ASSESSING CONTROL STRATEGIES AND TIMELINES FOR MYCOBACTERIUM TUBERCULOSIS ELIMINATION

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Abstract

Tuberculosis (TB) continues to inflict a disproportionate impact on Inuit communities in Canada, with reported rates of active TB that are over 300 times higher than those of Canadian-born, non-Indigenous populations. The Inuit Tuberculosis Elimination Framework aims to reduce the incidence of active TB by at least 50% by 2025, with the ultimate goal of eliminating it (i.e., reducing the incidence of active TB below 1 case per 1,000,000 population) by 2030. However, whether these goals can be achieved with the resources and interventions currently available has not been investigated.

This dissertation formulates an agent-based model (ABM) of TB transmission dynamics and control to assess the feasibility of achieving the goals of elimination framework in Nunavut, Canada. I applied the model to project the annual incidence of active TB from 2025 to 2040, taking into account factors such as time to case identification after developing active TB, contact tracing and testing, patient isolation and compliance, household size, and the potential impact of a therapeutic vaccine. In order to determine the potential reduction in TB incidence, various scenarios of treatment regimens were evaluated within the action plans for TB elimination. The scenario analyses demonstrate that the time-to-identification of active TB cases is a crucial factor in attainability of the goals, highlighting the importance of investment in early case detection. The findings also indicate that the goal of 50% reduction in annual incidence of TB by 2025 is only achievable under best case scenarios of combined interventions. However, TB elimination will likely exceed timelines indicated in the action plans.

To my beloved husband

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Table of Contents

List of Tables

List of Figures

Chapter 1

Introduction

Tuberculosis (TB) is a contagious disease that typically spreads by inhaling airborne droplets containing Mycobacterium tuberculosis bacteria (M.tb). Despite exhaustive and targeted global efforts dedicated in the past 25 years towards TB elimination, it is still one of the deadliest communicable diseases, ranked within the top 10 major causes of death [1]. In 2020, an estimated 10 million people developed TB disease (known as active TB), resulting in 1.5 million deaths, making TB the second leading cause of death from an infectious agent after COVID-19 [2].

Global End TB strategy outlined by the World Health Organization (WHO) aims to reduce the incidence of new TB infection or relapse by at least 90% compared with 2015 to less than 100 cases per 1 million population by 2035. This strategy also aims to achieve 95% reduction in TB-attributable deaths. Despite all the activities devoted to these goals, the cumulative reduction of TB incidence from 2015 to 2020 was only 11%, resulted in 9.2% reduction in mortality [3]. For achieving the goals set by the WHO in low-incidence countries (e.g., Canada), the WHO has established three strategy pillars of (i) early detection, treatment and prevention of all TB patients; (ii) policies and systems that supports adequate resources, quality care, and social protection; and (iii) targeted research and development pertaining to new interventions such as vaccines and therapeutics [4].However, several factors including ineffective treatment regimens, low treatment adherence, and incomplete preventive measures may delay achieving the goals of TB elimination, especially in high incidence regions such as Northern Canadian Indigenous communities.

While Canada is placed among low-incidence countries on a global scale, TB remains a major public health concern, especially among First Nations and Inuit communities, and continues to disproportionately affect them with estimated rates of over 300 times higher incidence of active TB than Canadian-born, non-Indigenous people [5]. Contributing risk factors to these rates among the northern Canadian population include, but not limited to, comorbidities, higher prevalence of diabetes, tobacco use, food insecurity and malnutrition, overcrowded houses that are poorly ventilated, poor access to health care and stigma [6, 7, 8].

In line with the WHO TB strategy, the Government of Canada, in joint efforts with Inuit Tapiriit Kanatami, has developed Region-specific TB elimination action plans to reduce the incidence of active TB by 50% (reduction from $\sim$200 to no more than 100 cases per 100,000 population) by 2025, and eliminate the disease by 2030 in the Inuit Nunangat[9, 10]. According to latest Canadian census data, nearly half of Canada's Inuit population live in Nunavut territory, with the highest average TB incidence rate of 180 cases per 100,000 population during past 10 years, considerably higher than Canada as a whole, with 4.8 per 100,000 population [11]. In alignment with Canadian Tuberculosis Standards, department of health in Nunavut released the TB manual as the primary reference guide in order to assist healthcare providers. This manual include plans for contact investigations to identify latent TB infection (LTBI) for treatment based on the recommended regimens [12, 13, 14, 4], in addition to investing $640 million over 10 years to address the housing need in Inuit communities [9, 10]. However, these plans must also address factors hindering TB control such as inadequate treatment adherence and late identification of active pulmonary cases in the cascade of care which refers to the various steps involved in the process of testing for LTBI towards completing the treatment regimen. These steps include testing, initiation of the treatment, contact tracing for secondary transmission and LTBI identification, and follow-ups for completion of the treatment regimen [11, 15].

Whether relying on these plans alone will be enough to make TB elimination goals reached and to what extend each intervention will contribute to the reduction of TB incidence has not been evaluated. In this dissertation I aim to conduct this evaluation for Nunavut, the largest Canadian territory, by developing a data-driven agent-based model (ABM). This model includes time-to-identification of active TB, contact-tracing

and testing, housing composition, isolation precautions and the effect of a therapeutic vaccine candidate.

In order to capture critical aspects of the disease dynamics and encapsulate individuals' characteristics, health status and interactions, we parameterized the ABM with available data and information. We show that in the absence of life-long protection, the ambitious goal of 50% reduction in active TB by 2025 would not be achievable using only the available resources and strategies. We also quantify the potential effect of a therapeutic vaccine on annual incidence of active TB to assess whether TB elimination goals are achievable within the expected timelines.

For this research, I will first provide a thorough review of the biology and epidemiology of TB. In Chapter 2, TB dynamics and the natural history of disease will be detailed, followed by the current situation of TB worldwide, in Canada, and among indigenous populations. The policies recommended by Canadian Tuberculosis Standards such as different treatment regimens for active and latent TB are also included in this Chapter. In Chapter 3, I carry out a review of recent TB-related modeling studies that considered indigenous populations. Chapter 4 incorporates the population structure of Nunavut territory including demographic characteristics, the prevalence of potential risk factors such as HIV, diabetes and renal disease. I also consider household composition in my model. The agent-based framework and its components with rules and description of parameters and assumption are described in Chapter 5.

I utilized this model under plausible scenarios of TB control strategies including contact-tracing and testing, time-to-identification of active TB, short-term out-of-home isolation as well as household size reduction. Using this model, I quantified the annual incidence reduction under each scenario. The results of the model for the baseline scenario as well as the best-case scenario of each intervention are discussed in 6. In Chapter 7 I discuss the therapeutic vaccines in clinical development with their efficacy against active TB activation. Given the expected effectiveness of therapeutic vaccines in improving treatment outcomes such as shorter treatment duration and lower risk of disease reactivation, we extended our model to quantify the effect of a TB vaccine on the reduction of annual incidence. In the light of the results presented in this dissertation, including various scenarios presented in the Appendix, Chapter 8 provides a discussion on how the quantitative assessment of TB control measures can inform action plans and

help policy makers address the shortcomings of End TB strategies.

