was utilized to assess the cost-effectiveness of a novel shortened regimen for LTBI (12 weeks of once weekly isoniazid and rifapentine (3HP)) compared to the current standard of care (9 months of isoniazid monotherapy (9H)).

### Results

Treatment non-initiation and non-completion were the largest sources of loss of TST positive patients from the cascade of care. LTBI testing via employment screening was associated with treatment non-initiation while older age was associated with both treatment non-initiation and non-completion. In cost-effectiveness analysis, 3HP was dominant over 9H: costs were lower ($835 vs $1229 per person) and health outcomes slightly improved (20.14 vs 20.13 QALYs gained per person treated), largely due to an improved treatment completion with 3HP.

### Conclusions

Interventions to increase LTBI treatment initiation and completion in Iqaluit are needed. This could include the use of 3HP instead of 9H for LTBI treatment which may improve treatment completion and result in cost savings and slightly improved health outcomes.

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**List of Abbreviations**

**3HP** = 12 weeks of once weekly isoniazid and rifapentine

**9H** = 9 months of isoniazid

**AE** = adverse event

**aRR** = adjusted risk ratio

**DOT** = directly observed therapy

**IGRA** = interferon gamma release assay

**ICER** = incremental cost-effectiveness ratio

**LTBI** = latent tuberculosis infection

**QALY** = quality-adjusted life year

**RR** = risk ratio

**TB** = tuberculosis

**TST** = tuberculin skin test

## Chapter 1 - General Introduction

### *1.1 Scope of the Problem*

Despite a gradual decline in incidence, tuberculosis (TB) remains a major global health challenge and is estimated to have caused 10 million new cases and 1.5 million deaths worldwide in 2018[1]. Although Canada has a low overall TB incidence, there remains considerable variation in TB incidence between different population groups. The burden of disease in Canada falls predominantly on the foreign-born as well as on Canadian-born Indigenous populations who together account for nearly 90% of active cases[2]. Among First Nations, who compromise the majority of Canadian-born Indigenous people, the incidence rate of active TB was 21.5/100 000 in 2017, far higher than the rate among Canadian-born non-Indigenous people which was only to 0.5/100 000 [2]. However, the rate of active TB in among Inuit is dramatically higher. In 2017, the rate was 205.8/100,000, over 400 times that of the Canadian-born, non-Indigenous population[2]. In fact, this rate is similar to that of high TB burden countries such as Nigeria, Ethiopia and Bangladesh[3]. Nearly half of the Inuit population in Canada resides in the Nunavut Territory with many of the rest living in adjacent arctic regions known as the Inuit Nunangat (homeland), this region has by far the highest TB incidence rates in Canada[4].

In an attempt to address this serious burden of disease, on March 23, 2018, the Government of Canada and the Inuit Tapariit Kanatami (Inuit National Organization) announced a goal to eliminate TB in the Inuit Nunangat by 2030[5]. Effective and feasible methods to achieve this are being investigated[6].

### *1.2 Latent Tuberculosis Infection*

Active TB occurs when a person is ill due to infection with *Mycobacterium tuberculosis*[7]. However, only approximately 5% of people who are infected with this organism develop active

TB initially[7]. Instead, the immune systems of most individuals sequesters *M. tuberculosis* bacilli, a condition known as latent tuberculosis infection (LTBI)[8]. People with LTBI are non-infectious and asymptomatic. However, 5-15% will subsequently develop active TB disease during their lifetimes as a result of reactivation of the previously sequestered bacilli [9].

After exclusion of active disease, LTBI is diagnosed with either tuberculin skin testing (TST) or the interferon-gamma release assay (IGRA)[8]. TST requires that a small amount of tuberculin protein be implanted beneath the skin of patients who then must be re-evaluated 48-72 hours later to determine whether or not they have a reaction indicative of LTBI. Results from the IGRA, on the other hand, require only collection of a small blood sample, eliminating the need for a return visit for test results to be obtained.

The overall burden of LTBI on a global scale is massive with an estimated 1.7 billion people carrying the infection[10]. Although rates of LTBI in the Canadian arctic have not been quantified, the high rate of active disease suggests that the burden is large. Individuals with LTBI represent a reservoir of people who can develop active TB at any time, meaning that TB elimination is impossible to achieve without addressing individuals with this condition.

Prior studies have modeled strategies for TB elimination globally and in the United States. These studies have concluded that widespread and effective treatment of LTBI is not only essential to achieve TB elimination but likely the most important single strategy available[11,12]. Further, a previous analysis of over 50 years of data from the United States, Canada and Greenland identified a decrease in rates of active TB among indigenous populations following the introduction of LTBI screening and treatment programs[13].

*1.3 Managing Latent Tuberculosis*

Treatment of LTBI reduces the future risk of developing active TB by up to 95%[14]. However, because LTBI treatments have a risk of causing adverse events and because the future risk of developing active TB is very low in some patients, the risks and benefits of initiating treatment for LTBI need to be carefully weighed and some patients with LTBI do not require treatment[7].

When indicated, therapy has traditionally consisted of 9 months of isoniazid (9H). However, not only is this treatment long but it is also associated with a substantial risk of adverse events, particularly hepatotoxicity[15,16]. In recent years, shorter course regimens have been developed. Of these, a regimen of rifapentine and isoniazid given once weekly for 12 weeks (3HP) has the shortest duration and by far the fewest required doses[17]. In comparison to 9H, 3HP offers comparable efficacy, higher treatment completion and a similar to improved safety profile[15,17].

However, since 3HP requires only a total of 12 doses, each dose represents a greater proportion of the total treatment course than is the case for other regimens. As a result, it is particularly important to minimize missed doses and so 3HP is most commonly given under direct observation by healthcare personnel, a technique referred to as directly observed therapy (DOT)[18–20]. This means that patients are either required to attend clinic or have healthcare personnel come to their home or workplace for each dose. In contrast, in most locales patients self-administer LTBI treatment regimens other than 3HP[18].

This is not the case in Nunavut, however. There all LTBI treatment, irrespective of regimen, is given by DOT[21]. This is done to reduce missed doses and thereby increase treatment completion but does require a higher number of clinician visits compered to self-administered

therapy[21]. Although 9H is more commonly given with daily dosing in other locales, in Nunavut a regimen of twice weekly high-dose isoniazid is given for 9 months to reduce the number of doses required[21].

*1.4 Latent Tuberculosis Infection Cascade of Care*

There are numerous steps between a decision to test for LTBI and completion of treatment (e.g. the patients must report for test reading/results, be offered treatment, accept treatment, start treatment etc.). This sequence of events has been termed the LTBI cascade of care[22]. There is the potential for loss from this cascade due to patient refusal, loss to follow up or other factors at each step in this cascade. In fact, a recent meta-analysis of 58 observational studies representing populations from a variety of high, low and middle income countries found that only 18.8% of those intended for screening and 26.1% of those who underwent testing complete therapy for LTBI[22]. These rates are strikingly below what would be expected if all patients were treated appropriately[22]. This suggests that there is substantial under-identification and undertreatment of LTBI, issues which will need to be improved if substantial reductions in the global TB burden are to be made[10].

*1.5 Latent Tuberculosis Infection Cascade of Care in the Canadian Arctic*

Two previous studies examined aspects of the LTBI cascade of care in the Inuit Nunangat but neither evaluated the cascade of care under routine conditions[23,24]. The first examined a program of LTBI screening in high-risk neighbourhoods in Iqaluit[23]. This found that, of the 444 people offered screening for LTBI, 296 initiated screening (67%)[23]. Of these, 246 people had a TST placed, 42 (17%) of whom had a positive result [23]. Among TST positive patients, 25/42 patients (60%) initiated treatment and of these 17/25 (68%) competed 100% of treatment doses within 12 months [23]. While this study is likely not fully representative of LTBI testing in Iqaluit

as a whole, this suggests that considerable losses may occur between those intended for screening and those who complete therapy.

In a recent study of a community wide screening program in remote community in Nunavik, Quebec, treatment completion was somewhat higher than observed in Iqaluit. Overall, 85/120 (71%) of newly identified or previously inadequately treated LTBI patients completed treatment[24]. However, a less stringent definition of treatment completion was used (≥80% of treatment doses completed) than in the Iqaluit study which may partially explain the apparently higher probability of completion[24].

*1.6 Importance and Limitations of Economic Analyses as a Decision Aid*

Further understanding the LTBI cascade of care may help identify opportunities to improve the proportion of patients who complete therapy. However, even when such opportunities have been identified, selecting the best approach to addressing them is unlikely to be straightforward. Many potential interventions exist and it is not feasible to perform clinical trials to evaluate each of them. Further, resources available to implement such interventions are limited and different potential interventions will have different implementation costs. As such, there is a need to allocate limited resources as efficiently as possible if progress is to be made in reducing the burden of TB in Canadian Arctic communities.

An important tool to guide such decisions is cost-effectiveness analysis. This technique seeks to delineate the incremental costs associated with incremental improvement in health outcomes of an intervention compared to a base case scenario (which is often current standard practice). The result is an incremental cost-effectiveness ratio (ICER) which is the incremental cost of the intervention compared with the standard of care or another approach divided by a measure of its incremental benefit, often measured in quality adjusted life years (QALYs)

gained. QALYs are a measure of health outcome that incorporates both length and quality of life in a single value[25].

This provides decision makers with an assessment of the relative value for money of different interventions and may therefore assist them in selecting which to implement.

While frequently useful, the technique does have limitations. To be accurate, cost-effectiveness analysis requires comprehensive information on costs required to implement and maintain the intervention and comparator of interest. Such costs may not be available and so assumptions and estimation are frequently required[26]. As such, appropriate sensitivity analyses must be made to address the resulting uncertainty. Similarly, the technique requires accurate information about the effectiveness of proposed interventions. Further, the costs associated with a particular intervention are typically highly setting-specific, meaning that the results from an analysis in one setting are frequently not generalizable to another setting[26]. This is likely to be particularly true in arctic settings since the geographical and climatic characteristics of the region engender unique challenges and higher costs associated with delivery of care compared with other regions.

*1.7 Economic Analyses of Tuberculosis Care in Arctic Settings*

Previous economic analyses of TB care in the Canadian Arctic have focused on active TB diagnosis. Specifically, a comparison of the costs of sputum induction in Iqaluit and Ottawa has been performed[27] as well as a study assessing the impact on costs and time to treatment of implementing rapid PCR based testing for the presence of TB in sputum among persons with TB symptoms in Iqaluit[28]. No published studies were identified which evaluated cost-effectiveness of LTBI treatment in this setting.

*1.8 Previous Economic Analyses of 3HP for the Treatment of LTBI*

Five previous studies have evaluated the cost-effectiveness of 3HP compared to 9H in non-Arctic settings[29–34] and one randomized trial has compared their costs[35].

A cost-effectiveness analysis by Holland et al (2009) compared 4 regimens: self-administered 9H, 9H by DOT, 3HP by DOT and self-administered rifampin for 4 months[34]. It included healthcare costs in an American setting[34]. This study found that 3HP dominated 9H by DOT (meaning that 3HP was both cost-saving and more effective)[34]. 3HP was cost-effective compared to both self-administered 9H and self-administered rifampin with ICERs of $3,753 dollars (2008 US dollars)/QALY gained and $48,997/QALY gained, respectively[34]. The cost-effectiveness of 3HP was increasingly favourable as LTBI reactivation risk increased[34]. However, this study was undertaken prior to a large randomized controlled trial comparing 3HP and 9H and estimated a completion probability of 54% for 9H and 94% for 3HP[34]. In the subsequent large RCT the observed a completion probability of 69% for 9H and 82% for 3HP[18]. Thus, the more favourable completion probability for 3HP used by Holland et al may have over-estimated the cost-effectiveness of 3HP. Similarly, the study also over-estimated the relative improvement in completion with rifampin vs 9H, compared to a subsequent large randomized controlled trial[36].

A later study included data from these large-scale trials and modelled large scale use of 3HP by DOT in place of self-administered 9H for LTBI in the United States[30]. It also found 3HP to be cost-effective with an ICER of $4,565(2010 US dollars)/QALY gained from a healthcare system perspective [30]. The higher cost of 3HP was driven largely by DOT visits while the improved effectiveness of 3HP was driven by higher treatment completion and consequently greater efficacy in preventing TB[30].

Also utilizing a healthcare system perspective, another recent study modelled the use of 3HP by DOT vs self-administered 9H as prophylactic therapy among Ugandan HIV patients[32]. This found an estimated ICER of $9402 (2017 US dollars) per disability-adjusted life-year averted for 3HP in comparison to 9H[32]. However, the ICER was quite sensitive to variations in the cost of rifapentine, 3HP completion and the prevalence of LTBI. This suggests that 3HP may not remain cost effective in settings in which the LTBI prevalence or cost or completion of 3HP differ from the values used in the study.

Kowada (2016) examined the cost-effectiveness of 3HP by DOT compared to 9H by DOT when each was combined with one of 4 diagnostic strategies for LTBI among immigrants from high TB-burden countries to Japan[29]. For each diagnostic strategy, 3HP was dominant over 9H (cost-saving and more effective)[29]. Treatment completion probabilities were a key influence on and driver of the comparative effectiveness of the two regimens[29]. Total costs of 3HP and 9H were extracted from the literature which prevented detailed analysis of the drivers of cost[29]

Doan et al (2019) compared the cost-effectiveness of 6 different LTBI treatment regimens to no treatment in a hypothetical cohort of 10 000 LTBI patients[33]. Costs were based on an American healthcare system perspective[33]. Regimens included self-administered 9H as well as both self-administered 3HP and 3HP by DOT in addition to several other treatments[33]. 3HP by DOT had the highest effectiveness (QALYs) of any regimen while self-administered 3HP was the cheapest regimen[33]. Both self-administered 3HP and 3HP by DOT were dominant over 9H[33]. The relative cost-effectiveness of both 3HP regimens was most sensitive to the treatment completion probability and risk of LTBI reactivation[33].

Finally, a single-centre randomized trial in Australia examined the healthcare system costs of 3HP vs. 9H when both regimens were self-administered[35]. The costs of medication, pathology and radiology testing, outpatient visits and hospitalization were considered[35]. The cost of 3HP was $511 Australian dollars/treatment course completed compared to $601 Australian dollars/treatment course completed for 9H ($p<0.01$) with outpatient visits contributing the most to total cost for both regimens[35].

Despite differing methodologies, comparator regimens, perspectives and settings, the above studies generally support the cost-effectiveness of 3HP with the strategy for drug delivery (self-administered vs DOT) as well as risk of reactivation of LTBI and treatment completion frequently being identified as key factors influencing cost-effectiveness.

*1.9 Thesis Overview and Objectives*

This thesis consists of two interrelated parts presented here as manuscript 1 and manuscript 2. Manuscript 1 has been published in *BMC Infectious Diseases* while manuscript 2 has been submitted to *Chest*. The first manuscript examines the LTBI cascade of care in Iqaluit Nunavut using retrospective data from 2012-2016. The second manuscript utilizes the findings of the first portion along with additional data including the results of a trial of 3HP implementation and data on local costs to examine the cost-effectiveness of introducing 3HP for LTBI treatment in this setting compared to 9H, the current standard of care. Specifically, this thesis had the following objectives:

1. To describe the LTBI cascade of care under regular program conditions in Iqaluit, Nunavut between January 2012 and March 2016 using retrospective chart review and to identify factors associated with non-initiation of LTBI treatment among patients offered

treatment and non-completion of treatment among patients who initiated treatment in Iqaluit, Nunavut between January 2012 and March 2016

2. To assess the cost-effectiveness of 3HP for the treatment of LTBI in comparison to 9H in Iqaluit, Nunavut over a 30-year time horizon.

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**Chapter 2 - Manuscript 1**

# The latent tuberculosis infection cascade of care in Iqaluit, Nunavut, 2012-2016

Christopher Pease[1,2] (cpease@toh.ca), Alice Zwerling[2] (azwerlin@uottawa.ca), Ranjeeta Mallick[3] (rmallick@ohri.ca), Mike Patterson[5] (mpatterson@gov.nu.ca), Patricia Demaio[5] (pdemaio@gov.nu.ca), Sandy Finn[5] (sfinn@gov.nu.ca), Jean Allen[6] (jallen@tunngavik.com), Deborah Van Dyk[3] (dvandyk@ohri.ca), Gonzalo G. Alvarez[1,2,3,4] (galvarez@toh.ca)

1=Ottawa Hospital, Department of Medicine, Ottawa, Canada
2= Ottawa University School of Epidemiology and Public Health, Ottawa, Canada
3=Ottawa Hospital Research Institute, Ottawa, Canada
4=Ottawa University Faculty of Medicine, Ottawa, Canada
5=Ministry of Health, Government of Nunavut, Iqaluit, Nunavut
6=Nunavut Tunngavik Inc, Iqaluit, Nunavut

**Correspondence:**
C. Pease
The Ottawa Hospital General Campus
501 Smyth Road
Ottawa ON K1H 8L6
cpease@toh.ca

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## 2.1 Abstract

### Background

The Territory of Nunavut is a remote arctic region of Canada predominantly populated by Inuit and has Canada's highest incidence of tuberculosis.