Chapter 2

TB Biology and Epidemiology

Members of the Mycobacterium Tuberculosis Complex (MTBC) species are responsible for TB disease. These include Mycobacterium tuberculosis (*M.tb*), which is the etiologic mediator of TB in humans; *M. africanum*, which causes TB in humans living in specific areas of Africa; *M. bovis*, *M. caprae* and *M. pinnipedii*, which trigger TB in wild and tame mammals; *M. microti*, which causes TB in the vole populations only [16].

Human TB, causes by *M.tb*, is an airborne disease that can be transmitted between individuals. One to five bacilli may be enough to transmit the infection [17]. The bacilli are typically released into the environment when an ill pulmonary TB patient coughs, sneezes, speaks, or sings, causing aerosolization of pulmonary secretions. Aerosol droplets dry quickly, leaving small droplet nuclei with a few bacilli in them [18]. Although larger droplets over 10 μm typically fall to the surface, the smaller nuclei between 1 and 10 μm can stay floated and be inhaled. Of these, the larger nuclei can attach to the upper nasal passages or move to the lower respiratory tract. Droplet nuclei may also reach the alveoli [1], leading to the infection [18]. When *tubercle bacilli* begin to develop in the lungs, the onset of *M.tb* infection is marked. Individuals with active pulmonary TB generate droplet nuclei bearing *tubercle bacilli* that is proportional to the fluidity of the discharges and the amount of bacilli ejected, most frequently in those who have positive sputum smears with frequent or recurrent coughs [18].

Although TB is most commonly discussed in terms of the symptoms and is primarily a lung disease, with pulmonary TB representing 70% of incidences, *M.tb* can also affect

[1] Small, thin-walled sacs located at the end of the bronchioles in the lungs [19]

other organs, such as lymph nodes, meninges and bone, and spread to other body parts, including the spine, kidney, and brain via the blood, causing extra-pulmonary disease [20].

The amount of bacilli discharged into the air, the density of bacteria that depend on the volume of space and available ventilation, the duration of time an individual inhales the air, and the immune status of the individual are the main factors that determine the probability of *M.tb* transmission [21]. After inhalation, *M.tb* confronts the first line of defense, which consists of airway epithelial cells and phagocytes [2](monocytes, neutrophils, and dendritic cells) [23, 24]. If this initial line of defense is successful in rapidly removing *M.tb*, the infection will be terminated. On the other hand, if phagocytes become infected, *M.tb* replicates within the cells and may (in rare cases) generate clinical signs during the early stages. [25]. In some people, alveolar macrophages can eliminate microbes by innate immune systems; while in others, the bacteria can replicate and cause TB infection. When innate macrophage microbicidal effect is insufficient to destroy the initial bacteria in the droplet nucleus, the bacteria can replicate exponentially, doubling every day until the macrophage bursts and the other fresh macrophages that are attracted to the site pulls the bacilli inside and the process repeats. The complex relationship between the infection process and host factors plays a major role in fast or slow progression to active TB (see Section 2.1 for more details) [26, 27]. Thus, the innate immunity provides a mechanism to eliminate the bacteria. Of those exposed, 30%-40% are infected, and only 5%-10% of them with latent TB infection (LTBI) will develop active TB during their remaining lifetime, most of which occurs in the first two years of infection. If left untreated, it is estimated that 50% of active TB cases die within five years. [28, 29].

2.1 Latent tuberculosis infection (LTBI)

An estimated one-third of the world population is infected with *M.tb* in the state of LTBI. Only 5%–10% of LTBI will develop active TB disease [30]. The incubation period of TB (the average time between infection and onset of active TB) can range from weeks to decades and varies. The median incubation period for those who develop active TB within 15 years

[2]A type of white blood cell that is specialized in engulfing and digesting foreign particles such as invading microorganisms, dead cells, and other debris. [22]

of infection is 1.26 years, with a span of 0–12.8 years [31]. Within 1, 2, and 5 years of infection, the Kaplan–Meier probability of developing active disease are estimated to be 45%, 62%, and 83%, respectively [31]. Several factors may increase the risk of active TB development in an infected person, with immune impairment playing an important role in TB vulnerability. Human immunodeficiency virus (HIV), renal failure, diabetes, cancer, malnutrition, age, and smoking, are among the known factors for weakened immune status.

2.2 Risk factors

Youth have the greatest incidence of active TB worldwide, although older adults and elderly people in industrialized nations have the highest prevalence of the disease and adults of all ages are susceptible to developing active disease. Age, HIV infection, and the presence of other immunocompromised conditions pose a significant risk for disease activation. Diabetes, alcoholism, intravenous drug usage, renal illness, gastrointestinal bypass surgery or gastrectomy, malnutrition, and cigarette use are also known as contributing factors [28].

2.2.1 Age

Infants are at heightened risk of TB infection and illness. It is worth noting that the risk of TB has a bimodal tendency. While children aged 5 to 10 years have the lowest risk of developing active TB, infants and adolescents have increased risks of *M.tb* activation. This risk is greatest under four years of age and fluctuates depending on the age of the individual. The risk of TB activation is estimated to be 30-40% during infancy (under one year of age), and 10-20%, 5%, 2%, 10% to 20% among 1-2, 3-5, 6-10, 11 to 15 years old respectively. This risk is estimated to be 5%-10% during adulthood [32].

2.2.2 HIV

The relationship between TB and HIV/AIDS has been well-documented [33]. The most significant immunosuppressive risk factor for the development of active TB is HIV co-infection. Cell-mediated immunity is a critical element of the host's defense against *M.tb*,

which is impaired by HIV infection, increasing the risk of TB activation [34]. Individuals of any age group with advanced HIV are expected to have a 9.9% greater risk of developing active TB as compared with those without HIV [35].

2.2.3 Renal disease

Chronic renal failure has a number of side effects, one of which is immunological derangement, which makes patients vulnerable to infections and diseases. The increased vulnerability of patients to TB has been attributed to a wide spectrum of immunological impairment and decreased cellular immune reactivity in chronic renal failure [36]. Renal disfunction is associated with a 2.4 fold increased risk of developing active TB [35].

2.2.4 Diabetes

Diabetes can increase the risk of progression to active TB by 1.7 times [35]. The link between TB and diabetes was well established in the early twentieth century. However, with the development of insulin therapy for diseases and antibiotics for TB patients, this relationship was largely neglected in the second half of the century. With the global rise in the prevalence of diabetes, the importance of diabetes in TB disease has received further attention in the past two decades [37]. On an individual level, HIV is by far the most important risk factor for TB, while diabetes may be more relevant at the population level. Diabetes, for instance, is predicted to account for 14.8% of pulmonary TB cases in India, whereas HIV is responsible for 3.4% of incidences [38].

In less than 30 years, the global prevalence of diabetes among the adult population has increased by 20% [39]. Furthermore, diabetes is expected to affect 642 million people globally by 2040, with the majority (80%) of patients residing in low and middle-income nations, where TB is most prevalent [40]. The World Health Organization has recognized diabetes as a previously overlooked, significant, and re-emerging risk factor for TB [41].

2.2.5 Cancer

The risk of TB activation is especially higher in cancer patients, as individuals with solid tumors and haematological malignancies are immunocompromised both by the

illness and the associated treatment [42]. In a meta-analysis [42], it was discovered that cancer patients have a statistically higher risk of developing TB than the overall population. Although not all types of cancers, are linked to an increase in TB incidence, some including colon, breast, and gastric have been linked to a two-fold increase in risk of developing TB in comparison to members of the general population, while lung cancer patients have a six-fold increase.

2.2.6 Smoking and other conditions

Tobacco products are used by an estimated 1.3 billion people globally, the majority of whom reside in impoverished or developing nations, where TB rates are also high. Smoking has a role in the etiology of TB by lowering immunological response and, hence, increasing vulnerability to *M.tb* infection [43]. Other risk factors include socioeconomic contexts, such as starvation, overcrowding, and indoor air pollution, as well as immunosuppressive medicines, alcohol usage, organ transplantation, or other conditions that cause a weakened immune system. Efforts to achieve the End TB targets might be hindered by these risk factors. [34].

2.3 Symptoms

A persistent cough lasting at least 2 to 3 weeks is the most common sign of pulmonary active TB. Coughing usually begins dry, but after a few weeks or months, it becomes productive. The determination of 2 or 3 weeks as a criterion is based on the location, the experience and epidemiology of TB in that setting. Fever and night sweats are frequent, although very young and old individuals may not experience them. Blood in the cough, loss of weight, chest discomfort, exhaustion, fever, chills, shivering, and loss of appetite are among signs of a more advanced illness [20]. When TB affects organs or body parts other than the lungs, the symptoms differ depending on the affected organ. For example, back discomfort can be caused by TB in the spine, while blood in the urine can be caused by TB affecting the kidneys [20].

2.4 Diagnosis of LTBI

M.tb infection is primarily confined and defeated by host immune system in most people, and infection stays dormant. This latent infection, can become an active disease at any time during life span (See Section 2.1). LTBI detection and treatment can significantly lower the risk of developing disease and, hence, contribute to protect both the infected person and the public health by decreasing the number of potential sources of future transmission.

While diagnosis and treatment of active TB is the highest priority for TB control (see Section 2.6), identifying and treating those with LTBI is a second priority. The World Health Organization recommends LTBI diagnosis and treatment as one of the main components of the strategies to eliminate TB globally [4]. People who have LTBI are asymptomatic and do not feel ill. A chest x-ray is often unremarkable and normal, and a sputum smear may be negative. Therefore, the only possible way to diagnose LTBI is through skin or blood testing.

The purpose of LTBI testing, as recommended by the Canadian Tuberculosis Standard, is to determine those who are at a higher risk of developing active TB and to benefit from LTBI treatment (i.e., prophylaxis or preventive therapy). Only those who will benefit from therapy should be assessed and tested. When the risk of active disease development is elevated, testing for LTBI is recommended [6].

The Canadian TB standard has classified contacts of active TB cases as high, medium, or low priority in order to test, and treat those with LTBI. Household members and close non-household contacts who are at a higher risk of developing TB following infection, such as children under the age of five or immunocompromised adults, are included in the high priority group. Daily or almost daily contacts, including frequent community contacts such as coworkers and classmates, are prioritized as medium importance. Casual interactions such as those occurring during daily activities infrequently and with short duration, are considered low priority [14].

The guidelines developed by WHO recommends using either a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) [44]. In Canada, high-risk patients are tested with TST or IGRA. Both tests look at cell-mediated immunity, but neither can differentiate between LTBI and active TB. The TST involves injecting a small quantity of

pure protein derivative (PPD) from *M.tb* bacteria inside the skin. A delayed hypersensitivity reaction will emerge within 48 to 72 hours in someone who has cell-mediated immunity to these tuberculin antigens. Localized edema and induration of the skin at the injection site will be the result of the response. IGRA is in vitro blood tests that assess the release of interferon-gamma (IFN-gamma) from T cells after stimulation with antigens specific to *M.tb* [6]. While these tests are reliable, there is a possibility of a false negative. Technical or physiological factors might result in false-negative responses. TST sensitivity is estimated to be lower than IGRA sensitivity (i.e., the likelihood of a positive TST result in the context of a confirmed TB infection) [45].

2.5 Treatment of LTBI

Before starting the treatment for LTBI, active TB must be rejected based on patient history, physical examination, and chest radiography. If an active disease is suspected, sputum specimens should be submitted for smear and culture, with other necessary examinations (See Section 2.6. Furthermore, because people who are treated for LTBI do not report with active disease, the risk of potential complications, side effects and adverse events during therapy should be monitored [46].

Given its history of usage, high safety profile, and documented efficacy in several randomized studies in HIV-infected patients, isoniazid (INH) is currently considered as the routine first-line treatment [47, 48]. INH is generally self-administered on a daily basis. According to data from Alaskan Inuit experiments, the most effective duration of treatment appears to be 9 months (9INH). The protective efficacy against reactivation of TB is higher with longer INH treatment, reaching a peak of 90% with 9 months of treatment. No additional increase has been observed in efficacy with a treatment duration longer than 9 months [49]. Six months of daily, self-administered INH (6INH) is also an appropriate alternative. Although this protocol has been shown to improve completion rates, it only has a protective effectiveness of 67% to 69%. In Canada, 6INH is considered as the second treatment regimen [13].

Three or four months of daily, self-administered INH and rifampin (RMP) (3-4 months INH/RMP) is another appropriate regimen recommended by the Canadian Tuberculosis Standard for LTBI. Efficacy and safety of daily combined INH and RMP have been evaluated

in a number of randomized studies. These findings were analyzed in a systematic review and meta-analysis, revealing that this regimen had similar effectiveness and safety to 6 to 9 months of INH treatment [13, 50].

Three months of once weekly, directly observed INH and rifapentine (RPT) (3INH/RPT) treatment regimen has acceptable efficacy; however, it is used only with extremely close supervision due to the high incidence of hypersensitive responses. The existing evidence suggests that this is a highly promising treatment with a high completion rates, and its efficacy is comparable to 9INH. Every dose, on the other hand, should be closely monitored, which might be challenging in some settings and populations. This regimen is not recommended for widespread usage [13].