### Methods

The study was undertaken to describe the latent tuberculosis infection (LTBI) cascade of care and identify factors associated with non-initiation and non-completion of LTBI treatment. Data were extracted retrospectively from medical records for all patients with a tuberculin skin test (TST) implanted in Iqaluit, Nunavut between January 2012 and March 2016. Associations between demographic and clinical factors and both treatment non-initiation and treatment non-completion were identified using log binomial regression models where convergence could be obtained and Poisson models with robust error variance where convergence was not obtained.

### Results

Of 2303 patients tested, 439 (19.1%) were diagnosed with LTBI. Treatment was offered to 328 patients, was initiated by 246 (75.0% of those offered) and was completed by 186 (75.6% of initiators). In multivariable analysis, older age (adjust risk ratio [aRR] 1.17 per 5-year increase, 95%CI:1.09-1.26) and undergoing TST due to employment screening rather than following TB exposure (aRR 1.63, 95%CI:1.00-2.65) were associated with increased non-initiation of treatment. Older age (aRR 1.13, 95%CI: 1.03-1.17, per 5-year increase) was associated with increased non-completion of treatment.

### Conclusions

A similar rate of treatment initiation and higher rate of treatment completion were found in Nunavut compared to previous North American studies. Interventions targeting older

individuals and those identified via employment screening may be considered to help to address the largest losses in the cascade of care.

## 2.2 Background

Canada has a low overall incidence of tuberculosis (TB), yet the burden of the disease disproportionally falls on Indigenous populations and, in particular, on Inuit people. Inuit had the highest incidence of active TB in Canada in 2016 with a rate of 170.1 per 100 000 compared to 4.8 per 100 000 in Canada as a whole[1]. Nearly half of the Inuit population in Canada resides in the Territory of Nunavut with many others living in adjacent arctic regions collectively known as Inuit Nunangat (Inuit homeland)[2]. In an attempt to address the high burden of TB in these regions, the Government of Canada and Inuit Tapariit Kanatami (Inuit National Organization) have announced a goal to eliminate TB in Inuit Nunangat by 2030[3]. Potential strategies to achieve this are being developed in a project led by Inuit[4].

Although analyses within arctic settings have yet to be performed, modelling studies assessing strategies for TB elimination globally and in the United States have been done[5,6]. These studies concluded that widespread and effective treatment of latent tuberculosis infection (LTBI) is likely to be necessary for TB elimination [5,6]. In order to design interventions to increase LTBI treatment rates, numerous steps between the decision to test for LTBI and completion of treatment (termed the LTBI cascade of care[7]) must be carefully examined and barriers overcome. Particular challenges in the Canadian arctic include the geographic isolation and challenging climate which limit access and available resources to the remote communities where many Inuit live[8]. Further, most healthcare professionals arrive from Southern Canada and are frequently unfamiliar with the local culture and language and there are difficulties in procurement and retention of experienced staff and prioritization among numerous competing health care priorities[8]. Finally, overcrowded housing and food insecurity are common[8].

Previous studies of LTBI in the Canadian arctic have focused on single interventions and none have examined the LTBI cascade of care under a routine program setting. In 2011, we

conducted a TB awareness campaign followed by a door to door screening program to augment the local TB program in high-risk neighbourhoods in Iqaluit, Nunavut's capital [9]. Among new LTBI cases identified, 24/31 (77%) who took at least one dose of directly observed twice weekly INH for nine months completed treatment (≥80% of doses within 1 year) [9]. In a recent study of a community screening program in Nunavik, Quebec, 85/120 (71%) newly identified or previously inadequately treated LTBI patients completed ≥80% of treatment doses (primarily self-administered rifampin for 4 months) [10].

The present study was undertaken to describe the LTBI cascade of care under regular program conditions in Iqaluit, Nunavut between January 2012 and March 2016 and to identify factors associated with non-initiation of LTBI treatment among patients offered treatment and non-completion of treatment among patients who initiated treatment.

**2.3 Methods**

*Study Design and Population*

Study data were collected retrospectively via review of electronic medical records and, where necessary, paper charts. Extracted data were entered into a Microsoft Excel (Microsoft Corporation, Redmond, WA, USA, 2017) database by a research nurse. Once the data were entered, a second research nurse reviewed the data to ensure completion and accuracy. Extracted data included demographic, clinical and treatment information for all patients in whom a tuberculin skin test (TST) was implanted in Iqaluit, Nunavut between January 2012 and March 2016. Key variables included patient age, ethnicity, TST result, TST indication, and whether treatment was offered, initiated and completed. Interferon gamma release assay (IGRA) results

were not comprehensively collected but discordance between IGRA and TST results was captured when provided as a reason for not offering LTBI treatment.

*Study Setting*

Iqaluit is a remote community in the Canadian arctic and is the largest community in Inuit Nunangat. There are no roads linking Iqaluit to other communities. It is accessible by air year-round and by sea in the summer. In 2016, Iqaluit's population was 7740, representing 21.5% of Nunavut's population[2]. A majority (4265 people, 55.1%) of people in Iqaluit identify as Inuit [2]. The community reported 178 cases of active TB between 2010 and 2016 (36% of all cases in Nunavut during this time) with a mean of 26 cases per year (range 9-50) (unpublished data). Between 2007 and 2014 there were no new cases of HIV reported in Nunavut[11].

Health care services available in Iqaluit include public health (including LTBI testing and treatment and management of active TB) as well as primary and secondary care. Advanced medical interventions require medical transport to facilities in southern Canada. Health care interventions including diagnostic testing, nursing and physician assessment and TB medication are provided without charge.

All testing for LTBI in Iqaluit is performed via Iqaluit Public Health with TST being the recommended modality[12]. The IGRA is not used routinely but is performed in select cases at the discretion of the patient's physician. TSTs are predominantly performed following exposure to active TB cases, following physician referral and as part of screening of school children in kindergarten and grade 6 and workers in some professions (e.g. healthcare workers)[12]. TSTs are strongly encouraged in these circumstances but not mandatory. Two step TSTs are performed when repeat testing is anticipated (e.g. healthcare workers)[12]. Public health nurses administer and read all tests as well as providing education regarding LTBI. TST interpretation was based

upon the Canadian TB Standards which recommend a 10mm cut off for test positivity in the absence of risk factors and a 5mm cut off for those with recent TB contacts or other risk factors[13].

All patients with a positive TST are referred for physician assessment and treatment may be offered at the discretion of the assessing physician. The standard LTBI treatment regimen during the study period was 9 months of isoniazid given twice weekly via directly-observed therapy[12]. BCG vaccination is recommended for all infants in Nunavut before 12 months of age but is not mandatory[12]. Repeat BCG vaccination and vaccination at older ages is not performed[12]. In a previous study of residents of a high-risk neighbourhood of Iqaluit undergoing LTBI screening, 79% of participants for whom records were available had received BCG vaccination[14].

*Statistical Analysis*

We performed descriptive statistics on patient demographics and quantified the amount and reasons for loss to follow-up along each step in the LTBI cascade of care.

The primary analyses assessed the association between demographic and clinical factors and both treatment non-initiation among TST positive patients offered LTBI treatment and treatment non-completion among TST positive patients starting LTBI treatment. Patients could have had previous negative TSTs results but were included at the time of their first positive TST result. Clinical factors included the reason for performing TST. When TST was performed as part of a contact tracing investigation, the reason for TST was termed "TB exposure". Treatment non-initiation was defined as failure to receive at least one dose of a drug for LTBI. Treatment non-completion was defined as taking <80% of prescribed doses within 12 months of treatment

initiation. There is no universally accepted definition of treatment completion for LTBI regimens and widely variable definitions have been used in previous studies[15]. Given this, sensitivity analyses were performed in which treatment non-completion was defined as taking <90% of doses within 12 months and as taking <100% of doses within 12 months.

Unadjusted risk ratios (RRs) for each demographic and clinical factor were estimated using univariable regression models while adjusted RRs (aRRs) were estimated using multivariable models. Log binomial models were used for all analyses except for those examining treatment non-initiation. In this instance, log binomial models failed to converge therefore Poisson models with robust error variance[16] were used. Key variables were included in multivariable models based on their clinical importance while additional variables were assessed for inclusion based on descriptive and univariate analyses as well as model fit statistics (see Supplementary Appendix 1).

Two secondary analyses were performed. The first examined factors associated with TST positivity among those for whom a TST result was obtained and the second evaluated factors associated with failure to obtain a TST result among all patients in whom a TST was implanted. Risk ratios in both of these analyses were estimated using log binomial regression models fit using generalized estimating equations. All TST results were included in the analysis and an exchangeable correlation matrix was used to adjust for correlation between the results of multiple TSTs performed on the same individual.

For regression models in which all variables had <10% missing data, a complete case analysis was performed. This cut off was selected *a priori* with the assistance of a biostatistician. When ≥10% of values were missing for at least one variable, all missing values were imputed with the imputation model including variables including sex, age, indication for

TST, year of TST and ethnicity. Twenty datasets were imputed using the SAS PROC MI procedure and regression models were fit for each. Estimates of coefficients and variance from these models were then combined according to Rubin's Rules as implemented in the SAS PROC MIANALYZE procedure. Complete case analyses were performed for comparison.

Statistical analysis was carried out using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA, 2017).

## 2.4 Results

*Demographic characteristics*

Characteristics of the 2303 patients in whom TSTs were implanted during the study period are presented in Table 2.1. The mean age at first TST was 25.3 years (standard deviation 16.3, range 0-86). The ethnicity of 425 patients (18.5%) was unknown while 1220 (53.0%) were Inuit and 658 (28.6%) were non-Inuit. There were 619 patients (26.9%) with more than one TST. The most common reason for repeat TST was TB exposure (441/870 tests, 50.7%) followed by self or physician referral (182/870 tests, 20.9%), employment screening (175/870 tests, 20.1%) and school screening (30/870 tests, 3.4%). There were 42 repeat tests performed for unknown or other reasons (4.8%).

**Table 2.1.** Demographic characteristics of included patients (n = 2303 individuals with 3173 tuberculin skin tests). TST = tuberculin skin test, SD = standard deviation.

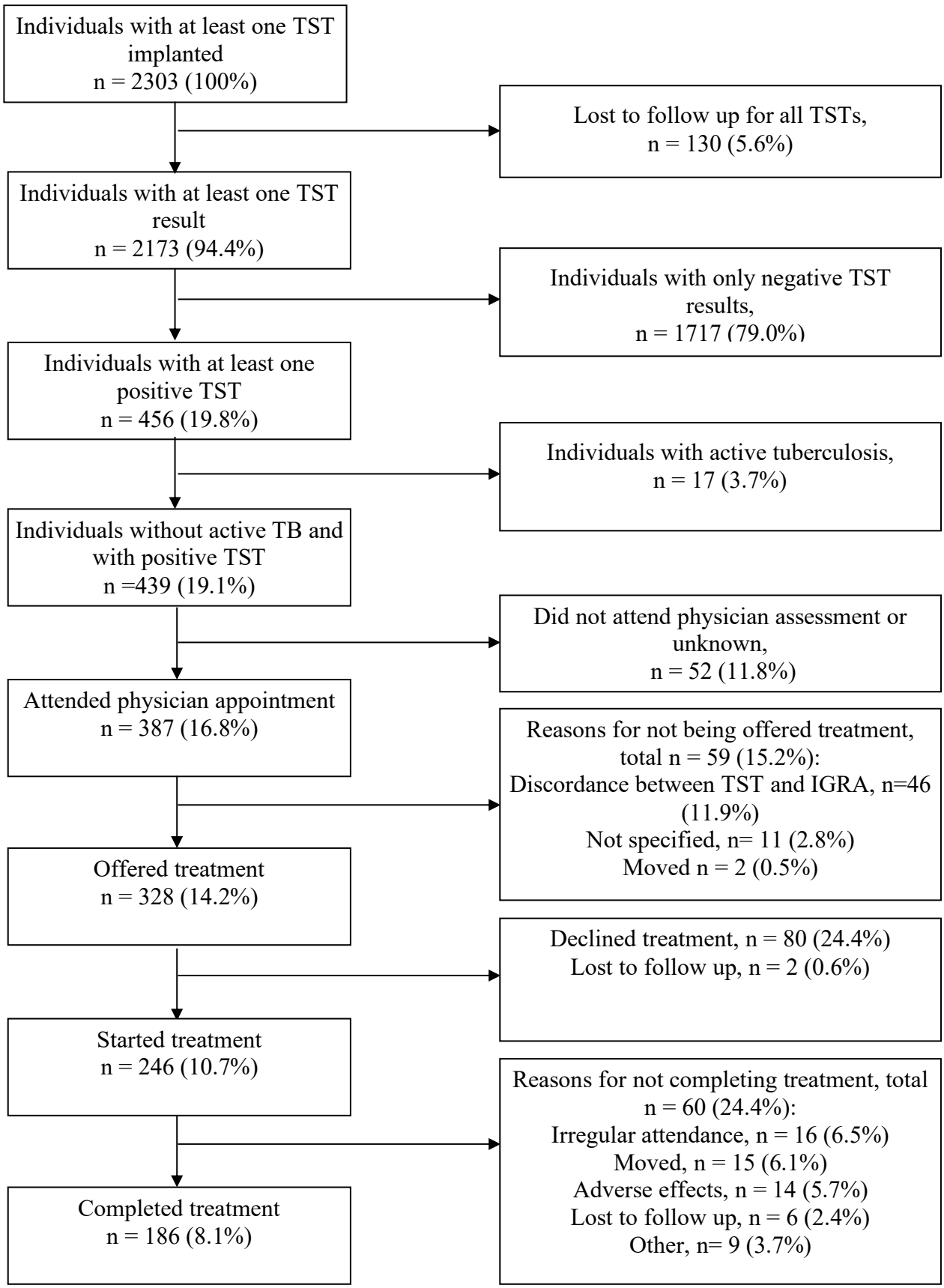
| Characteristic | All patients (n=2303) | Diagnosed with latent tuberculosis infection (n = 439) | Diagnosed with active tuberculosis (n = 17) | Not diagnosed with latent or active tuberculosis (n = 1847) |
|---|---|---|---|---|
| Age at first TST, mean (SD) | | | | |
| Males | 25.2 (17.1) | 25.1 (17.7) | 30.6 (18.7) | 25.1 (16.9) |
| Females | 25.4 (15.6) | 24.4 (16.5) | 29.1 (19.5) | 25.6 (15.3) |
| Total | 25.3 (16.3) | 24.8 (17.1) | 29.9 (18.5) | 25.4 (16.0) |
| Age at first TST, n (%) | | | | |
| <18 years | 784 (34.0) | 169 (38.5) | 4 (23.5) | 611 (33.1) |
| 18-35 years | 919 (39.9) | 157 (35.8) | 4 (23.5) | 758 (41.0) |
| >35 years | 600 (26.1) | 113 (25.8) | 9 (52.9) | 478 (25.9) |
| Sex, n (%) | | | | |
| Male | 1065 (46.2) | 224 (51.0) | 9 (52.9) | 832 (45.0) |
| Female | 1238 (53.8) | 215 (49.0) | 8 (47.1) | 1015 (55.0) |
| Ethnicity, n (%) | | | | |
| Inuit | 1220 (53.0) | 290 (66.1) | 16 (94.1) | 914 (49.5) |
| Non-Inuit | 658 (28.6) | 90 (20.5) | 0 (0) | 568 (30.8) |
| Unknown | 425 (18.5) | 59 (13.4) | 1 (5.9) | 365 (19.8) |
| Number of TSTs performed, n (%) | | | | |
| 1 | 1684 (73.1) | 344 (78.4) | 16 (94.1) | 1324 (71.7) |
| 2 | 441 (19.1) | 74 (16.9) | 1 (5.9) | 366 (19.8) |
| 3 | 128 (5.6) | 17 (3.9) | 0 (0) | 111 (6.0) |
| >3 | 50 (2.2) | 4 (0.9) | 0 (0) | 46 (2.5) |
| TST Result, n (%) | | | | |
| Ever positive | 456 (19.8) | 439 (100) | 17 (100) | 0 (0) |
| Never positive | 1847 (80.2) | 0 (0) | 0 (0) | 1847 (100) |

*LTBI Cascade of Care*

The LTBI cascade of care for the study period is presented in Figure 2.1. A total of 3173

TSTs were performed with a median of 1 test per patient (range 1-8). Of the 2303 patients with at least one implanted TST, no TST result was obtained for 130 (5.6%). Overall, 462 TSTs (14.6%) performed in 456 patients were positive. The 456 patients with a positive TST result represent 19.8% of all patients tested. Of these 456 patients, 17 were subsequently determined to have active tuberculosis. Thus, 439 patients (19.1% of screened patients) were considered to have LTBI and referred for consideration of treatment. Thus, 5.2 patients were screened for each LTBI case identified.