Four months of daily, self-administered RMP, is another safe regimen for LTBI treatment (4RMP). Since 2000, 4RMP has been suggested as a substitute program in the United States and Canada. Under programmed condition, this regimen has performed well, and its completion rates have been higher than those seen with 9INH, while toxic side effects have been minimal [13, 51].

Noncompliance is the most severe challenge delaying TB control. Compliance with treatment necessitates the patient's active engagement in treatment, self-management, and cooperation with the healthcare practitioner. The cause of poor adherence is complex, but it may include patient attributes as well as socioeconomic factors such as accessibility to treatment, communication between healthcare provider and patients, treatment duration and the amount of drugs required, side effects, cost of care, competing demands on time, conflicting social standards or preconceptions of families and cultural groups, and poor quality of the TB control infrastructure [52].

The efficacy and success of any regimen is an essential consideration. because the primary goal of diagnosis and treatment is to enhance the patient's health, the diagnosis must be accurate, and the suggested treatment regimen should be effective. Treatment efficacy is characterized as the effect in ideal settings, and the efficacy endpoint is usually considered as negative outcomes that may include mortality, recurrence, and treatment failure, as well as change in treatment as a result of adverse events [53].

In Nunavut, the regimen which consists of a weekly dose of INH and RMP is administered under direct observation for 3 months with high compliance and efficacy rates [54, 55, 56]. In this dissertation, I have included this regimen (3HP) as the only LTBI

treatment regimen (see Sections 5.7.3 and 5.4).

2.6 Diagnosis of active TB

The methods for TB diagnosis via laboratory tests are constantly improving in order to be faster, less costly, and more accurate. Anyone who has clinical symptoms of TB or is thought to be at higher danger of TB should be tested for active TB. IGRA has low sensitivity and specificity for diagnosing active TB, especially in those from areas with high incidence of TB. Because these groups (for example, new immigrants) are likely to have LTBI, immune-based assays are unable to distinguish between current active disease or latent infection. On the other hand, because of a temporary anergy during acute illness, sensitivity of IGRA may be reduced. A high IGRA test result may not necessarily indicate active TB, while a negative IGRA result does not rule out active TB. Thus, IGRAs should not be utilized to diagnose active TB in adults and it remains a method of testing LTBI [57].

Canadian Tuberculosis Standards outline four main approaches to diagnosing active TB [58]:

- Pulmonary x-rays, with 70% to 80% sensitivity
- Sputum smear microscopy with fast turnaround time of less than 2 days, and sensitivity with and without PCR of 95% and 60%, respectively. This allows the evaluation of contagiousness.
- Polymerase chain reaction (PCR) which is a laboratory technique to amplify and detect specific DNA sequences. TB is confirmed by detecting the presence of the DNA of the *M.tb* in clinical samples [59]. PCR is usually completed within 3 to 24 hours. The sensitivity of commercial NAATs (Nucleic Acid Amplification Tests) to detect TB is high (>95%) in sputum smear-positive samples
- Culture, which is known as the gold standard to establish the diagnosis. It's sensitivity is around 90% for 3 sputum cultures. However, this test can take up to 6 weeks to obtain results.

An early diagnosis and rapid initiation of a suitable treatment regimen are crucial in TB management. A longer delay results in a higher risk for the patient to develop a more advanced condition with severe outcomes, and increasing potential for transmission to others[60, 61, 62].

The overall timelines of diagnosis can be broken down into different types of delays. Initially, there is a time lag between the onset of symptoms (when the activation happens) and the patient's first visit to seek care (known as patient delay). Following that, there is a lag between the initial medical consultation and the start of TB laboratory testing (known as suspicion delay). The pre-test delay is equal to the sum of these two delays. Finally, there is a time lag between the first sputum sample and the diagnostic confirmation, whether by PCR or culture (known as test delay) [62]. Such delays significantly affect TB management in Indigenous populations in Canada. Furthermore, diagnostic services, such as smear microscopy and radiologic equipment, may be restricted in rural settings, and isolated communities may encounter delays in transporting patients and specimens due to logistical constraints and sometime adverse weather conditions.

2.7 Treatment of active TB

The treatment of active TB has three main goals:

- Rapidly eradicate TB bacilli to result in fast recovery of the patient's clinical status and hence avoid complications and severe disease (causing lower morbidity), death (reducing mortality), and transmission (reducing contagiousness).
- Prevent drug resistance from developing and consequently spreading.
- Prevent relapse of active disease and establish a long-term cure.

Active TB treatment is divided into two phases of an initial intense period and a follow-up phase. To fulfil the first and second objectives, several effective medications are utilized concomitantly during the early phase. The follow-up phase, in which just two medications are normally administered, addresses the third goal. The timeline of this phase varies based on markers of relapse risk, the medications used during the first phase, and the findings of drug susceptibility testing performed prior to the treatment. Therapy can continue on a daily or intermittent basis [12].

Section 5.3 summarizes the treatment regimens recommended by the Canadian Tuberculosis Standards for adults with fully drug-susceptible (or expected to be fully drug-susceptible) illnesses. If there is a higher probability of relapse, such as having more advanced form of disease and/or cavities on a chest x-ray in the first two months of treatment, being culture-positive after two months of treatment, or having a cavity on a chest x-ray at the end of treatment, the second phase may be extended from four months to seven months, for a total of nine months of therapy [12, 63].

2.8 TB vaccines

Bacille Calmette-Guérin (BCG) refers to a group of live, attenuated vaccines produced from *Mycobacterium bovis* by Calmette and Guerin. Between 1908 and 1921, the initial strain was created at the Pasteur Institute in Paris. Other strains have been further developed in many laboratories across the world by repeated sub-culturing. These strains now vary widely in terms of the genome and a variety of physiologically fascinating characteristics, such as the capability to produce virulence lipids and antigens [64, 65]. Currently, BCG is the only TB vaccine available.

Recommended by WHO, BCG immunization is required in 161 member nations. The BCG World Atlas [66], a global online report of BCG usage, has been recently updated to provide specific insights into current and previous BCG policies in an accessible, online format The National Research Council Canada [67] began funding controlled trials of BCG safety and effectiveness in Quebec and Saskatchewan in 1926 and 1933, respectively [68, 69]. BCG vaccination, whether universal or selective, was then widely administered across Canada. BCG vaccination was gradually phased out in most communities as anti-TB medications and treatments became available and incidence rates decreased. Its administration has been limited in recent years to First Nations and Inuit people, and it has been used as part of TB elimination efforts. However, following reports of disseminated BCG in children with congenital immunodeficiencies and uncertainties regarding its appropriateness, BCG is being phased out in this population as well [70].