**Figure 2.1.** Latent tuberculosis cascade of care in Iqaluit, Nunavut for January 2012-March 2016. TST= tuberculin skin test; IGRA = interferon gamma release assay. Percentages in the left-hand column represent the percentage of patients remaining in the cascade compared to the total number of patients who underwent at least one TST. Percentages in the right-hand column represent the percentage of patients exiting the cascade compared to the total number of patients remaining at that point in the cascade.


Individuals with at least one TST implanted
n = 2303 (100%)
Lost to follow up for all TSTs,
n = 130 (5.6%)
Individuals with at least one TST result
n = 2173 (94.4%)
Individuals with only negative TST results,
n = 1717 (79.0%)
Individuals with at least one positive TST
n = 456 (19.8%)
Individuals with active tuberculosis,
n = 17 (3.7%)
Individuals without active TB and with positive TST
n =439 (19.1%)
Did not attend physician assessment or unknown,
n = 52 (11.8%)
Attended physician appointment
n = 387 (16.8%)
Reasons for not being offered treatment, total n = 59 (15.2%):
Discordance between TST and IGRA, n=46 (11.9%)
Not specified, n= 11 (2.8%)
Moved n = 2 (0.5%)
Offered treatment
n = 328 (14.2%)
Declined treatment, n = 80 (24.4%)
Lost to follow up, n = 2 (0.6%)
Started treatment
n = 246 (10.7%)
Reasons for not completing treatment, total n = 60 (24.4%):
Irregular attendance, n = 16 (6.5%)
Moved, n = 15 (6.1%)
Adverse effects, n = 14 (5.7%)
Lost to follow up, n = 6 (2.4%)
Other, n= 9 (3.7%)
Completed treatment
n = 186 (8.1%)

Physician appointments were attended by 387 (88.2 %) of the 439 patients referred and 328 (84.8 % of assessed patients) were offered treatment. The most common reason for not offering treatment was discordance between TST and IGRA (46 of 59 patients not offered treatment). Treatment was started by 246 patients which is 75.0% of the 328 patients offered treatment and 56.0% of the 439 patients with LTBI. Treatment was completed by 186 (75.6%) of the 246 patients who initiated treatment. The most common reasons provided for not completing treatment were irregular attendance (16 of 60 non-completers), moving (15 of 60 non-completers) and adverse effects of treatment (14 of 60 non-completers). When defining completion as receipt of 90% or 100% of doses within 12 months, 175 patients (71.1% of those initiating treatment) and 150 patients (60.9% of those initiating treatment) completed treatment, respectively. Isoniazid for 9 months was the treatment regimen for 232 (94.3%) of patients starting therapy while 6 patients (2.4%) were treated with 4 months of rifampin and 8 (3.3%) with unknown or other regimens. The number of patients screened for each patient who completed treatment was 12.4.

*Primary analysis – Factors associated with non-initiation and non-completion of treatment*

Table 2.2 describes associations between clinical and demographic factors and non-initiation of LTBI treatment. In unadjusted analyses, increased age (RR 1.17 per 5-year increase, 95% confidence interval 1.13-1.25), non-Inuit ethnicity (RR 2.92, 1.97-4.32) and undergoing TST due to employment screening (RR 2.13,1.34-3.39, compared to following TB exposure) were associated with increased non-initiation of treatment. However, in the adjusted analysis, only increased age (aRR 1.17 per 5-year increase, 1.09-1.26) and undergoing TST due to

employment screening (aRR 1.63, 1.00-2.65, compared to following TB exposure) were associated with increased non-initiation of treatment.

**Table 2.2.** Risk ratios for non-initiation of treatment by demographic and clinical characteristic among patient offered latent tuberculosis infection treatment. Risk ratios marked with an asterisk (*) are statistically significant. CI = confidence interval.

| Potential Risk factor | Non-initiators/category total (%) | Unadjusted risk ratio (95% CI) | Adjusted risk ratio[2] (95% CI), n= 280 patients[1] |
|---|---|---|---|
| Age, years (per 5-year increase) | - | 1.19 (1.13-1.25)* | 1.17 (1.09-1.26)* |
| Sex | | | |
| Male | 37/163 (22.7%) | Reference | Reference |
| Female | 43/163 (26.4%) | 1.16 (0.79-1.70) | 1.08 (0.71-1.65) |
| Ethnicity | | | |
| Inuit | 40/242 (16.5%) | Reference | Reference |
| Non-Inuit | 27/56 (48.2%) | 2.92 (1.97-4.32)* | 1.52 (0.91-2.54) |
| Indication for TST | | | |
| Tuberculosis exposure | 34/173 (19.7%) | Reference | Reference |
| Employment screening | 18/43 (41.9%) | 2.13 (1.34-3.39)* | 1.63 (1.00-2.65)* |
| School screening | 1/14 (7.1%) | 0.36 (0.05-2.31) | 1.11 (0.16-7.58) |
| Self or physician referral | 22/76 (28.9%) | 1.47 (0.93-1.14) | 0.99 (0.56-1.74) |
| Year of assessment | | | |
| 2012 | 28/129 (21.7%) | Reference | - |
| 2013 | 12/72 (16.7%) | 0.78 (0.42-1.43) | - |
| 2014 | 23/71 (32.4%) | 1.47 (0.92-2.36) | - |
| 2015 | 14/37 (37.8%) | 1.74 (0.99-2.97) | - |
| 2016 | 3/12 (25.0%) | 1.15 (0.41-3.23) | - |

[1]Among the 328 patients offered treatment, complete data were available for 280. Data were missing regarding ethnicity in 29 (8.8%), year of assessment in 5 (1.5%), indication for TST in 20 (6.1%) and treatment initiation in 2 (0.6%).
[2]Model included age, sex, ethnicity and indication for TST.

Table 2.3 lists risk ratios for non-completion of LTBI treatment among those who started treatment. In both unadjusted and adjusted analyses, increased age (RR 1.10, 1.03-1.17; aRR 1.13, 1.03-1.17, per 5-year increase) was associated with increased non-completion of treatment.

This association remained in a sensitivity analysis defining treatment non-completion as receipt of <90% of treatment doses, (aRR 1.08, 1.01-1.15). However, when defining treatment non-completion as receipt of <100% of treatment doses, this association was not statistically significant (aRR 1.04, 0.98-1.10).

**Table 2.3.** Risk ratios for non-completion of treatment among patients starting treatment for latent tuberculosis infection. Risk ratios marked with an asterisk (*) are statistically significant. CI = confidence interval.

| Potential Risk factor | Non-completers/ category total (%) | Unadjusted risk ratio (95% CI) | Adjusted risk ratio[2] (95% CI), n = 208 patients[1] |
|---|---|---|---|
| Age, years (per 5-year increase) | - | 1.10 (1.03-1.17)* | 1.13 (1.04-1.22)* |
| Sex | | | |
| Male | 25/124 (20.2%) | Reference | Reference |
| Female | 23/110 (20.9%) | 1.04 (0.63-1.72) | 1.19 (0.71-1.99) |
| Ethnicity | | | |
| Inuit | 39/193 (20.2%) | Reference | Reference |
| Non-Inuit | 8/27 (29.6%) | 1.47 (0.77-2.80) | 0.84 (0.41-1.73) |
| Indication for TST | | | |
| Tuberculosis exposure | 29/133 (21.8%) | Reference | Reference |
| Employment screening | 8/23 (34.8%) | 1.60 (0.84-3.04) | 1.44 (0.75-2.75) |
| School screening | 1/14 (7.1%) | 0.33 (0.05-2.23) | 0.68 (0.10-4.57) |
| Self or physician referral | 9/51 (17.6%) | 0.81 (0.41-1.59) | 0.73 (0.38-1.43) |
| Year of assessment | | | |
| 2012 | 20/98 (20.4%) | Reference | - |
| 2013 | 7/46 (15.2%) | 0.75 (0.34-1.64) | - |
| 2014 | 12/56 (21.4%) | 1.05 (0.56-1.98) | - |
| 2015 | 6/21 (28.6%) | 1.40 (0.64-3.06) | - |
| 2016 | 2/9 (22.2%) | 1.09 (0.30-3.93) | - |

[1]Among the 246 patients who started treatment, complete data were available for 208. Data were missing regarding ethnicity in 15 (6.1%), year of assessment in 16 (6.5%), indication for TST in 14 (5.7%) and treatment completion in 12 (3.7%).
[2]Model included age, sex, ethnicity and indication for TST.

*Secondary analyses - TST positivity and failure to obtain a result*

Factors potentially associated with TST positivity are presented in Table 2.4. A reduced risk of having a positive result was associated with female sex (aRR 0.80, 0.68-0.95), non-Inuit ethnicity (aRR 0.68, 0.54-0.86) and obtaining a TST due to employment screening (aRR 0.58, 0.45-0.75), school screening (aRR 0.48, 0.33-0.70) or physician or self-referral (aRR 0.69, 0.57-0.83). TSTs performed in 2013, 2014 and 2015 were less likely to be positive than those performed in 2012 (Table 2.4).

**Table 2.4.** Risk ratios for TST positivity by demographic and clinical characteristic. Adjusted results are presented for complete case analysis (n= 1878 patients[1]) and analysis using combined results of 20 imputed datasets (n=2303 patients). Risk ratios marked with an asterisk (*) are statistically significant. CI = confidence interval.

| Potential Risk factor | Patients with positive TST/ category total (%) | Risk ratio from univariate models[2] (95% CI) | Adjusted risk ratio[3] (95% CI), complete case | Adjusted risk ratio[3] (95% CI), multiple imputation |
|---|---|---|---|---|
| Age, years (per 5-year increase) | - | 0.99 (0.97-1.02) | 1.00 (0.97-1.04) | 1.01 (0.98-1.04) |
| Sex | | | | |
| Male | 233/1065 (21.9%) | Reference | Reference | Reference |
| Female | 223/138 (18.0%) | 0.80 (0.68-0.95)* | 0.78 (0.65-0.94)* | 0.80 (0.68-0.95)* |
| Ethnicity | | | | |
| Inuit | 306/1220 (25.1%) | Reference | Reference | Reference |
| Non-Inuit | 90/658 (13.7%) | 0.58 (0.47-0.73)* | 0.64 (0.50-0.83)* | 0.68 (0.54-0.86)* |
| Indication for TST | | | | |
| Tuberculosis exposure | 199/606 (32.8%) | Reference | Reference | Reference |
| Employment screening | 67/506 (13.2%) | 0.45 (0.35-0.57)* | 0.59 (0.45-0.78)* | 0.58 (0.45-0.75)* |
| School screening | 34/297 (11.4%) | 0.40 (0.28-0.57)* | 0.36 (0.22-0.60)* | 0.48 (0.33-0.70)* |
| Self or physician referral | 124/746 (16.6%) | 0.62 (0.51-0.75)* | 0.67 (0.55-0.83)* | 0.69 (0.57-0.83)* |
| Year of TST | | | | |
| 2012 | 201/759 (26.5%) | Reference | Reference | Reference |
| 2013 | 101/547 (18.5%) | 0.64 (0.52-0.80)* | 0.64 (0.51-0.80)* | 0.65 (0.53-0.80)* |
| 2014 | 95/498 (19.1%) | 0.75 (0.61-0.92)* | 0.73 (0.59-0.92)* | 0.77 (0.63-0.94)* |
| 2015 | 45/425 (10.6%) | 0.39 (0.30-0.51)* | 0.41 (0.30-0.56)* | 0.45 (0.34-0.59)* |
| 2016 | 12/74 (16.2%) | 0.66 (0.42-1.05) | 0.75 (0.45-1.24) | 0.77 (0.50-1.20) |

[1]Data regarding ethnicity were missing for 472 TSTs (14.9%) in 425 patients (18.5%) and were estimated using multiple imputation. Data on indication were missing for 189 TSTs (6.0%) in 148 patients (6.4%).
[2]Univariate models adjusted for the correlation between multiple TSTs performed on the same individual using an exchangeable correlation matrix.
[3]Model included age, sex, ethnicity, indication for TST and year of TST and adjusted for multiple TSTs performed on the same individual using an exchangeable correlation matrix.

Associations with failure to obtain a TST result are presented in Table 2.5. Having a TST planted in 2015 (aRR1.52, 1.04-2.22, compared to 2012) and obtaining a TST due to physician or self-referral (aRR 1.64, 1.17-2.30, compared to following TB exposure) were associated with an increased risk of failure to obtain a TST result.

**Table 2.5.** Risk ratios for failure to obtain a TST result by demographic and clinical characteristic. Results are presented for complete case analysis (n= 1878 patients[1]) and analysis using combined results of 20 imputed datasets (n=2303 patients). RRs marked with an asterisk (*) are statistically significant. CI = confidence interval.

| Potential Risk factor | Patients with no TST results/ category total (%) | Risk ratio from univariate models[2] (95% CI) | Adjusted risk ratio[3] (95% CI), complete case | Adjusted risk ratio[3] (95% CI), multiple imputation |
|---|---|---|---|---|
| Age, years (per 5-year increase) | - | 0.98 (0.95-1.02) | - | - |
| Sex | | | | |
| Male | 69/1065 (6.5%) | Reference | - | - |
| Female | 61/1238 (4.9%) | 0.87 (0.67-1.13) | - | - |
| Ethnicity | | | | |
| Inuit | 48/1220 (3.9%) | Reference | Reference | Reference |
| Non-Inuit | 28/658 (4.3%) | 0.76 (0.54-1.06) | 0.68 (0.47-0.98)* | 0.79 (0.58-1.06) |
| Indication for TST | | | | |
| Tuberculosis exposure | 20/606 (3.3%) | Reference | Reference | Reference |
| Employment screening | 26/506 (5.1%) | 1.22 (0.82-1.83) | 1.08 (0.65-1.78) | 1.16 (0.77-1.76) |
| School screening | 25/297 (8.4%) | 1.52 (0.95-2.42) | 1.26 (0.68-2.29) | 1.32 (0.83-2.11) |
| Self or physician referral | 45/746 (6.0%) | 1.72 (1.22-2.42)* | 1.65 (1.12-2.44)* | 1.64 (1.17-2.30)* |

| | | | | |
|---|---|---|---|---|
| Year of TST | | | | |
| 2012 | 28/759 (3.7%) | Reference | Reference | Reference |
| 2013 | 29/547 (5.3%) | 1.27 (0.88-1.83) | 1.38 (0.88-2.16) | 1.25 (0.87-1.81) |
| 2014 | 31/498 (6.2%) | 1.18 (0.80-1.74) | 1.08 (0.65-1.79) | 1.16 (0.79-1.71) |
| 2015 | 36/425 (8.5%) | 1.52 (1.05-2.19)* | 1.19 (0.70-2.02) | 1.52 (1.04-2.22)* |
| 2016 | 6/74 (8.1%) | 1.76 (0.93-3.34) | 1.98 (0.94-4.15) | 1.71 (0.91-3.21) |

[1]Data regarding ethnicity were missing for 472 TSTs (14.9%) in 425 patients (18.5%) and were estimated using multiple imputation. Data on indication were missing for 189 TSTs (6.0%) in 148 patients (6.4%).
[2]Univariate models adjusted for the correlation between multiple TSTs performed on the same individual using an exchangeable correlation matrix.
[3]Model included ethnicity, indication for TST and year of TST and adjusted for the correlation between multiple TSTs performed on the same individual using an exchangeable correlation matrix.

**2.5 Discussion**

In this retrospective cohort study, 19.1% of referred patients were diagnosed with LTBI during a 51-month period in a routine screening program in a remote Canadian arctic region with a predominantly Inuit population. The cascade of care demonstrated high rates of LTBI treatment initiation (75%) and completion (76%). Older age and receiving a TST during employment screening were associated with non-initiation of treatment while only older age was associated with non-completion of treatment.