2.9 Drug-resistant TB

Drug-resistant TB is defined as a strain of *Mycobacterium* tuberculosis that exhibits resistance to one or more first-line medicines, such as isoniazid (INH), rifampin (RMP), pyrazinamide (PZA), and ethambutol (EMB). Drug resistance has a variable influence on the result of TB treatment depending on which drug, or a combination of drugs are used in TB treatment [71]. Two systems have been implemented in Canada to monitor drug-resistant TB: (i) the Canadian TB Reporting System and (ii) the Canadian TB Laboratory Surveillance System. Susceptibility of individuals to developing drug-resistance TB depends on several factors including [72]:

- previously treated for active TB, especially inadequate and incomplete therapy that lasted more than 3 months,
- originated from, resided in, or travelled to a place where drug-resistant TB is widespread
- had contact with a person with infectious drug-resistant TB

In Canada, prior TB treatment and foreign birth are the two main risk factors for drug-resistant TB, but the rate of drug resistance among Indigenous population is relatively low at $\sim$2% [73].

2.10 Global epidemiology

In 2020, an estimated 9.9 million individuals had contracted TB worldwide, equivalent to 127 cases per 100,000 people [3]. TB has a worldwide distribution, with an estimated two billion individuals (about 30% of the population) harbouring *M.tb*. The worldwide prevalence of TB peaked in 2003 but has since been steadily decreasing. Asia ($\sim$45%) hosts the highest number of new cases of the disease in 2016, followed by Africa ($\sim$25%) [74]. The epidemiology of the disease varies greatly depending on the location. For example, India, sub-Saharan Africa, Micronesia, and the islands of Southeast Asia have the highest incidence with 100 or higher cases per 100,000 population. China, Eastern

Europe, Central, and South America, and northern Africa are among intermediate incidence rate regions with 26 to 100 cases per 100,000 population. The Lowest rates are reported in the United States, Canada, Japan, Western Europe, and Australia (below 25 cases per 100,000 population) [28].

As a result of efforts towards the global Stop TB Strategy, the annual number incidence cases has been consistently reducing since 2006. Similarly, after the peak of 141 cases per 100,000 in 2002, the prevalence rate has been steadily declining. However, the COVID-19 pandemic has hindered the progress towards TB goals and objectives. In 2020, the number of people dying from TB increased, the pace of decline in the annual number active TB slowed, significantly fewer cases were diagnosed and treated for TB or given TB preventive treatment than in 2019, and funding for essential TB services reduced [3]. While the WHO End TB strategy intended to decrease TB prevalence by 20% and fatalities by 35% between 2015 and 2020, only 11% and 9% reductions in incidence and mortality were achieved globally in the same period [3].

2.11 TB in Canada

TB was a major cause of illness and mortality in Canada throughout the first half of the twentieth century. Statistics on the reported number of cases and the fatality rate are available as of 1924 onward. In 1933, a nationwide system for reporting TB cases was established, providing a more accurate picture of TB burden in Canada. According to published records, TB was responsible for 1 in 13 recorded deaths in Canada in 1926. Both the reported TB cases and the overall incidence in Canada have continued to decline over the last two decades, but at a much slower pace than the reduction seen between 1950 and 1990. In 1990, incidence the rate was reported to be 7 cases per 100,000 population, but it was decreased to an all-time low rate of 4.6 cases per 100,000 population in 2010, with a total 1,577 cases reported in 2010. [75].

Despite declining TB in Canada, the disease continues to be a significant burden among foreign-born individuals and Indigenous communities, with the incidence of TB in Inuit communities being over 290 times higher than in the non-Indigenous, Canadian-born community. Foreign-born individuals are also disproportionately affected.

The number of active TB disease cases grew from 1,642 in 2015 to 1,737 in 2016,

equivalent to a 4.6–4.8 cases per 100,000 population rise in the prevalence rate. Foreign-born individuals accounted for 70% of the cases and the incidence rate remained greatest among Canadian-born Indigenous people (23.5 cases per 100,000 population), especially among the Inuit (170.1 per 100,000 population) [76].

Persistently high incidence of TB in Inuit Nunangat highlights the health inequities between Inuit and other Canadian communities. Deaths from TB, as well as rising TB rates and incidence in some areas, emphasize the need for a national strategy to stop TB among Inuit people, as well as tackling economic inequality and the socioeconomic conditions of Inuit health such as housing, mental wellness, food security and nutrition, and access to wider health services [9, 10].

Chapter 3

Literature Review

Indigenous populations in Canada have experienced the highest rates of TB morbidity and mortality, with a peak of 9.3% annual mortality in western Canada. Mitigating TB among these populations has received much attention, especially in the context of global efforts for TB elimination [77, 78].

Even before Koch discovered Mycobacterium Tuberculosis *M.tb* as the causal agent of TB in 1882, it was widely accepted that the disease was linked to socioeconomic factors such as poverty, lack of nutrition, and overcrowding [79]. It has now been well-established that social and behavioral factors (such as living conditions, overcrowding, and lack of nutrition), as well as other comorbid illnesses such as diabetes and HIV are linked to the development of TB [80].

The National Collaborating Centre for Indigenous Health has released a report by Reading and Wien, delineating the health inequalities experienced by a diverse group of Aboriginal people in Canada from existing data [81]. This report classifies social determinants of health into three categories: proximal (e.g., health behavior, social, and physical environment); intermediate (e.g., resources, systems, community infrastructure, and capacities); and distal (e.g., historical, political. social, and economic). These variables continue to impact Indigenous people's health from various perspective throughout their lives [81].

In 2011, the reported incidence rate of TB among the Inuit population exceeded 254 times higher than non-Indigenous Canadians and around 38 times higher than the entire Canadian population [82]. Recognizing the importance of reducing TB rates among Inuit

Nunangat, Inuit Tapiriit Kanatami (ITK) has been working along with the Inuit Public Health Task Group and additional Inuit health partners to establish an Inuit-specific plan. Health Canada launched its *Strategy Against Tuberculosis for First Nations On-Reserve Communities* to assist combat TB in on-reserve communities. Inuit Tapiriit Kanatami also presented the *Inuit-specific Tuberculosis Strategy* in March 2012 to promote awareness for the need to implement more effective TB prevention, control, and care, as well as to propose a pathway for decreasing the rate of active TB within the Inuit Nunangat population [9, 10]. The Framework for Action aimed to reduce the national incidence of recorded TB in Canada to 3.6 per 100,000 or less by 2015.

The key areas of attention in this framework were: 1) Improving and optimizing ongoing efforts to prevent and control active TB disease; 2) Making it easier to detect and treat latent TB infection in those who are at high risk of developing active TB illness; and 3) Advancing collaborative actions to address the risk factors of TB [83]. However, evidence that the goal was not attained indicates that action plans were inadequate and further public health interventions, in addition to routine contact-tracing and screening, are needed to combat TB in Nunavut. Understating the impact of these interventions and their individual or combined effects on TB incidence has therefore become an important line of research, highlighting the important role for mathematical and computational models.