Despite the challenges of delivering care in a remote setting, the rate of treatment initiation in the present study was broadly similar to those from large North American studies while the rate of treatment completion was higher. In a 2003 study of over 13 000 LTBI cases across 29 American jurisdictions, 69.9% of all LTBI patients took at least one treatment dose while 63.7% of these patients completed ≥80% of prescribed doses [17]. In a 2010 study involving 32 clinics, 82.9% of LTBI patients offered treatment initiated it and 47.3% of initiators completed 100% of treatment doses within one year[18]. Finally, only 31.3% of patients prescribed LTBI treatment filled prescriptions for all doses in a 2013 analysis of health

administrative data in Quebec[19]. The higher rates of treatment completion in Iqaluit may be related to the use of directly observed therapy and a twice weekly regimen which requires fewer total doses than traditional daily therapy.

In our study, non-initiation of treatment among patients for whom treatment was recommended represented the largest source of loss of TST positive patients from the cascade of care. The increased risk of non-initiation among older patients and those identified via employment screening may reflect a less favourable balance of treatment risk and benefit among these groups. The risk of adverse effects, particularly hepatotoxicity, due to isoniazid increases with age[20,21] which may have led to reluctance among older patients to start treatment. Further, LTBI reactivation risk is highest within the first 2 years following infection[22]. Thus, those with positive testing in screening programs but with unknown or remote TB exposure may anticipate less benefit from treatment than those with a known, recent exposure. Of note, the Canadian TB standards do not include an age-based cut off above which LTBI treatment is not recommended but, instead, recommend weighing the risks and benefits of treatment on an individual basis[13].

To improve initiation rates, interventions targeting older individuals and those identified via employment screening should be considered. This could include the expanded use of less hepatotoxic regimens such as the 12- week regimen of rifapentine and isoniazid (3HP)[23] which could be particular beneficial for older patients. Further, providing videos of community elders discussing the nature and benefits of LTBI treatment to older patients may help to assist in establishing understanding and openness to considering such therapies potentially increasing initiation. Finally, providing education regarding the importance of LTBI testing and treatment to employees starting jobs which will require LTBI screening. This may help to shape opinions on these topics early, potentially increasing treatment initiation later when LTBI is diagnosed.

Non-completion of treatment represented the second largest loss of TST positive patients from the cascade of care and was associated with older age. As noted above, adverse effects related to isoniazid are more common among older patients[20,21] and may have contributed to reduced completion in this group. The use of 3HP has been associated with both increased completion rates and reduced hepatotoxicity compared to isoniazid alone[15,23]. As such, this alternative regimen may be of particular benefit in this setting with the potential to increase both initiation and completion.

Irregular appointment attendance was the most commonly listed reason for non-completion. The use of shorter treatment regimens has been associated with increased completion[15]. In the present study, the vast of majority of patients (94.3%) used a 9-month regimen. Thus, a change to a shorter regimen, which could include the 3HP regimen mentioned above, may improve appointment attendance by reducing the number of required clinic visits.

Physicians frequently cited discordance between TST and IGRA results as a reason for not offering LTBI treatment. The use of IGRA as a confirmatory test following TST is not endorsed by Canadian or World Health Organization guidelines[13,24]. However, this strategy is recommended for some low risk patients in American guidelines[25] and a recent trial found it to be non-inferior to TST alone[26], suggesting that it may be reasonable in some cases.

A moderate number of patients were lost to follow up before obtaining a TST result and many patients with positive TSTs did not attend physician appointments. Perhaps standardized videos emphasizing TB prevention presented by Inuit community members to Inuit patients could improve attendance.

By including the results of all TSTs performed in Iqaluit over the study period, our study provides a comprehensive overview of LTBI identification and management in the largest

community in Canada's highest TB incidence region. This represents the first comprehensive data published from the Inuit Nunangat. A further strength is that all LTBI treatment in Iqaluit is directly observed, minimizing misclassification error.

However, the study is limited by the relatively small number of variables on which data were obtained. This is in part related to this study's retrospective design which meant that only data listed in medical records could be extracted. As a result, the potential impact of important clinical and socioeconomic factors could neither be assessed nor adjusted for. Additionally, post-hoc statistical analysis regarding the listed reasons for treatment non-completion was considered but rejected because numbers in each category were low ($n \leq 16$ for all categories), leading to very limited statistical power. This prevented a more detailed analysis of potential causes of non-completion. While power could have been increased by increasing sample size, study dates were limited by the availability of data.

Given these limitations, richer detail may be better obtained in future through qualitative studies exploring patients' reasons for not initiating or completing treatment. The common themes could then provide targets for future interventions to improve treatment initiation and completion.

A further limitation is that IGRA results were not comprehensively captured. Although it would not have been in keeping with recommended local practices[12], it is possible that some patients were tested exclusively with IGRA and thus not included in our study.

An additional limitation is that it is possible that some patients underwent LTBI treatment prior to the study but were included following a repeat TST. This could have led to an underestimation of the treatment completion rate. However, we feel that this would not be not common. This is because it is not standard practice in Iqaluit to treat patients unless they have a

positive TST (no patient with a negative TST received LTBI therapy during the study period) and nearly all of those with repeat testing initially had negative TSTs (only 6 patients with a positive TST had a repeat test). Since TSTs relatively infrequently revert to negative after treatment[27], it is unlikely that many of those with repeat TSTs had undergone a previous course of treatment.

## 2.6 Conclusions

In our analysis of a routine TB program in the largest community of a remote Canadian arctic region over a 51-month period, 19.1% of referred patients were diagnosed with LTBI. Despite the challenges of delivering care in this setting, a similar rate of treatment initiation and higher rate of treatment completion were found compared to previous North American studies. Interventions targeting older individuals and those identified via employment screening may be considered to help to address the largest losses seen in the cascade of care.

## 2.7 Declarations

*Ethics approval and consent to participate*

A Nunavut Research Institute Research license was obtained for the study. Approval of the Ottawa Health Science Network Research Ethics Board was also obtained for the collection and analysis of the data. Permission to access data was provided by Iqaluit Public Health.

*Consent for publication*

Not applicable.

*Availability of data and material*

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available because they contain information that could compromise research participant privacy/consent.

*Competing interests*

AZ is an editorial board member for BMC Infectious Diseases. The authors declare that they have no other competing interests.

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*Authors' contributions*

CP, GGA, AZ, GGA, AZ, MP, PD, SF, JA, and DVD developed the study concept. CP, GGA, AZ, DVD and RM were involved in study design. MP, PD, SF and JA were involved in data collection. Data analysis was performed by CP with assistance from RM. The manuscript was written by CP with assistance from GGA, AZ and RM. The final manuscript was read and approved by all authors.

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## Chapter 3 - Bridging section

The first manuscript explored the LTBI cascade of care in Iqaluit and found that non-initiation and non-completion of treatment represented the largest sources of loss from the cascade of care, highlighting these steps as potential targets for interventions. Older individuals were also noted to be at increased risk of non-initiation and non-completion of treatment perhaps in part due to the higher risk of adverse events in this group[1,2].

3HP, a novel LTBI treatment regimen, is a shorter alternative to traditional LTBI treatment and been associated with higher treatment completion[3]. Further, it also has a lower risk of adverse events overall and hepatotoxicity in particular[4] which may make it more suitable for older individuals. A reduced number of doses would be particularly advantageous in Iqaluit because all LTBI treatment there is directly observed by health care personnel. This means that fewer doses may reduce the use of healthcare resources and lower costs, making 3HP a potentially appealing option for use in Iqaluit.

In the second manuscript, a cost-effectiveness analysis was performed examining using 3HP for LTBI treatment compared to the standard 9H regimen in Iqaluit.

For this cost effectiveness analysis, a Markov model was built to reflect the local practices for LTBI diagnosis and management which was described in Manuscript 1. Where possible, parameters for the model were based on an expanded version of the retrospective dataset used for the first manuscript. This expanded dataset covered the period from January 2010 and March 2016 (compared to January 2012 to March 2016 in the first manuscript). The first 2 years of this dataset were not used in Manuscript 1 because they did not include demographic information but such data were not required for the cost-effectiveness analysis. For parameters not available

from this dataset, values were obtained from a recent implementation trial of 3HP in Iqaluit, empirically collected costing data and from the published literature.

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**Chapter 4 - Manuscript 2**

# Cost-effectiveness of 3 months of weekly rifapentine and isoniazid in a Canadian arctic setting

C Pease, MD [1,2]; GG Alvarez, MD[1,2,3,6]; R Mallick, PhD[3]; M Patterson, MD[4]; S Finn, MA[4]; Y Habis, MD[5,6]; K Schwartzman, MD[5,6]; E Kilabuk, MD[1], S Mulpuru, MD[1,3], A Zwerling, PhD[2,6]

1=Ottawa Hospital, Department of Medicine, Ottawa, Canada
2=University of Ottawa, School of Epidemiology and Public Health, Ottawa, Canada
3=Ottawa Hospital Research Institute, Ottawa, Canada
4=Ministry of Health, Government of Nunavut, Iqaluit, Canada
5=Montreal Chest Institute, Montreal, Canada
6=McGill International Tuberculosis Centre, Montreal, Canada

**Correspondence:**

C. Pease
The Ottawa Hospital General Campus
501 Smyth Road
Ottawa ON, Canada
K1H 8L6
cpease@toh.ca

**Conflicts of Interest:**

The authors have no conflicts of interest to declare.

**Funding Information:**

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## 4.1 Abstract

*Background*

The incidence of tuberculosis (TB) among Inuit is over 400 times that of Canadian-born non-indigenous people. Novel interventions, such as shortened preventive treatment are urgently needed.

*Methods*

To assess the cost-effectiveness of a novel shortened regimen for latent TB infection (LTBI) in Iqaluit, Nunavut, a Markov model was developed reflecting local practices for LTBI treatment. The primary outcome was the incremental cost-effectiveness ratio measured in 2019 United States dollars/quality adjusted life year (QALYs) among persons offered treatment for LTBI comparing 3 months of weekly rifapentine and isoniazid (3HP) to the current standard of care: 9 months of twice weekly isoniazid (9H). Results were projected over a 30-year time horizon using model parameters derived from historical programmatic data on 9H, a local implementation study of 3HP and published literature. Costs were estimated from the perspective of the Nunavut health care system and were obtained primarily from local, empirically collected data.

*Results*

The 3HP regimen was dominant over 9H: costs were lower ($628 vs $924 per person) and health outcomes slightly improved (20.14 vs 20.13 QALYs per person). 3HP treatment also resulted in fewer TB cases (27.89 vs 30.16 per 1000 persons) and TB deaths (2.29 vs 2.48 per 1000 persons). 3HP completion, initiation and risk of fatal adverse events were the most important drivers of cost-effectiveness.

*Interpretation*

In a remote Canadian arctic setting, using 3HP instead of 9H for LTBI treatment may result in cost savings and similar or improved health outcomes.

## 4.2 Introduction

Canadian Inuit face high rates of tuberculosis (TB) despite Canada's low overall incidence of TB disease. In 2017, the incidence of active TB among Inuit was 205.8 per 100,000 compared to only 4.9 per 100,000 among Canadian-born non-indigenous people[1].

The Government of Canada and Inuit Tapariit Kanatami (Inuit National Organization) announced goals to eliminate TB across Inuit Nunangat (Inuit homeland) by 2030[2]. However, challenges persist since Inuit in Arctic communities face geographic isolation and difficult climatic conditions resulting in high costs and limited availability of human and material resources[3].

Treatment of latent tuberculosis infection (LTBI) is critical to achieving TB elimination[4,5] and reduces future risk of developing active TB by over 90%[6] but is hindered by lengthy treatment, traditionally involving 9 months of isoniazid (9H). Recently, regimens with a shorter duration have been developed, including once weekly rifapentine and isoniazid for 12 weeks (3HP). In a large randomized controlled trial and subsequent meta-analysis, 3HP demonstrated comparable efficacy, higher completion and similar safety profiles to 9H[7–9]. Although not approved in Canada for general use, rifapentine can be obtained for LTBI treatment under urgent public health need criteria[10].

Our group recently conducted an implementation study of 3HP for LTBI treatment in Iqaluit, Nunavut. We demonstrated the feasibility of implementing 3HP and found increased (non-statistically significant) completion compared with historical 9H data[11].

While studies have found 3HP to be cost effective in American, Taiwanese and other settings [12–16], no data on 3HP cost-effectiveness in Canadian or Arctic settings exist. Unique challenges delivering healthcare in this remote region make generalizations from other settings

difficult. An understanding of the cost-effectiveness of 3HP in Nunavut would provide critical evidence to support decision makers across the Inuit Nunangat in allocating health care resources efficiently.

The objective of this work was to assess the cost-effectiveness of 3HP for the treatment of LTBI in comparison to 9H in Iqaluit, Nunavut over a 30-year time horizon.

## 4.3 Methods

*Study Setting*

Iqaluit is the capital of Nunavut (7740 residents, 55.1% of whom identify as Inuit[17]) and its largest community. Throughout most of the year, access is only by air with sea access possible during the brief summer. Between 2010 and 2016, 178 cases of active TB were reported in Iqaluit (median: 26/year, range: 9-50)[18] representing 36% of all cases in Nunavut[18].

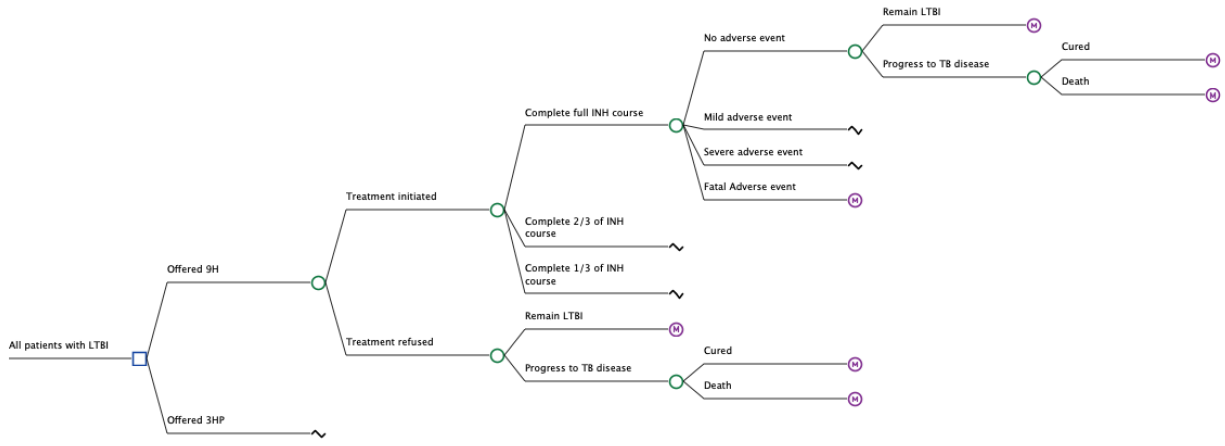
Testing and treatment for LTBI and active TB in Iqaluit are coordinated by Iqaluit Public Health. Direct costs of all TB testing and treatment are covered by the healthcare system. Secondary level care is available in Iqaluit but patients requiring tertiary care require transport out of the territory, typically to Ottawa. This cost is also covered by the Nunavut healthcare system. Testing for LTBI is performed for contacts of active TB cases, employment screening (e.g. healthcare workers) and in other high risk individuals[19]. All persons with a positive tuberculin skin test or IGRA are assessed by a physician and may be offered LTBI treatment. Standard LTBI treatment has been 9 months of twice weekly isoniazid via directly-observed therapy(DOT)[19].