3.1 Modeling of TB dynamics

TB has always been a top candidate for mathematical modeling [84]. Mathematical models have delivered several advantages in the TB epidemiological research, and computational analysis of TB dynamics has already made major contributions [85, 86, 87]. The frameworks employed by more recent studies have included dynamical systems, traditional differential equations, deterministic and stochastic compartmental models [88, 89, 87], as well as detailed agent-based or network-based simulations and fractional models [90, 91, 92]. Models of TB have been used to characterize the epidemiology of disease, and evaluate the impact and cost-effectiveness of therapeutic options, interventions and strategies to understand the correlation between population structure and epidemics [93].

3.1.1 Compartmental models

Since 1968, various form of state-transfer compartmental models of TB have been used to approximate TB epidemiologic patterns, model the interaction between TB and other infectious diseases, explore how the attributes of the disease vary according to different strategies, and better understand TB transmission mechanisms, antimicrobial resistance in highly endemic areas, and investigate the effect of contact-tracing [94, 87, 89, 84]. For example, Kumar Das et al. developed a five-dimensional compartmental model that took into account the infectivity of both smear-positive and smear-negative individuals, and derived the expression for the basic reproduction number using the next-generation matrix approach [95]. Five groups were classified within the population: Uninfected, Latent TB, Smear positive, and Smear negative and Treated individuals. Their study revealed that the presence and infectivity of smear negative individuals in a TB epidemic has a significant impact on determining the accurate epidemic threshold, R_0 (referred to the reproduction number) [95].

Another compartmental model formulation consisting of seven classes, included the susceptible, vaccinated, exposed, undiagnosed infectious, diagnosed infectious, treated, and recovered compartments [96]. According to the findings, maintaining the basic reproduction number below one may not guarantee TB elimination [96]. Vyambwera et al. [88] proposed a stochastic SEIT (Susceptible, Exposed, Infected, Treated) model for TB mechanisms that is especially suitable for densely populated contexts like camps or crowded prisons. Other studies applied the model with appropriate adjustments depending on the needs and the research question.

3.1.2 Agent-based models

With advancement in computational modelling and increase in computing power, more details models have been used to study the TB dynamics. For instance, Ragonnet et al. [97] created a Python-based stochastic agent-based model that generated realistic demographic composition and social mixing using a family, school, and workplace framework. A TB disease dynamics was coupled with the population level transmission, simulating infection, transmission, and numerous available control strategies. The findings revealed that integrating agent-based simulation with social mixing data and TB

control history can yield significant insights into the dynamics of local TB epidemics [97]. Agent-based computational models have also been used to study the dynamics of drug-resistance. For example, Espindola et al [90] studied the emergence and spread of extensively drug-resistance while accounting for spatial structure [90]. Agent-based TB epidemic simulation models have also been used to forecast outcomes, for example in household contact-tracing within a moderate-burden context. Contact-tracing could have a significant epidemiological effect, but requires a large population coverage [98].

3.1.3 Within-host models

Mathematical models have been used not only to describe the population-level dynamics of TB under various scenarios, but also to investigate the immune response to infection, including the development of lung granulomas, as well as to qualitatively and quantitatively characterize the cellular and cytokine control network during infection [99, 100]. In-host computational models of *M.tb* infection concentrate on activities that take place in target host components, such as the lungs, lymph nodes, and blood. Continuous, discrete , and hybrid models are among possible formulations. These models provide the foundations for studying disease dynamics, treatment and prevention mechanisms [99]. For instance, a multi-compartment model has been developed [99, 101], which comprises connected sub-models that replicate several physiological compartments. Lung, lymph node, lymphatic, and blood components can be readily included in TB models. The use of within-host agent-based models has shown the importance of T-cell-related processes in TB infection development, for example, T-cell recruitment volume and timing, T-cell mobility, and macrophages activation [102, 103, 100]. Although there has been a significant progress in within-host modeling, the frameworks remain relatively simple, and modelling approaches require improvements to offer an appropriate level of complexity. It is also important to develop models that capture within-host and population-scale dynamics together to investigate the effects of disease and interventions at both levels [99].

3.1.4 Models of therapeutic vaccines

Novel TB vaccine candidates are currently under investigation, and some have progressed to clinical trial phases [104]. There are few studies investigating the effect of therapeutic vaccines at population level, including a simple compartmental deterministic model that accounts for key biological, clinical, and epidemiological features of the disease to evaluate therapeutic vaccines based on their expected effects [105]. A recent study considers possible effects of new TB vaccinations in China, South Africa, and India by altering vaccine efficacy in preventing infection or disease as well as effectiveness in those who are not infected or those who are infected with *M.tb*, and the duration of vaccine-induced protection [106]. This research used R programming language to create a population-level compartmental deterministic transmission model that was age-stratified.

In order to capture the potential impact of therapeutic vaccines, *in-silico* models have also been developed that are capable of predicting the combined success of a traditional anti-TB chemotherapeutic strategy with a possible therapeutic vaccination such as RUTI (see Chapter 7). The *in-silico* Trial for Tuberculosis Vaccine Development (STriTuVaD) project used a new computational modeling platform called the Universal Immune System Simulator (UISS) to assess a particular therapeutic vaccine against tuberculosis. UISS for Tuberculosis is thought to be capable of simulating the immune system processes affected by tuberculosis and predicting the result of a practical clinical trial that involves the administration of treatment like the RUTI vaccination [107, 108, 109]. We will further review literature on therapeutic vaccines in Chapter 7.

3.2 TB modelling of Indigenous populations

Historical data from First Nations communities in the late nineteenth and early twentieth centuries have not been fully investigated through the use of modelling tools to explore the TB epidemic. In 2009, Clark and Cameron used compartmental models to assess and forecast future changes in annual risk of infection using data dating back to 1926 [110]. As the first study to forecast future TB disease burden among the Canadian First Nations population, the study set attainable targets for TB elimination within First Nations communities. Using a maximum likelihood model, the study quantified the impact of medical and public health interventions on the overall pandemic using data from

1974 to 2002. The estimates were then used to forecast future TB prevalence using a state-transfer, compartmental framework, demonstrating that the incidence of the TB cases would not fall below 1 per 100 000 persons by 2034, but eliminating TB among Indigenous peoples in Canada would be an attainable goal. However, the study did not simulate the effect of any specific intervention or identify what control plan should be used in order to eliminate TB [110].

Using a differential equation model and historical TB mortality data, Ackley et al. [111] explicated high TB mortality and accelerated epidemic reduction in First Nations from 1885 to 1940. They examined two possible explanations of the epidemic characteristics found in this setting. First, they considered the impact of malnutrition on both TB and population dynamics prior to 1900. Second, they evaluated the impact of heterogeneity in TB susceptibility [111]. The findings revealed that changes in the population nutritional condition can have a major impact on TB behavior. This study also discovered that including heterogeneity in the model, susceptibility to *M.tb* infection or risk of active TB disease improves fit to both TB mortality and census data [111].

Recently, Tuite et al. [112] created a stochastic, agent-based model of TB transmission that took into account both household and community contact structure. Early treatment of current cases, rapid contact-tracing, increased screening programs for Latent TB infection, and lower household density were among the strategies evaluated. The goal of this research was to learn more about how to appropriately deploy limited resources so that disease transmission is minimized and at-risk groups are protected. In a 10-year period, the study outcomes of interest were TB incidence and total diagnosed active TB patients. It was found that shortening the duration between the onset of active disease and the start of treatment was an effective way of lowering TB burden. Expanding general population screening was also likely to lower the burden of TB in the short term, whereas other possible interventions were expected to be ineffective [112]. While this research employed mathematical modelling to assess how interventions may improve existing TB control efforts in the Nunavut region, it did not define the time for start of simulation, nor not did it provide a clear analysis of the effect of each intervention over time [112].

There are also modelling studies that target TB dynamics among Canadian Indigenous populations, focusing on the epidemiology of TB from alternative perspectives. For instance, Doroshenko et al. [113] investigated the genomics and epidemiological drivers of

two TB outbreaks in Canadian First Nations communities, finding little evidence to support the concept that endemic *M.tb* strains gained mutations, resulting in their development as outbreak strains. They discovered that the transmission of TB epidemics appears to be driven by a mix of source case characteristics, contacts, and the environment [113]. In a separate study, Cormier et al. [114] undertook a comprehensive assessment of the proximate drivers of TB among Indigenous peoples across the world. Their goal was to ascertain how each variable contributed to TB among Indigenous populations and what efforts were made to address each factor. After reviewing 475 studies, it was discovered that Indigenous populations had a greater incidence of proximal factors than the general population. Diabetes was shown to be more common among Indigenous groups in high-income nations than in low-income countries. The incidence of alcohol usage was found to be comparable to that of non-Indigenous populations, while drinking patterns varied widely [114]. Smoking prevalence and smokeless tobacco usage were found to be much greater among Indigenous communities than non-Indigenous groups. Malnutrition was found to be widespread in the majority of Indigenous communities investigated in the study. Substance abuse was more common among Indigenous people in high-income nations compared to low-income nations, with substantial disparities amongst Indigenous groups. There was insufficient research conducted on HIV, overcrowding, and housing conditions among Indigenous peoples to draw concrete conclusions [114].

In a recent study, Kilabuk et al. [115] conducted in-person home surveys (as part of a door-to-door TB prevention campaign in Iqaluit, Nunavut) among those who lived in predefined residential areas that were deemed to be at high risk for TB. The study found that overcrowded housing conditions and Inuit ethnicity were closely linked with Latent TB infection among high-risk residential areas for TB in a remote Arctic region of Canada. This suggests that a comprehensive screening and treatment program in combination with addressing the persistent housing scarcity in the Canadian Inuit Nunangat will be critical to eliminating TB. A report published by Heffernan and Long [116] illustrates the challenges and inform policymakers that TB elimination targets are unlikely to be met in the absence of significant programmatic modifications. As a result, there is a need for a nationally coordinated response to disease elimination to ensure that the care and interventions provided meet necessary standards. Basham et al. [117] also suggest that the system is currently ill-equipped to eliminate TB and that a nationally coordinated TB

plan is essential.

In response to the inadequacy of Stop TB program, on March 23, 2018, the President of Inuit Tapiriit Kanatami (ITK) announced a collaborative Inuit Tapiriit Kanatami (ITK)-federal government pledge to eliminate TB across Inuit Nunangat by 2030, with an additional goal of decreasing active TB incidence by at least 50% by 2025. Despite the significance of Canada's commitment to achieve TB elimination, no study has examined whether these goals in Nunavut, Canada, can be met within proposed timelines under the standards for treatment regimens. This dissertation aimed to address this void through mathematical modelling and simulations encapsulating the key components of action plans for TB elimination.

Chapter 4

Study Population

With a total area of nearly 2 million km^2, Nunavut, which means 'Home Land' in the native Inuktitut language, is the largest territory of Canada with 39,535 inhabitants, 85% of whom are Inuit [118]. The people who live in Nunavut have a rich history of thousands of years and have a distinctive culture which is characterized by beliefs and practices [119].

The territory of Nunavut is sub-divided into three regions: Qikiqtaaluk in the east, Kivalliq in the center of the Arctic along Hudson Bay western coast, and Kitikmeot in the west. The traditions and beliefs of the Inuit people have been incorporated into the modern political structure, which is overseen by the territorial government of Nunavut. Inuktitut, along with French, English, and Inuinnaqtun, are recognized as official languages in Nunavut. The economy of Nunavut is built on tourism, on and off-shore fishing, arts and crafts, and renewable resources. The territory's major employer is the government, closely followed by the private sector and services [120].

According to the 2016 Census, the Inuit population is young, with a median of 25 years of age, considerably lower than median age of 42 years for general population in Canada [118].

4.1 Nunavut health status

The Inuit people encounter significant health and well-being issues in comparison to the rest of Canadian population, and there are considerable health disparities between Indigenous and non-Indigenous populations [121]. The Social Determinants of Indige-

nous Peoples' Health Framework lists nine significant hurdles that make it difficult for Indigenous populations to access healthcare [81, 122].

As was described in Chapter 3, these obstacles can be divided into three groups: proximal, intermediate, and distal. Proximal barriers include geographical location (such as geographic isolation and unreliable transportation infrastructure), educational attainment, discriminatory attitudes, colonization, historical inter-generational traumas and stigma, and limited access to healthcare professionals who may also have less training than is necessary for their roles. Employment, income, and the absence of a healthcare professional education system that is culturally relevant to the needs of Indigenous populations are considered as intermediate impediments. Distal impediments are racism, colonialism, and social marginalization, which contribute to a complexity in social determinants of health for Indigenous populations [81, 122].

Delays in diagnosis and start of treatment may be caused by the obstacles that prevent access to health services in these remote Indigenous communities and by ongoing shortages and high staff turnover [123]. Furthermore, Indigenous people suffer from lack of adequate housing infrastructure which has been reported to enhance health and social inequalities [124]. Inuit people in Canada have the greatest housing disparities; their rates of overcrowding and housing impairment are 10 and 5 times greater than the national average, respectively [124].