*Markov Model Overview*

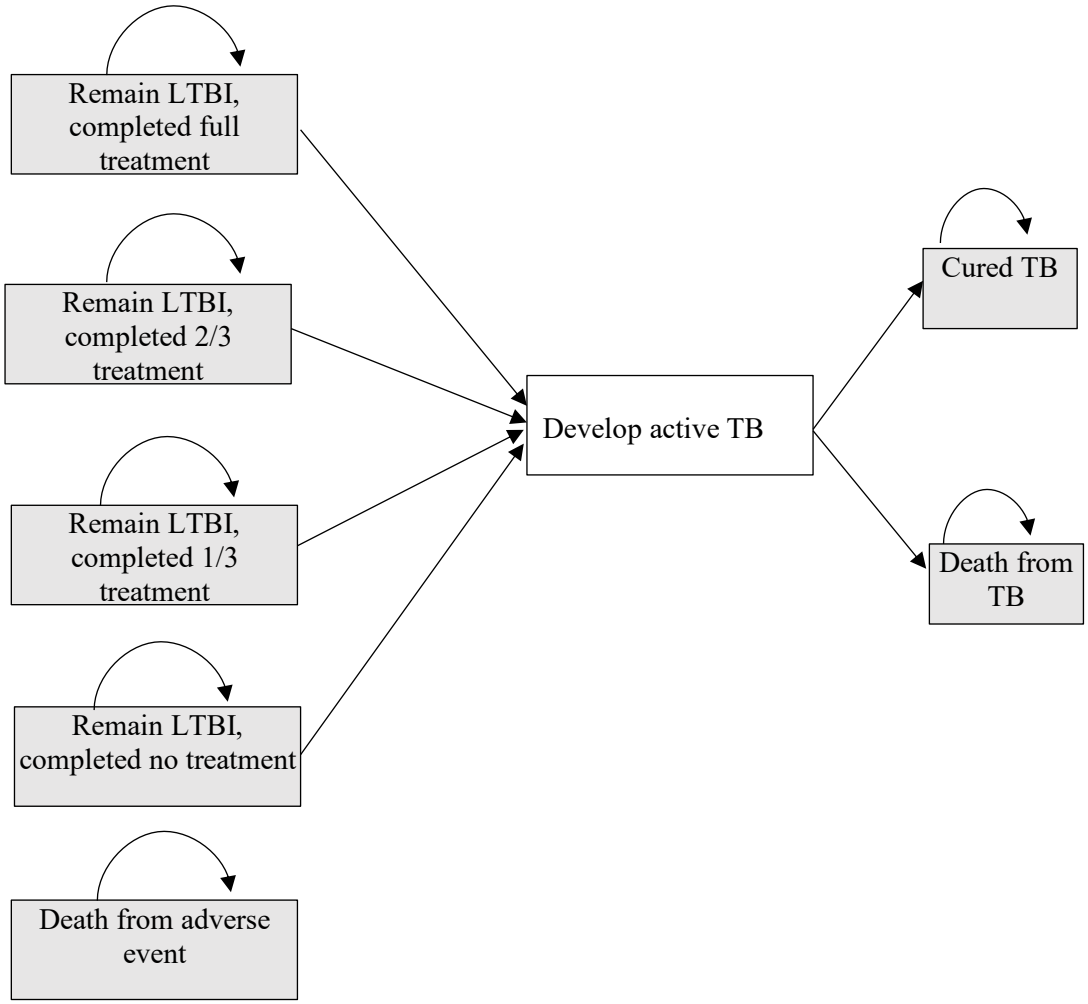
A Markov model was developed reflecting local practices for LTBI treatment using TreeAge Pro (version 2019; TreeAge Software Inc., Williamstown, MA, USA). This was used to assess the cost-effectiveness of LTBI treatment with 3HP compared to 9H treatment. The primary outcome was the incremental cost-effectiveness ratio (ICER). The primary health outcome was quality-adjusted life years (QALYs). Costs were calculated in 2019 United States dollars from the perspective of the Nunavut healthcare system. Secondary health outcomes included estimated TB cases and TB deaths averted using 3HP vs 9H. A simplified schematic of the model structure is shown in Figure 4.1.

**Figure 4.1.** Simplified schematics of model structure. 9H = 9 months of twice weekly isoniazid; 3HP = 12 weeks of once weekly rifapentine and isoniazid; LTBI = latent tuberculosis infection; TB = tuberculosis.

a) Model decision structure. Two strategies were compared: treating LTBI with 9H vs 3HP. Schematically these strategies are separated by a square representing a decision node. Green circles represent chance nodes where patients may experience one of several possible events shown on subsequent lines. The probabilities of developing each event are listed in Table 4.1. Jagged lines represent model structure omitted for simplicity. In all cases, this omitted structure parallels that shown. The "M" symbol represents transition to the Markov portion of the model (shown in Figure 4.1b).



b) Schematic representation of Markov states. Patients enter this portion of the model in a Markov state (grey boxes) and may remain in that state (curved arrows) or, in some cases, transition to a different one (straight arrows). Patients in all states apart from cured TB disease and death have the possibility to develop active TB with the probability of doing so dependent on the duration of LTBI treatment completed. If active TB develops, it is either cured or results in death within that cycle.




The target model population included all persons with LTBI who were offered treatment. A mean age of 25 was assumed based on local historical data[20]. A cohort of LTBI patients offered treatment during the first modelled year were followed over a 30-year time horizon to allow sufficient time for reactivation of LTBI and to approximate the average lifespan among

Inuit. Markov cycle length was one year with half cycle correction applied. Future costs and effectiveness were discounted at a rate of 3% [21,22].

In both 3HP and 9H arms, LTBI patients could initiate or decline treatment. Declining treatment resulted in a period of surveillance involving biannual clinical assessments, chest x-rays and sputum testing for 2 years among those ≥13 years and quarterly clinical assessments without additional investigations among those <13 years[19]. If initiated, treatment could be partially completed (<1/3, 1/3 or 2/3 of complete treatment duration) or fully completed (12-week duration for 3HP, 9-month duration for 9H). Patients in both arms could experience adverse events (AEs) of varying severity (none, mild, severe, fatal) which might or might not result in stopping treatment. The probability of active TB disease varied with LTBI treatment duration. All active TB was assumed to be diagnosed and treated, and patients could either be cured or die.

*Key Model Assumptions*

The probability of treatment initiation, fatal AEs and reduction in LTBI reactivation risk (based on a large non-inferiority trial[7]) were assumed to be equal between 3HP and 9H in base case analysis but all variables were varied independently in sensitivity analyses. No fatal AEs related to 3HP have been reported among several randomized trials [23] yet long term data comparable to 9H are not available, therefore we assumed equal fatal toxicity risk between regimens, consistent with previous cost-effectiveness studies[13,16,24] .

The risk of AEs and the reduction in LTBI reactivation risk were assumed to be directly proportional to the treatment duration with no risk of AEs or reduction in reactivation risk among those completing less than 1/3 of treatment.

*Definitions*

Treatment initiation was defined as taking ≥1 dose of medication. Mild AEs included grade 1-2 events and severe AEs included grade 3-4 events as defined by the Common Terminology Criteria for Adverse Events[25].

*Epidemiologic parameters*

Model epidemiologic parameters are provided in Table 4.1. Where possible, model parameters were based on historical data from Iqaluit and from a recent 3HP implementation study done in Iqaluit[11,18].

**Table 4.1.** Epidemiologic parameter estimates. 9H = 9 months of twice weekly isoniazid; 3HP = 12 weeks of once weekly rifapentine and isoniazid.

| Parameter | Base case estimate | Univariable analysis range | Reference(s) |
|---|---|---|---|
| *Probability of treatment initiation* | | | [11,20,26] |
| 9H | 0.79 | 0.72-0.80 | |
| 3HP | 0.79[1] | 0.72-0.80[i] | |
| *Probability of treatment completion* | | | |
| *9H* | | | [20] |
| Probability of stopping isoniazid before 3 months among all those who initiated treatment | 0.103 | 0.077-1.37 | |
| Probability of stopping isoniazid at 3 months among all those who completed at least 3 months of treatment | 0.088 | 0.063-0.122 | |
| Probability of stopping isoniazid at 6 months among all those who completed at least 6 months of treatment | 0.078 | 0.054-0.112 | |
| Probability of completing 9 months of treatment among all persons who initiated treatment[ii] | 0.750 | | |
| *3HP* | | | [11] |
| Probability of stopping 3HP before 4 weeks among all those who initiated treatment | 0.082 | 0.038-0.168 | |
| Probability of stopping 3HP at 4 weeks among all those who completed at least 4 weeks of treatment | 0.075 | 0.032-0.163 | |
| Probability of stopping 3HP at 8 weeks among all those who completed at least 8 weeks of treatment | 0.032 | 0.009-0.110 | |

| | | | | |
|---|---|---|---|---|
| Probability of completing 12 weeks of treatment among all persons who initiated treatment[ii] | | 0.820 | | |
| *Mild adverse event*[iii] | | | | 7 |
| | 9H | 0.091 | 0.082-0.100 | |
| | 3HP | 0.077 | 0.069-0.085 | |
| *Severe adverse events*[iii] | | | | 7 |
| | 9H | 0.065 | 0.058-0.073 | |
| | 3HP | 0.057 | 0.050-0.064 | |
| *Fatal adverse events*[iii] | | | | 6,27 |
| | 9H | 0.00014 | 0.00004-0.00057 | |
| | 3HP | 0.00014[1] | 0.00004-0.00057[1] | |
| *Risk of reactivation of latent tuberculosis infection* | | | | 16,28,29 |
| | First 2 years | 0.025 | 0.01-0.05 | |
| | Subsequent years | 0.001 | 0-0.0016 | |
| *Reduction in risk of tuberculosis disease*[iii] | | | | 6,30 |
| | 9H | 0.93 | - | |
| | 3HP | 0.93[1] | - | |
| *Risk of death following tuberculosis disease diagnosis* | | 0.082 | 0.070-0.094 | 31–39 |
| *Health Utilities (quality adjusted life years)* | | | | |
| | LTBI without treatment | 1 | - | Assumed |
| | LTBI treatment | 1 | 0.99-1 | 40 |
| | Mild adverse event | 1 | 0.99-1 | 41 |
| | Severe adverse event | 0.75 | 0.65-0.85 | 24 |
| | Tuberculosis disease | 0.88 | 0.86-0.90 | 40 |
| | Death | 0 | - | Assumed |

[i] Assumed identical values for 9H and 3HP in base case analysis
[ii] Overall completion among initiators given for reference. Only the component probabilities provide were used in the model.
[iii] Values for partially completed regimens were interpolated assuming a linear relationship between duration of treatment and parameter values

*Cost parameters*

The cost parameters were derived from local unit costs with the exception of TB treatment cost which was derived from total TB treatment costs in Iqaluit divided by the number of persons treated (Table 4.2). Estimates of personnel time were determined by direct onsite observation of TB activities supplemented by interviews with local personnel. Local unit costs of medications, consumables, and salaries were obtained from Iqaluit Public Health and the Government of Nunavut Department of Health. Local unit costs of diagnostics, hospitalization and medical transport were obtained from published literature[42]. All costs were adjusted to 2019 Canadian dollars using the Canadian Consumer Price Index[43] then converted to United States dollars using the average 2019 exchange rate[44].

**Table 4.2.** Cost parameter estimates. Costs are in 2019 United States dollars. 9H = 9 months of twice weekly isoniazid; 3HP = 12 weeks of once weekly rifapentine and isoniazid; DOT = directly observed therapy.

| Parameter | Base case estimate | Univariable analysis range | Reference(s) |
|---|---|---|---|
| *Complete 9H treatment* | $806 | $489-$1,207 | [42,45,46] |
| Drug costs | $5 | | |
| DOT costs | $500 | | |
| Other clinician costs | $173 | | |
| Chest x-ray | $55 | | |
| Sputum testing | $64 | | |
| Liver function testing | $9 | | |
| *Partial isoniazid treatment* | | | |
| 3 months | $388 | $271-$543 | [42,45,46] |
| 6 months | $597 | $389-$874 | [42,45,46] |
| *Complete 3HP treatment* | $383 | $296-$492 | [42,45,46] |
| Drug costs | $87 | | |
| DOT costs | $77 | | |
| Other clinician costs | $96 | | |

| | | | |
|---|---|---|---|
| Chest x-ray | $55 | | |
| Sputum testing | $64 | | |
| Liver function testing | $5 | | |
| *Partial isoniazid + rifapentine treatment* | | | |
| 4 weeks | $126 | $103-$159 | [42,45,46] |
| 8 weeks | $194 | $151-$253 | [42,45,46] |
| *Mild adverse event* | $13 | $0-$197 | [13,47] |
| Nursing costs | $13 | | |
| *Severe adverse event* | $2,584 | $1,379-$6,614 | [13,42,45,46] |
| Hospitalization in Iqaluit x 1.2 days[i] | $2,411 | | |
| Outpatient clinician assessment | $156 | | |
| Laboratory monitoring | $17 | | |
| *Fatal adverse events* | $65,737 | $41,365-$75,725 | [42,45,48] |
| Hospitalization in Iqaluit x 7 days | $14,059 | | |
| Medical evacuation | $19,951 | | |
| Hospitalization in Ottawa x 7 days | $7,366 | | |
| Intensive care unit in Ottawa x 7 days | $24,359 | | |
| *Cured tuberculosis disease* | $1,517 | $1,214-$28,841 | [42,45] |
| *Fatal tuberculosis disease* | $66,495 | $41,365-$76,635 | [42,45,48] |
| Tuberculosis treatment costs x 3 months | $759 | | |
| Hospitalization in Iqaluit x 7 days | $14,059 | | |
| Medical evacuation | $19,952 | | |
| Hospitalization in Ottawa x 7 days | $7,366 | | |
| Intensive care unit in Ottawa x 7 days | $24,359 | | |
| *Surveillance for those < 13 years old* | $54 | $50-$65 | [45,46] |
| Nursing costs | $54 | | |
| *Surveillance for those ≥ 13 years old* | $531 | $431-$638 | [45,46] |
| Nursing costs | $54 | | |
| Chest x-ray x 4 | $220 | | |
| Sputum testing x 4 | $257 | | |

[i]The number of days of hospitalization was used assuming that, as in Sterling et al 2011, 17% of these patients would have a grade 4 adverse event and all those with a grade 4 adverse would require 7 days of hospitalization.

*Sensitivity and scenario analyses.*

One-way (univariable) sensitivity analyses were conducted across all model parameters, time horizon (10-50 years) and discounting rate (0-5%). Probabilistic sensitivity analysis was also performed by specifying underlying distributions for model parameters and using Monte Carlo simulation with 10,000 iterations to generate uncertainty ranges around model outputs (95% UR). Probability distributions for model parameters are provided in Tables D1 and D2 (Appendix D). Finally, scenario analyses were performed to more comprehensively explore the impact of select model parameters. Scenario analyses included variation in the probabilities of initiation and overall completion of 3HP +/- 10% vs 9H, increasing risk of 3HP severe AEs to twice that of 9H and varying annual LTBI reactivation from 0.1% to 10% for the first two years. The impact on cost of self-administration of both regimens was also assessed.

*Budget impact analysis*

A budget impact analysis was performed over 1-, 2- and 5-year horizons estimating the total difference in healthcare cost of 3HP compared to 9H. Average per patient incremental costs for the relevant year(s) were determined from the model and multiplied by the average annual number of patients initiating LTBI treatment in Iqaluit between 2010-2016 which was 69[20].

**4.4 Results**

3HP dominated 9H with cost savings (mean $628 vs $924 per person) and slight improvement in health outcome (mean 20.14 vs 20.13 QALYs per person) (Table 4.3). This resulted in a negative ICER.

**Table 4.3.** Base case cost-effectiveness model outcomes. Costs are in 2019 United States dollars. 9H = 9 months of twice weekly isoniazid; 3HP = 12 weeks of once weekly rifapentine and isoniazid; QALY = quality-adjusted life years.

| | 9H | 3HP |
|---|---|---|
| *Clinical Outcomes* | | |
| Overall effectiveness (QALYs) | 20.13 | 20.14 |
| TB cases, per 1000 LTBI cases | 30.16 | 27.89 |
| TB deaths, per 1000 LTBI cases | 2.48 | 2.29 |
| *Cost Outcomes (2019 United States $)* | | |
| Total cost | $924 | $628 |
| Costs of latent TB infection treatment | $535 | $260 |
| Costs of adverse events | $116 | $108 |
| Costs of TB disease treatment | $182 | $168 |
| Surveillance costs | $92 | $92 |

Cost savings were driven by fewer visits required to deliver 3HP (12 doses) compared to 9H (78 doses). Cost-savings also resulted from fewer AEs with 3HP and fewer TB cases (27.89 vs 30.16 per 1000 LTBI cases) due to its higher probability of completion (Table 4.3). The improvement in health outcomes was driven primarily by higher completion for 3HP, resulting in fewer TB cases (noted above) and TB deaths (2.29 vs 2.48 per 1000 LTBI) in the 3HP arm.

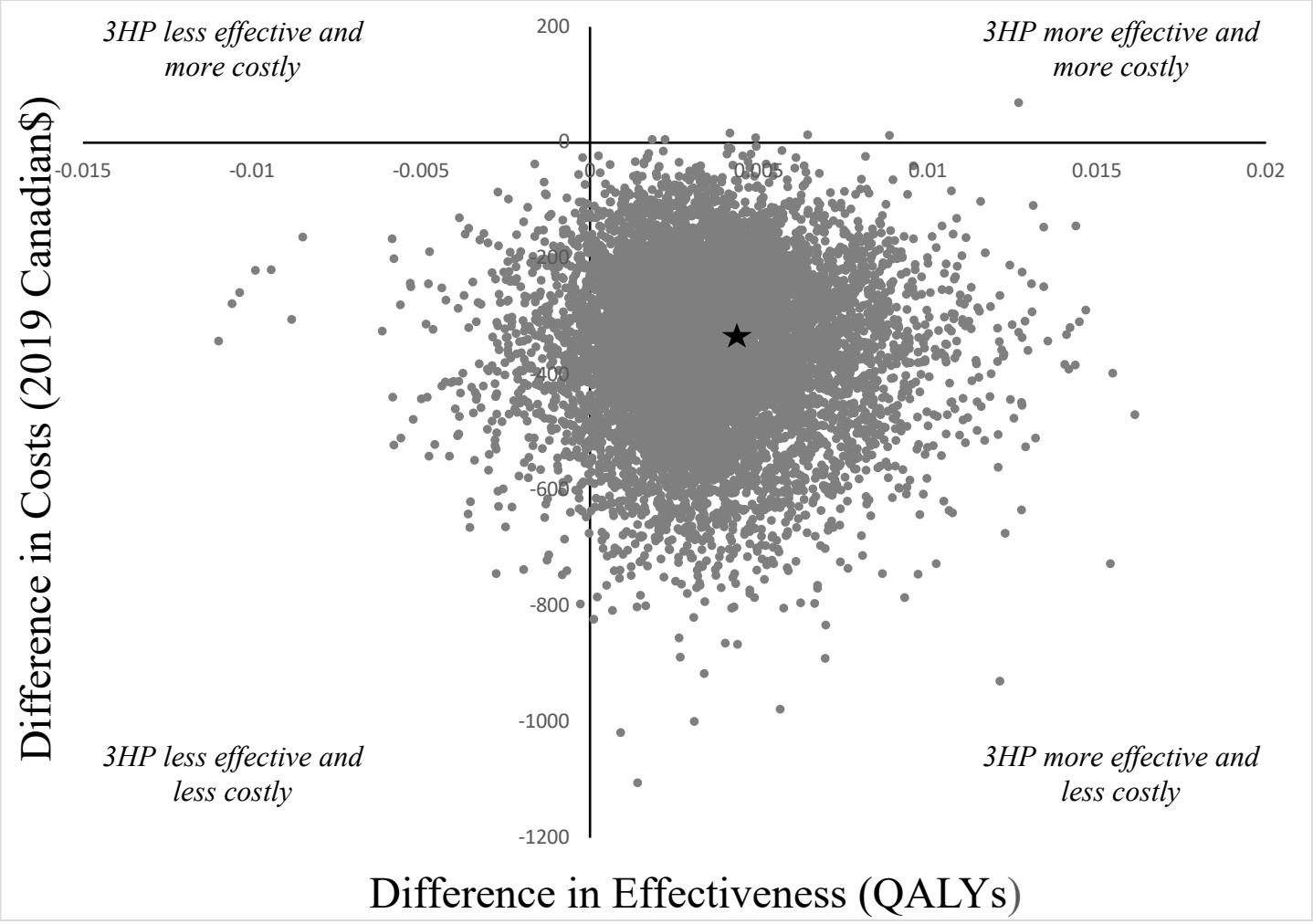
In budget impact analysis, 3HP resulted in cumulative savings of $19,888 over one year, $40,122 over 2 years and $100,904 over 5 years compared with 9H, assuming a constant annual probability of LTBI treatment initiation.

*Sensitivity and Scenario analyses*

In one-way sensitivity analyses, the model was most sensitive to variables related to 3HP completion and initiation and fatal AEs during 3HP treatment. These were the only variables with the potential to result in worsened health outcomes in the 3HP arm compared to 9H (Appendix D, Figures D1& D2). 3HP remained dominant despite varying discounting rate (0-5% per year), time horizon (10 - 50 years) and all other variables (Appendix D, Tables D3 and D4).

In the probabilistic sensitivity analysis, the probability of 3HP being dominant over 9H was 94.1% (Figure 4.2). The median cost per LTBI case was $614 (95% UR: $487-$1,005) for 3HP vs $888 (95% UR: $662-$1,335) for 9H and the median QALYs per LTBI case were 20.13 (20.10-20.16) for 3HP vs 20.13 (20.09-20.15) for 9H. The probability of 3HP being cost saving compared to 9H was 99.9% and the probability of 3HP being more effective than 9H was 94.2%.

**Figure 4.2.** Cost-effectiveness plane showing the differences in costs and quality-adjusted life years (QALYs) of using 3HP compared to using 9H from 10,000 simulations. The star represents the base case scenario. 3HP = weekly rifapentine and isoniazid for 12 weeks; 9H = 9 months of twice weekly isoniazid.

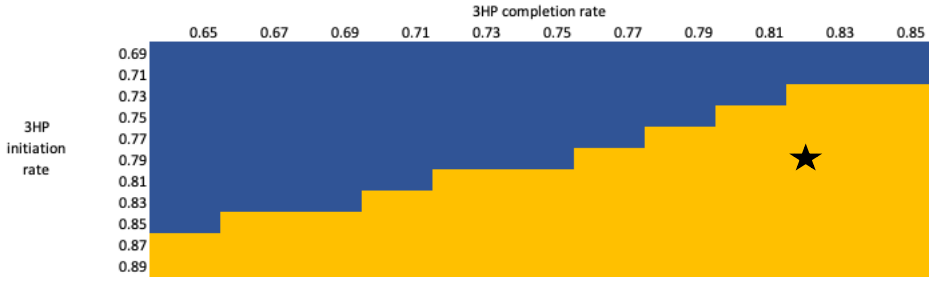



*Scenario analyses*

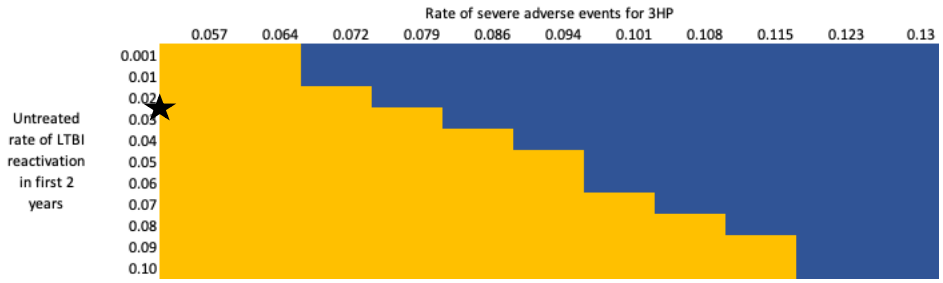
When 3HP initiation and completion probabilities were varied +/- 10%, 3HP remained cost saving (Appendix D, Table D5a) but 3HP was no longer dominant over 9H when the 3HP initiation probability was <73.4% (vs 79.0% for 9H) and when the 3HP completion probability was <74.4% (vs 75% for 9H and 82.0% in the base case analysis) due to worsened health outcome(Figure 4.3a). If the severe AE probability for 3HP increased to >7.4% (5.6% in base case analysis), 3HP also resulted in worsened health outcome compared to 9H (Figure 4.3b) but remained cost saving (Appendix D, Table D5b). 3HP remained dominant over 9H across a broad range of LTBI reactivation probabilities (Figure 4.3b and 4.3c; Appendix D, Tables D5b and c). If both 3HP and 9H were self-administered, 3HP remained dominant (Appendix D, Table D6). Cost savings were reduced but 9H cost remained above 3HP because higher medication cost was offset by additional clinical visits during the longer 9H regimen and slightly higher costs from more active TB cases and AEs in the 9H arm.

**Figure 4.3.** Influence on the relative effectiveness of 3HP vs 9H of variation in a variety of parameters to extreme values. Blue areas indicate that 3HP is less effective than 9H while orange areas indicate that 3HP is more effective than 9H. The stars represent the values in the base case. 3HP = weekly rifapentine and isoniazid for 12 weeks; 9H = 9 months of twice weekly isoniazid; LTBI = latent tuberculosis infection.

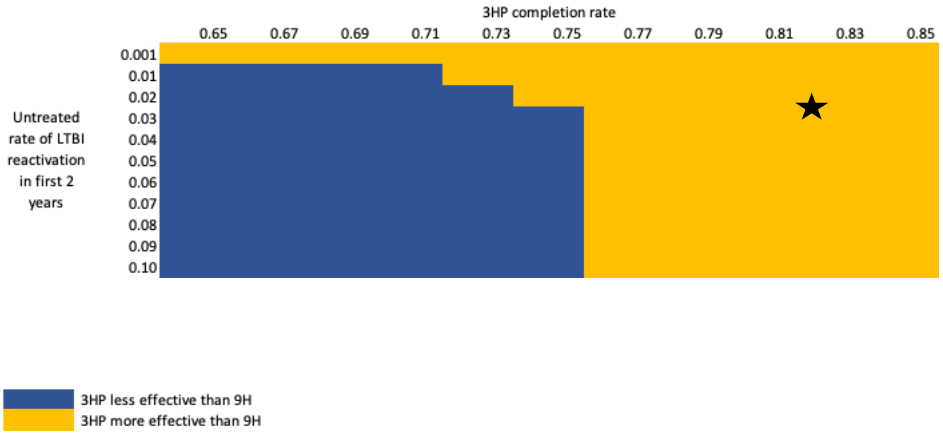
a) Impact of variation in 3HP initiation and 3HP completion probabilities to 10% above and below those of 9H.




b) Impact of variation in LTBI reactivation in the first 2 years of the model and the probability of severe adverse events while taking 3HP




c) Impact of variation in LTBI reactivation in the first 2 years of the model and 3HP completion.




## 4.5 Discussion

Using a Markov model of LTBI treatment in a Canadian Arctic setting, our study suggests that the 3HP regimen will be superior to 9H (both cost saving and slightly more effective) across a range of assumptions. Both TB cases and TB deaths were projected to be lower with the use of this regimen.

The finding of cost savings with the 3HP regimen was very robust across a broad range of sensitivity and scenario analyses. As such, it is highly likely that implementation of 3HP would result in reduced costs for the Iqaluit TB program and likely other similar settings as well. In budget impact analysis, the total savings were estimated at over $19,000 annually assuming that LTBI diagnosis and treatment continue at a similar pace. The primary driver of 3HP cost-

savings was the lower number of DOT visits due to shorter treatment duration. Additional savings accrued from fewer AEs and fewer active TB cases in 3HP arm meaning that modest cost savings were maintained even when both regimens were self-administered.

While 3HP results in a slightly improved health outcome compared with 9H in most sensitivity analyses, extreme values of 3 key parameters (3HP initiation <73.4%, 3HP completion <74.4% and 3HP fatal AE probability >0.00042) resulted in 3HP producing a worsened health outcome compared with 9H. A substantial decrease in 3HP initiation compared with 9H was modelled to evaluate the robustness of our findings but is unlikely to occur: the 3HP initiation probability was similar to the historical one during a recent community rollout in Nunavut (80% with 3HP vs 79% historically)[11] and a recent study in an urban setting found a stable initiation probability following the introduction of 3HP (78% with 3HP vs 79% historically)[26].

Another key influence on the relative effectiveness of the two regimens was the probability of 3HP completion. When 3HP completion dropped below 74.4% (vs 82% in base case), 3HP resulted in a worsened health outcome compared with 9H. Previous studies have demonstrated consistently higher completion for 3HP than 9H suggesting such a scenario is unlikely[7,8]. However, unlike many settings, 9H is delivered via DOT in Iqaluit resulting in higher 9H completion compared with other settings[18]. Despite this, within the recent 3HP implementation trial in Iqaluit, there was a non-statistically significant trend to improved completion among those taking 3HP vs historical data (82% vs 73%). Further, even if 3HP completion was modestly overestimated in our model, 3HP would remain cost saving.

As mentioned, given the absence of reported fatal AEs associated with 3HP[23], the assumption of equal risk of fatal toxicity between 3HP and 9H is likely quite conservative. In

sensitivity analysis, only when risk of fatal AEs associated with 3HP was 3.5 times higher than 9H (0.00042 vs 0.00012) was 3HP associated with a worse health outcome compared with 9H. Such an increase seems unlikely.

The most recent Canadian Tuberculosis Standards note concern regarding potential AEs associated with 3HP[49]. In scenario analysis, the risk of severe AEs related to 3HP would need to rise to 7.4% for 3HP to be associated with a worse health outcome than 9H. This is substantially higher than the 5.6% observed in a large clinical trial of 3HP[7].

This study has a number of strengths. First, it is the first study of cost effectiveness of 3HP in Canada and the first in an Arctic region. Second, local data were used to obtain most key costs and epidemiologic parameters.

Study limitations include an inability to account for TB transmission which would have greatly increased model complexity. However, including transmission would likely have favoured 3HP since this strategy resulted in fewer active TB cases and thus 3HP would be expected to remain the dominant strategy. Second, societal costs including costs borne by patients were not included. Inclusion would again likely favour 3HP given its shorter duration and lower burden of AEs compared to 9H. Third, the costs associated with the implementation and scale-up of 3HP such as additional staff training were not included. Finally, reinfection with TB was not modelled but would be unlikely to substantially change the relative standing of 3HP and 9H since reinfection risk is not related to previous treatment regimen.

### 4.6 Interpretation

The findings of the present study suggest that in a remote Canadian arctic setting, 3HP is likely to offer cost savings and slightly improved health outcomes compared to 9H driven by

higher anticipated treatment completion. This would support the implementation of 3HP as standard therapy for LTBI treatment in Iqaluit and other similar settings.

## 4.7 Acknowledgements

*Author contributions*

GGA, MP, SF and AZ conceived of the study. The study was designed by AZ, CP and GGA. SF and EK collected data. Data analysis was performed by CP with assistance from AZ. CP, AZ, GGA interpreted the data with assistance from KS, RM, SM, MP, SF, EK and YH. CP drafted the initial manuscript which was revised and approved by all authors. CP takes responsibility for the integrity of the data and accuracy of the data analysis.

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The authors have no financial disclosures or conflicts of interest to declare.

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## Chapter 5 - Overall Conclusions and Knowledge Translation

This project consisted of two parts: an examination of the LTBI cascade of care in Iqaluit and a cost-effectiveness analysis examining the introduction of the novel 3HP regimen for treating LTBI in this setting. In the first part, the treatment initiation in Iqlauit was found to be similar to and treatment completion higher than previous North American studies. Despite this, treatment initiation and completion were the steps with the largest numbers of TST positive patients lost from the LTBI cascade of care. Older patients and those identified through employment screening were at particular risk for treatment non-initiation and education interventions targeting these groups for educational interventions may be beneficial in improving the proportion of patients initiating and ultimately completing treatment. In addition, shorter, less toxic treatment regimens such as 3HP may also improve treatment completion since patients may be more willing to initiate a treatment of 3 months vs 9 months.

In the second manuscript which assessed cost-effectiveness of 3HP compared with 9H in Iqaluit, 3HP was found to be dominant over 9H meaning that 3HP was both cost-saving and slightly more effective. The latter finding was driven by a higher completion probability for 3HP as was observed in a recently completed 3HP trial conducted in Iqaluit. These findings support the introduction of the 3HP regimen as standard treatment for LTBI in Iqaluit.

The results of our research have been presented to local stakeholders including our local research partners, Iqaluit Public Health, the Nunavut Ministry of Health and Nunavut Tunngavik Incorporated (Nunavut Inuit organization) through a series of telephone and in-person meetings. The 3HP regimen has now been adopted as standard therapy for LTBI in Nunavut. However, interventions targeting key steps in the LTBI cascade have not been implemented and represent a

potential opportunity to improve the proportion of LTBI patients initiating and thus completing treatment.

There remain a number of potential avenues for further research to better understand the LTBI cascade of care and improve treatment initiation and completion. In particular, detailed reasons for why some patients did not progress through the cascade could not be obtained from the data used in our study. A better understanding of this could be obtained from qualitative examination of reasons for declining to pursue assessment and/or treatment for LTBI. Further, additional evaluation of the cost-effectiveness of 3HP in other settings such as remote communities would be worthwhile. Finally, since 3HP has now been implemented as standard of care in Nunavut, ongoing evaluation and monitoring of 3HP initiation and completion is warranted to determine whether the estimated values used in our model reflect real world practice.

## Appendix A - Supplementary Methods for Manuscript 1

*Variable Definitions*

Tuberculin skin tests (TSTs) were defined as positive based on the assessment of Iqaluit Public Health. Territorial guidance during the study period stated that TSTs should be interpreted based on the Canadian Tuberculosis Standards, 5th edition(1). Briefly, these standards recommend that a TST be considered positive if the induration size is ≥5mm in those with a close infectious contact, fibronodular disease on chest x-ray or HIV; and ≥10mm in all others(2).

Treatment non-initiation was defined failure to receive at least one dose of a drug for LTBI. Treatment non-completion was defined as taking <80% of prescribed doses within 12 months of treatment initiation.

*Model building*

The general approach to building regression models involved the inclusion of certain variables based on their clinical importance and additional variables being included or excluded based on the results of descriptive and univariate analyses as well as model fit statistics.

*Primary Analysis*

For the primary analyses, the indication for performing TST was included in final models because treatment indication has been a strong predictor of treatment initiation (3,4) and treatment completion(3) in other populations. Inuit ethnicity was included because uniquely high rates of TB among this group (5) make it of a priori interest. Further, age was included because the risk of adverse effects of isoniazid increases which age(6,7). It was thus suspected that older patients may be less likely to compete therapy for this reason making it a potential confounder if also related to other variables in the analysis. Although data are less robust for

LTBI, important differences between sexes in the burden and treatment active TB disease have long been recognized(8,9). For this reason, sex was included in the final models.

Year of physician visit was not included in the final treatment non-initiation or non-completion regression model based on examination of study data. Specifically, to evaluate a potential temporal effect, the year of physician visit was compared to treatment initiation and completion graphically. No clear temporal trend was noted (data not shown). The potential impact of this variable was further evaluated in univariate analysis and no association was found for either treatment initiation or completion (95% confidence intervals of risk ratios (RRs) included 1). Finally, model fit statistics did not substantially improve with inclusion in the model. For the model of treatment initiation, the quasi-likelihood under the independence model criterion (QIC) was QIC 410.45 in the model including year of physician visit and QIC 404.38 without it (smaller numbers indicating better fit). For the completion model, the Akaike's Information Criterion (AIC) was 303.42 with inclusion and 302.87 without (smaller numbers indicate better fit) and the Bayesian information criterion (BIC) was 340.45 with inclusion and 326.57 without (smaller numbers indicate better fit). As such, this variable was not included in the final model.

*Secondary Analyses*

For secondary analyses, a similar approach was used. For the analysis of risk factors for TST positivity, previous analyses of high risk neighbourhoods in Iqaluit have shown age(10) and ethnicity (insert SDH citation) to be associated with LTBI and thus these variables were included in the model. Indication for TST and sex were retained based on significant associations in univariate analyses (95% confidence intervals of RRs not including 1) and because of improved model fit with the variables. Specifically, the QIC was substantively increased in the model

without these variables than in those with them included, indicating worse fit (QIC 1977.64 with both variables vs 2143.25 without indication for TST and 1982.62 without sex). Year of TST was included based on graphical analysis suggesting a possible trend (data not shown), statistical significance of univariate analyses (95% confidence intervals of RRs not including 1) and worsened model fit without the variable (QIC 1977.64 with the variable vs 2013.87 without).

For the analysis of factors associated with failure to obtain a TST result, indication for testing was included based on a previous meta-analysis showing an association between test indication and completion of latent tuberculosis infection testing(3). Ethnicity was included both because of the high rates of active TB in the population and because high levels of adverse socioeconomic indicators among Inuit people (11,12) was felt to put them at higher risk of loss to follow up. Year of TST was included based on a possible trend in graphical analysis and statistical significance in the risk of failure to return for TST reading in univariate analysis between tests performed in 2012 vs 2015 (95% confidence intervals of RR not including 1) although model fit was similar with and without the variable (QIC 1111.02 with the variable and 1110.97 without). Sex and age were not included because univariate analysis showed no significant associations with the outcome (95% confidence intervals of RR not including 1) and model fit worsened with its inclusion (QIC 1111.015 with sex and age vs 1108.97 without sex and 1109.39 without age).

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**Appendix B - Results of sensitivity analyses from Manuscript 1.**

Table B1 shows the results of regression models examining associations between clinical and demographic factors and non-completion of treatment defined as receipt of <90% of prescribed doses of therapy within 12 months of the first dose. Table B2 shows similar results when defining treatment non-completion as receipt of <100% of prescribed doses of therapy within 12 months of the first dose.

**Table B1.** Results of a sensitivity analysis defining treatment non-completion as receipt of <90% of prescribed doses of therapy within 12 months of the first dose. Risk ratios (RRs) by demographic and clinical characteristic for non-completion of treatment among patients starting treatment for latent tuberculosis infection in Iqaluit, Nunavut between January 2012 and March 2016. RRs marked with an asterisk (*) are statistically significant. CI = confidence interval. n = 208 patients[1].

| Potential Risk factor | Unadjusted risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|---|---|---|
| Age, years (per 5-year increase) | 1.05 (1.00-1.11)* | 1.08 (1.01-1.15)* |
| Sex | | |
| Male | Reference | Reference |
| Female | 1.35 (0.91-2.01) | 1.49 (0.98-2.28) |
| Ethnicity | | |
| Inuit | Reference | Reference |
| Non-Inuit | 1.18 (0.68-2.04) | 0.90 (0.50-1.65) |
| Indication for TST | | |
| TB exposure | Reference | Reference |
| Employment screening | 1.32 (0.77-2.28) | 1.19 (0.69-2.06) |
| School screening | 0.24 (0.04-1.59) | 0.40 (0.06-2.62) |
| Self or physician referral | 0.86 (0.51-1.44) | 0.83 (0.49-1.41) |
| Year of assessment | | |
| 2012 | Reference | - |
| 2013 | 1.00 (0.81-1.22) | - |
| 2014 | 1.06 (0.87-1.30) | - |
| 2015 | 0.85 (0.60-1.21) | - |
| 2016 | 1.09 (0.75-1.58) | - |

[1]Among the 246 patients who started treatment, complete data were available for 207. Data were missing regarding ethnicity in 15 (6.1%), indication for TST in 14 (5.7%) and treatment completion in 12 (3.7%).

**Table B2.** Results of a sensitivity analysis defining treatment non-completion as receipt of <100% of prescribed doses of therapy within 12 months of the first dose. Risk ratios (RRs) by demographic and clinical characteristic for non-completion of treatment among patients starting treatment for latent tuberculosis infection in Iqaluit, Nunavut between January 2012 and March 2016. RRs marked with an asterisk (*) are statistically significant. CI = confidence interval. n = 208 patients[1].

| Potential Risk factor | Unadjusted risk ratio (95% CI) | Adjusted risk ratio (95% CI) |
|---|---|---|
| Age, years (per 5-year increase) | 1.03 (0.99-1.08) | 1.04 (0.98-1.10) |
| Sex | | |
| Male | Reference | Reference |
| Female | 1.24 (0.91-1.70) | 1.25 (0.90-1.74) |
| Ethnicity | | |
| Inuit | Reference | Reference |
| Non-Inuit | 1.50 (0.78-2.86) | 0.76 (0.45-1.30) |
| Indication for TST | | |
| TB exposure | Reference | Reference |
| Employment screening | 1.24 (0.78-1.95) | 1.29 (0.81-2.05) |
| School screening | 0.55 (0.20-1.54) | 0.86 (0.33-2.27) |
| Self or physician referral | 1.10 (0.75-1.59) | 0.88 (0.53-1.46) |
| Year of assessment | | |
| 2012 | Reference | - |
| 2013 | 1.01 (0.78-1.31) | - |
| 2014 | 1.08 (0.84-1.40) | - |
| 2015 | 0.86 (0.57-1.32) | - |
| 2016 | 1.10 (0.68-1.80) | - |

[1]Among the 246 patients who started treatment, complete data were available for 207. Data were missing regarding ethnicity in 15 (6.1%), indication for TST in 14 (5.7%) and treatment completion in 12 (3.7%).

## Appendix C - Supplementary methods from Manuscript 2

*Model Assumptions*

A variety of simplifying assumptions were made when developing the Markov model. These included:

1. *Once latent tuberculosis infection (LTBI) treatment is declined, it is not offered again in subsequent years*. This is in keeping with the usual practice in Iqaluit[1].
2. *Patients cannot change LTBI regimens*. This assumption was made to avoid unnecessary complexity and is in keeping with the practice of previous cost-effectiveness analyses[2–4].
3. *Probabilitiess of treatment initiation, fatal adverse events and reduction in risk of LTBI reactivation are equal between 12 weeks of weekly rifapentine and isoniazid (3HP) and 9 months of twice weekly isoniazid monotherapy (9H).* This assumption is more fully described in the main text.
4. *Receipt of less than 3 months of INH and less than 4 weeks of 3HP treatment carries the same risk of reactivation as no treatment.* Since only a minimal amount of treatment was received, the benefit was likely to be negligible and thus not modelled.
5. *Receipt of less than 3 months of INH and less than 4 weeks of 3HP treatment carries no risk of adverse events*. Similar to the above assumption, the short duration of treatment received was likely to result in only very small risk of adverse events.
6. *Patients who develop tuberculosis (TB) disease and are cured do not become re-infected*. The risk of re-infection was not likely to be different between 3HP and 9H since the target population was the same for both treatments. Thus, this risk was not included in the model. However, if included, any impact would have been slight given the small proportion of patients who develop TB disease. Further the slightly increased cost and

worsened health outcomes would have favoured 3HP since TB disease was more frequent in the 9H arm of our study. Thus inclusion re-infection in our model would have very slightly increased the estimated benefit of 3HP and as a result would not have changed our study's overall conclusions.

7. *Development of drug resistance was not considered.* Drug resistance is rare in Nunavut with only 1/129 isolates tested between 2016-2018 showing resistance to a single drug and no poly- or multidrug resistant isolates[5–7].
8. *The risk of adverse events and the reduction in risk of developing TB disease are linear with respect to time on LTBI treatment*. A previous analysis of large scale clinical trial data found that the reduction in risk associated with isoniazid monotherapy decreased linearly with time over a period of 9-10 months of treatment[8]. Similarly, the risk of adverse events associated with isoniazid monotherapy increased in an approximately linear fashion with treatment duration over 12 months of treatment in a large clinical trial[9]. No analogous data are available for 3HP but no reason to suggest that this relationship would differ for this regimen compared to isoniazid monotherapy was identified.
9. *Death to due factors other than TB and adverse events was not considered*. This was not expected to be different between 3HP and 9H since the target population for both was the same. As a result, it was not included in the model.

*Costing of LTBI treatment regimens*

Costs of completed 3HP and 9H included the cost of clinician assessments, DOT visits, monitoring of liver enzymes, medication, as well as sputum testing and chest x-ray which are

routinely performed in Iqaluit after 12 weeks of LTBI treatment. Costs incurred in diagnosing LTBI and ruling out active TB were not included as they were expected to be equal between 3HP and 9H. During LTBI treatment in Iqaluit, liver enzymes are monitored monthly for those aged ≥35 years, once at 3 months for those 13-34 years and not at all for those <13 years[1]. As a result, the costs of LTBI treatment were calculated separately for each age category. These were then combined based the proportions of LTBI patients undergoing treatment in each age category in retrospective programmatic data from Iqaluit.

For partially completed regimens, the costs of completing 1/3 or 2/3 of treatment were calculated based upon the cost of clinician assessments, DOT visits, monitoring of liver enzymes, medication, sputum testing and chest x-ray which would have been expected to occur within the time period that the patient was on treatment (i.e. during 4 weeks for those completing 1/3 of 3HP, during 3 months for those completing 1/3 of 9H etc.). As for completed treatment, costs were tabulated separately for patients aged ≥35 years, 13-34 years and <13 years and then combined as described above. Costs of treatment for those completing <1/3 of treatment were not included since they were assumed to be minimal.

Costs of other parameters were not divided by age category since age was not expected to change costs substantially.

*Additional Methods Regarding Scenario Analyses*

Due to its structure, the model broke treatment completion into component probabilities rather than including overall completion. As a result, where overall completion was varied in scenario analyses, component probabilities were adjusted to maintain the relative proportions completing <1/3, 1/3 and 2/3 of treatment.

For the scenario modeling self-administered therapy, the costs of DOT visits were removed from estimates of treatment cost but other costs and epidemiologic parameters were not changed.

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**Appendix D - Supplementary data from Manuscript 2.**

*Additional data regarding sensitivity analyses*

The probability distributions of model epidemiologic and cost parameters are provided in Tables D1 and D2. Distribution parameters were estimated based on mean and standard deviation utilizing TreeAge Pro (version 2019; TreeAge Software Inc., Williamstown, MA, USA).

**Table D1.** Probability distributions of epidemiologic parameters for probabilistic sensitivity analysis. Dashes indicate that the parameter was not varied in probabilistic sensitivity analysis. 9H = 9 months of twice weekly isoniazid; 3HP = 12 weeks of once weekly rifapentine and isoniazid.

| Parameter | Probability distribution type (alpha, beta) | Reference(s) |
|---|---|---|
| *Probability of treatment initation* | | [11,19,29] |
| 9H | Beta (505.76,208.59) | |
| 3HP | Beta (505.76,208.59)[1] | |
| *Probability of treatment completion* | | |
| *9H* | | [19] |
| Probability of stopping isoniazid before 3 months among all those who initiated treatment | Beta (31.30, 324.39) | |
| Probability of stopping isoniazid at 3 months among all those who completed at least 3 months of treatment | Beta (24.85, 293.77) | |
| Probability of stopping isoniazid at 6 months among all those who completed at least 6 months of treatment | Beta (1.42, 0.12) | |
| *3HP* | | [11] |
| Probability of stopping 3HP before 4 weeks among all those who initiated treatment | Beta (4904.37, 60487.22) | |
| Probability of stopping 3HP at 4 weeks among all those who completed at least 4 weeks of treatment | Beta (31.30, 324.39) | |
| Probability of stopping 3HP at 8 weeks among all those who completed at least 8 weeks of treatment | Beta (-0.95, -0.03) | |
| *Mild adverse event*[ii] | | [7] |

| | | | |
|---|---|---|---|
| | 9H | Beta (340.67, 3402.86) | |
| | 3HP | Beta (310.15, 3717.81) | |
| *Severe adverse events*[ii] | | | [7] |
| | 9H | Beta (246.83, 3550.60) | |
| | 3HP | Beta (236.35, 3910.11) | |
| *Fatal adverse events*[ii] | | | [6,31] |
| | 9H | Beta (2.84, 20315.56) | |
| | 3HP | Beta (2.84, 20315.56)[1] | |
| *Risk of reactivation of latent tuberculosis infection* | | | [32,33] |
| | First 2 years | Beta (6.07, 236.68) | |
| | Subsequent years | Beta (6.24, 6236.51) | |
| *Reduction in risk of tuberculosis disease* | | | |
| | 9H | - | |
| | 3HP | - | |
| *Risk of death following tuberculosis disease diagnosis* | | Beta (129.57, 1450.53) | [35–43] |
| *Health Utilities (quality adjusted life years)* | | | |
| | LTBI without treatment | - | Assumed |
| | LTBI treatment | - | [44] |
| | Mild adverse event | - | [45] |
| | Severe adverse event | Beta (55.50, 18.50) | [24] |
| | Tuberculosis disease | Beta (3.86, 0.53) | [44] |
| | Death | - | Assumed |

[i] Assumed identical values for 9H and 3HP

[ii] Values for partially completed regimens were interpolated assuming a linear relationship between duration of treatment and parameter values

**Table D2.** Probability distributions of cost parameters for probabilistic sensitivity analysis. Dashes indicate that the parameter was not varied in probabilistic sensitivity analysis. 9H = 9 months of twice weekly isoniazid; 3HP = 12 weeks of once weekly rifapentine and isoniazid.

| Parameter | Probability distribution type (alpha, lambda) | Reference(s) |
|---|---|---|
| *Complete 9H treatment* | Gamma (21.31, 0.02) | [26,46,47] |
| *Partial isoniazid treatment* | | |
| 3 months | Gamma (32.49, 0.06) | [26,46,47] |
| 6 months | Gamma (24.21, 0.03) | [26,46,47] |
| *Complete 3HP treatment* | Gamma (61.01, 0.12) | [26,46,47] |
| *Partial isoniazid + rifapentine treatment* | | |
| 4 weeks | Gamma (79.61, 0.48) | [26,46,47] |
| 8 weeks | Gamma (57.75, 0.22) | [26,46,47] |
| *Mild adverse event* | Gamma (0.07, 0.01) | [13,48] |
| *Severe adverse event* | Gamma (3.90, 0.00) | [13,26,46,47] |
| *Fatal adverse events* | Gamma (58.57, 0.00) | [26,46,49] |
| *Cured tuberculosis disease* | Gamma (0.05, 2.39) | [26,46] |
| *Fatal tuberculosis disease* | Gamma (56.87, 0.00) | [26,46,49] |
| *Surveillance for those < 13 years old* | Gamma (181.40, 2.50) | [46,47] |
| *Surveillance for those ≥ 13 years old* | Gamma (105.53, 0.15) | [46,47] |

In univariable sensitivity analyses, only 3 variables had the potential to result in 12 weeks of weekly rifapentine and isoniazid (3HP) no longer being dominant over 9 months of twice weekly isoniazid monotherapy (9H) when varied across uncertainty ranges (Figure D1). These were the probabilities of completing <4 weeks of 3HP treatment among those who completed a

minimum of 4 weeks of treatment (3HP dominant at values ≤ 0.155), having a fatal adverse event during 3HP treatment (3HP dominant at values ≤0.00042) and initiating 3HP (3HP dominant at values ≤ 0.734). However, 3HP remained cost saving in all univariable analyses. The variables with the largest impact on costs are shown in e-Figure 2.

**Figure D1.** Results of one-way sensitivity analysis on incremental effectiveness. The 10 most influential parameters are shown. Bars show the incremental effectiveness in quality-adjusted life years of 3HP relative to 9H, holding all other parameters constant. Red bars represent the high value and blue bars the low value of the relevant parameter. The vertical lines represent equal effectiveness (left) and the base case outcome (right). Numbers in brackets following parameter descriptions indicate the uncertainty range. 9H = 9 months of twice weekly isoniazid; 3HP = 12 weeks of once weekly rifapentine and isoniazid; QALY = quality-adjusted life years.

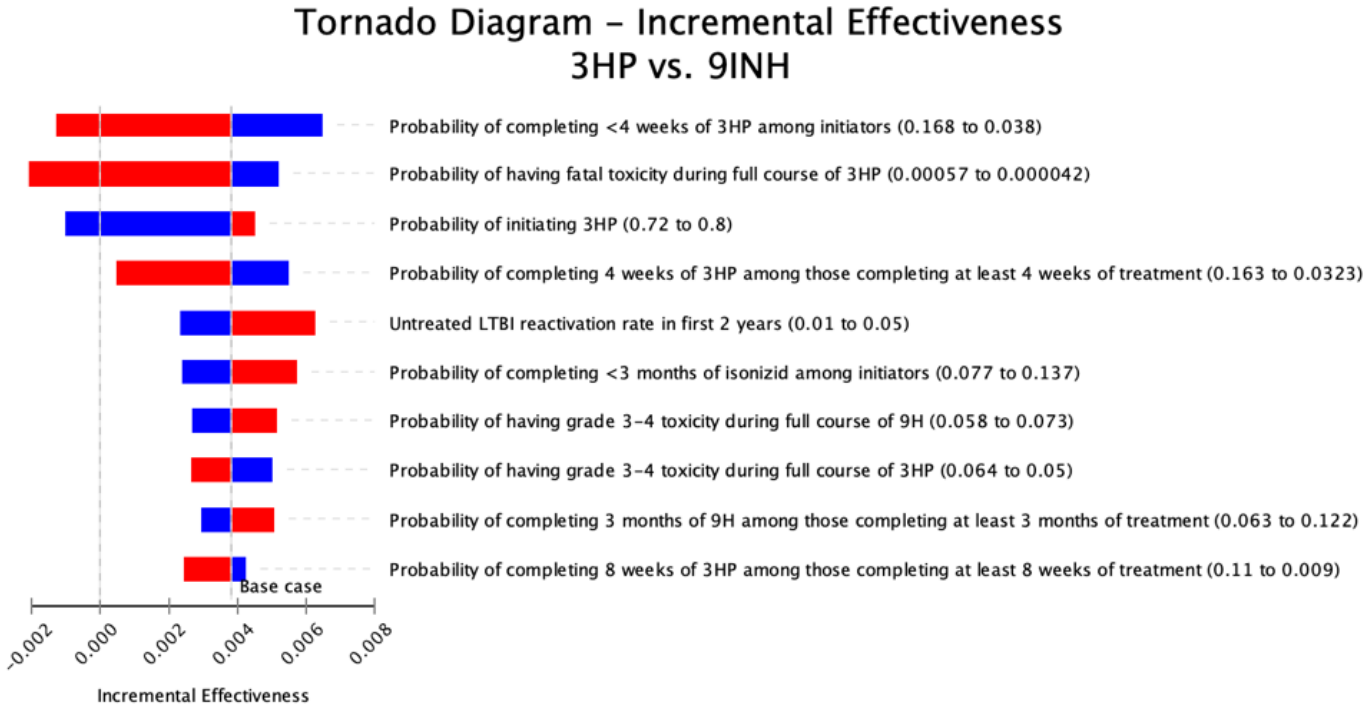
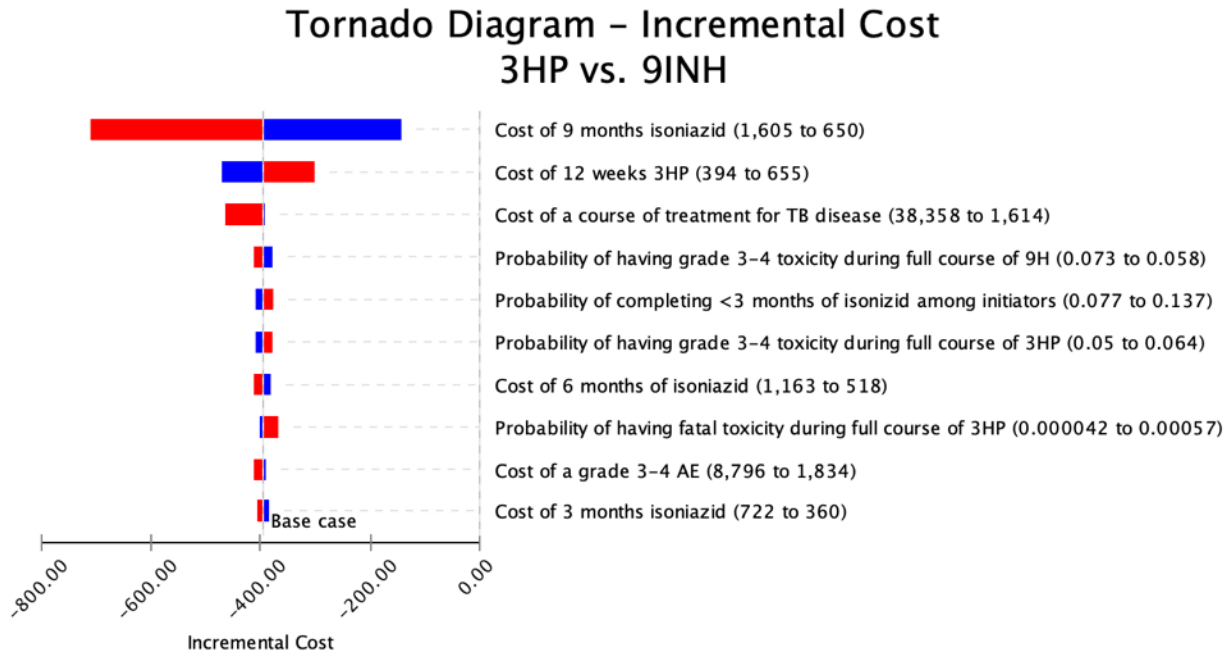


**Figure D2.** Results of one-way sensitivity analysis on incremental costs. The 10 most influential parameters are shown. Bars show the incremental costs in 2019 Canadian dollars of 3HP relative to 9H, holding all other parameters constant. Red bars represent the high value and blue bars the low value of the relevant parameter. The vertical lines represent the base case outcome (left) and equal costs (right). Numbers in brackets following parameter descriptions indicate the uncertainty range. 9H = 9 months of twice weekly isoniazid; 3HP = 12 weeks of once weekly rifapentine and isoniazid; QALY = quality-adjusted life years.




In sensitivity analyses varying discounting (Table D3) and the model time horizon (Table D4), 3HP remained dominant (both more effective and cost saving compared to 9H).

**Table D3.** Costs in 2019 Canadian dollars and effectiveness in quality-adjusted life years (QALYs) by annual discounting rate. 9H = twice weekly isoniazid for 9 months; 3HP = weekly rifapentine and isoniazid for 12 weeks.

| | | Costs | | Effectiveness (QALYs) | |
|---|---|---|---|---|---|
| | | 9H | 3HP | 3HP | 9H |
| Discounting rate (% per year) | 0 | $1,269 | $871 | 29.929 | 29.923 |
| | 1 | $1,254 | $857 | 26.003 | 25.998 |
| | 2 | $1,241 | $845 | 22.789 | 22.784 |
| | 3 | $1,230 | $835 | 20.138 | 20.134 |
| | 4 | $1,221 | $827 | 17.938 | 17.935 |
| | 5 | $1,213 | $819 | 16.099 | 16.096 |

**Table D4.** Costs in 2019 Canadian dollars and effectiveness in quality-adjusted life years (QALYs) by model time horizon. 9H = twice weekly isoniazid for 9 months; 3HP = weekly rifapentine and isoniazid for 12 weeks.

| | | Cost | | Effectiveness (QALYs) | |
|---|---|---|---|---|---|
| | | 9H | 3HP | 9H | 3HP |
| Time horizon (years) | 10 | $1,190 | $798 | 8.758 | 8.760 |
| | 20 | $1,212 | $819 | 15.282 | 15.285 |
| | 30 | $1,230 | $835 | 20.134 | 20.138 |
| | 40 | $1,242 | $846 | 23.744 | 23.749 |
| | 50 | $1,251 | $855 | 26.430 | 26.435 |

*Additional data regarding scenario analyses*

The 3HP regimen remained cost saving compared to 9H across a broad range of scenarios (Table D5). The regimen remained both cost saving and more effective than 9H when costs of directly observing therapy were removed (Table D6).

**Table D5.** Influence on the incremental cost of 3HP vs 9H of variation in a variety of parameters to extreme values. 3HP = weekly rifapentine and isoniazid for 12 weeks; 9H = 9 months of twice weekly isoniazid; LTBI = latent tuberculosis infection.

a) Impact of variation in 3HP initiation and 3HP completion probabilities to 10% above and below those of 9H.

| | | 3HP completion probability | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 0.65 | 0.67 | 0.69 | 0.71 | 0.73 | 0.75 | 0.77 | 0.79 | 0.81 | 0.83 | 0.85 |
| 3HP initiation probability | 0.69 | -$365 | -$363 | -$361 | -$360 | -$358 | -$357 | -$354 | -$352 | -$351 | -$349 | -$347 |
| | 0.71 | -$374 | -$372 | -$371 | -$369 | -$367 | -$366 | -$363 | -$361 | -$360 | -$358 | -$356 |
| | 0.73 | -$384 | -$382 | -$380 | -$378 | -$376 | -$375 | -$372 | -$371 | -$369 | -$367 | -$365 |
| | 0.75 | -$393 | -$391 | -$389 | -$387 | -$386 | -$385 | -$382 | -$380 | -$378 | -$376 | -$374 |
| | 0.77 | -$403 | -$401 | -$399 | -$397 | -$395 | -$394 | -$391 | -$389 | -$387 | -$385 | -$383 |
| | 0.79 | -$412 | -$410 | -$408 | -$406 | -$404 | -$403 | -$400 | -$398 | -$396 | -$394 | -$392 |
| | 0.81 | -$422 | -$419 | -$417 | -$415 | -$413 | -$412 | -$409 | -$407 | -$405 | -$403 | -$401 |
| | 0.83 | -$431 | -$429 | -$427 | -$425 | -$423 | -$421 | -$418 | -$416 | -$414 | -$412 | -$409 |
| | 0.85 | -$441 | -$438 | -$436 | -$434 | -$432 | -$431 | -$427 | -$425 | -$423 | -$421 | -$418 |
| | 0.87 | -$450 | -$448 | -$446 | -$443 | -$441 | -$440 | -$436 | -$434 | -$432 | -$430 | -$427 |
| | 0.89 | -$460 | -$457 | -$455 | -$453 | -$450 | -$449 | -$446 | -$443 | -$441 | -$439 | -$436 |

b) Impact of variation in LTBI reactivation in the first 2 years of the model and the probability of severe adverse events while taking 3HP

| Probability of TB reactivation in first 2 years(3HP-9H) | 3HP completion probability | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.65 | 0.67 | 0.69 | 0.71 | 0.73 | 0.75 | 0.77 | 0.79 | 0.81 | 0.83 | 0.85 |
| 0.001 | -$441 | -$434 | -$427 | -$421 | -$414 | -$411 | -$400 | -$393 | -$386 | -$379 | -$372 |
| 0.01 | -$429 | -$424 | -$419 | -$415 | -$410 | -$407 | -$400 | -$395 | -$390 | -$385 | -$380 |
| 0.02 | -$417 | -$414 | -$411 | -$409 | -$406 | -$404 | -$400 | -$397 | -$394 | -$391 | -$388 |
| 0.03 | -$405 | -$404 | -$404 | -$403 | -$402 | -$401 | -$400 | -$399 | -$398 | -$397 | -$396 |
| 0.04 | -$394 | -$395 | -$396 | -$397 | -$398 | -$398 | -$400 | -$401 | -$402 | -$403 | -$404 |
| 0.05 | -$382 | -$385 | -$388 | -$391 | -$394 | -$395 | -$400 | -$403 | -$406 | -$409 | -$412 |
| 0.06 | -$371 | -$376 | -$381 | -$385 | -$390 | -$392 | -$400 | -$405 | -$410 | -$415 | -$419 |
| 0.07 | -$359 | -$366 | -$373 | -$380 | -$386 | -$389 | -$400 | -$407 | -$413 | -$420 | -$427 |
| 0.08 | -$348 | -$357 | -$366 | -$374 | -$382 | -$386 | -$400 | -$409 | -$417 | -$426 | -$435 |
| 0.09 | -$337 | -$348 | -$358 | -$369 | -$379 | -$383 | -$400 | -$411 | -$421 | -$432 | -$442 |
| 0.10 | -$326 | -$339 | -$351 | -$363 | -$375 | -$381 | -$400 | -$413 | -$425 | -$437 | -$450 |

c) Impact of variation in LTBI reactivation in the first 2 years of the model and the 3HP completion probability.

| Probability of TB reactivation in first 2 years(3HP-9H) | Probability of severe adverse events for 3HP | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.057 | 0.064 | 0.072 | 0.079 | 0.086 | 0.094 | 0.101 | 0.108 | 0.115 | 0.123 | 0.13 |
| 0.001 | -$382 | -$366 | -$347 | -$330 | -$314 | -$295 | -$279 | -$262 | -$246 | -$227 | -$211 |
| 0.01 | -$387 | -$371 | -$352 | -$336 | -$319 | -$300 | -$284 | -$268 | -$251 | -$233 | -$216 |
| 0.02 | -$392 | -$376 | -$357 | -$341 | -$324 | -$306 | -$289 | -$273 | -$256 | -$238 | -$221 |
| 0.03 | -$397 | -$381 | -$362 | -$346 | -$330 | -$311 | -$294 | -$278 | -$262 | -$243 | -$226 |
| 0.04 | -$403 | -$386 | -$367 | -$351 | -$335 | -$316 | -$299 | -$283 | -$267 | -$248 | -$231 |
| 0.05 | -$408 | -$391 | -$372 | -$356 | -$340 | -$321 | -$304 | -$288 | -$272 | -$253 | -$237 |
| 0.06 | -$413 | -$396 | -$377 | -$361 | -$345 | -$326 | -$309 | -$293 | -$277 | -$258 | -$242 |
| 0.07 | -$418 | -$401 | -$382 | -$366 | -$350 | -$331 | -$314 | -$298 | -$282 | -$263 | -$246 |
| 0.08 | -$422 | -$406 | -$387 | -$371 | -$354 | -$336 | -$319 | -$303 | -$287 | -$268 | -$251 |
| 0.09 | -$427 | -$411 | -$392 | -$376 | -$359 | -$341 | -$324 | -$308 | -$291 | -$273 | -$256 |
| 0.10 | -$432 | -$416 | -$397 | -$381 | -$364 | -$345 | -$329 | -$313 | -$296 | -$277 | -$261 |

**Table D6.** Costs in 2019 Canadian dollars and effectiveness in quality-adjusted life years (QALYs) when latent tuberculosis infection treatments are provided by self-administered therapy. 9H = twice weekly isoniazid for 9 months; 3HP = weekly rifapentine and isoniazid for 12 weeks.

| | 9H | 3HP |
|---|---|---|
| *Clinical Outcomes* | | |
| Overall effectiveness (QALYs) | 20.13 | 20.14 |
| *Cost Outcomes (2019 Canadian $)* | | |
| Total cost | $809 | $765 |
| Costs of latent TB infection treatment | $291 | $276 |
| Costs of adverse events | $154 | $143 |
| Costs of TB disease treatment | $242 | $224 |
| Surveillance costs | $122 | $122 |

TB = tuberculosis; 9H = 9 months of twice weekly isoniazid; 3HP = 12 weeks of weekly rifapentine and isoniazid.