4.2 Housing

Over 80% of the population of Nunavut and Nunavik currently resides in social (supported) housing, making the housing market in Inuit Nunangat predominantly subsidized [124]. The need for new housing continues to be driven by the young and expanding population. Between 2006 and 2016, the Canadian population increased by 11%; in contrast, the Inuit population increased by 20% [118]. The average family size in Canada is currently about 2.9 while the average household size in Nunavut is 3.8 [125].

The annual residential construction is insufficient to meet the demand for housing due to the short construction season and high material costs. There are complex and dynamic interactions between the shortage of housing, the prevalent poor housing conditions, and the various social and health inequalities that directly affect disease spread and control

[124].

Although it is outside the scope of this dissertation to discuss social, cultural, economic, and environmental factors that have direct or indirect impact on TB incidence in Inuit populations, we consider and evaluate the extent to which household size reduction can contribute to TB elimination.

Chapter 5

Modelling Framework

5.1 Compartmental modelling

Before delving into the ABM, I start with a classical, compartmental structure model of TB dynamics. Considering the natural history of the disease, I stratified the population (*N*) into six compartments. Susceptible (*S*) individuals may become exposed to the disease, and if infected, enter the latent TB (*L*) class, referred to as LTBI. Latent TB individuals are not infectious until they develop active TB (*A*). As a result of contact-tracing, LTBI may be identified and treated (L_T). All active TB patients are expected to be identified and receive appropriate treatment (A_T). All successfully treated individuals, either latent or active, will regain susceptible status. The relationship and movement between these classes, illustrated by the schematic diagram in Figure 5.1, can be described by the following system of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \beta AS + \delta\gamma L_T + \theta\eta A_T - \mu S \\
\frac{dL}{dt} &= \beta AS - (\tau + \alpha + \mu)L + (1-\theta)\eta A_T \\
\frac{dL_T}{dt} &= \tau L - (\gamma + \mu)L_T \\
\frac{dA}{dt} &= \alpha L + (1-\delta)\gamma L_T - (\xi + \mu)A \\
\frac{dA_T}{dt} &= \xi A - (\eta + \mu)A_T,
\end{aligned} \tag{5.1}$$

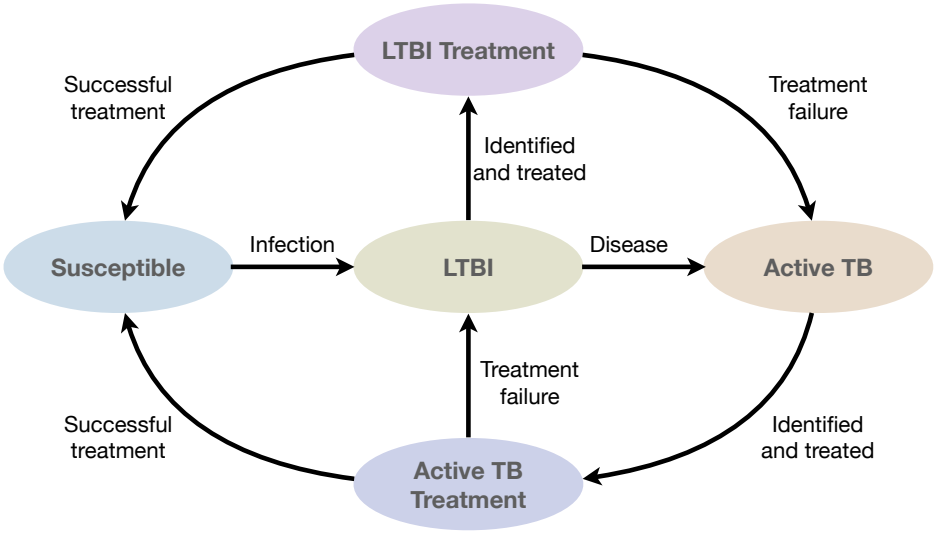

Figure 5.1: Schematic structure of the model for the transmission dynamics and treatment of TB.

where β is the transmission rate; α is the rate of developing active TB; τ is the rate of diagnosis and treatment LTBI; γ is the rate of successful treatment completion (reflecting treatment efficacy); δ is the fraction of successfully treated LTBI; ξ is the rate of diagnosis and treatment of active TB; η is the rate of treatment completion in active TB; and θ is the fraction of successfully treated active TB (reflecting the treatment efficacy). Death and birth rates are both represented by μ, maintaining a constant population size.

5.1.1 Reproduction number

Using the next generation matrix method derived by Diekmann et al. [126], in this section I calculate the basic reproduction number (R_0) of TB. The basic reproduction number is

$$R_0 = \rho(FV^{-1}) \tag{5.2}$$

where F represents the Jacobin of the rate of the flow from susceptible class to infected compartment (Jacobin of $\mathcal{F}$) and V is the Jacobin of all other flows of other classes (Jacobin of $\mathcal{V}$), calculated at the disease-free equilibrium. The disease classes in the compartmental model in Equation 5.1 are L, L_T, A, A_T and the only non-disease compartment is S. The secondary infection happens when an individual from the susceptible

compartment contracts the infection and enters to the latent class with the term βAS, or the treatment of active TB fails and the relapse happens with the rate of $(1-\theta)\eta$. Therefore, $\mathcal{F}$ and $\mathcal{V}$ are calculated as follow:

$$\mathcal{F} = \begin{pmatrix} \beta AS \\ 0 \\ 0 \\ 0 \end{pmatrix} \tag{5.3}$$

$$\mathcal{V} = \begin{pmatrix} (\tau+\alpha+\mu)L - (1-\theta)\eta A_T \\ (\gamma+\mu)L_T - \tau L \\ (\xi+\mu)A - \alpha L - (1-\delta)\gamma L_T \\ (\eta+\mu)A_T - \xi A \end{pmatrix} \tag{5.4}$$

F and V which are the derivatives of $\mathcal{F}$ and $\mathcal{V}$ with respect to disease compartments is obtained by:

$$F = \begin{pmatrix} 0 & 0 & \beta S & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix} \tag{5.5}$$

$$V = \begin{pmatrix} (\tau+\alpha+\mu) & 0 & 0 & -(1-\theta)\eta \\ -\tau & (\gamma+\mu) & 0 & 0 \\ -\alpha & -(1-\delta)\gamma & (\xi+\mu) & 0 \\ 0 & 0 & -\xi & (\eta+\mu) \end{pmatrix} \tag{5.6}$$

The disease free equilibrium solution with $L = L_T = A = A_T = 0$ has the form of $x_0 = (N, 0, 0, 0, 0)$. Therefore $\rho(FV^{-1})$ gives R_0 as:

$$R_0 = \frac{N\beta(\eta+\mu)[\alpha(\gamma+\mu)+\gamma\tau(1-\delta)]}{\det(V)} \tag{5.7}$$

Where

$$\det(V) = (\tau+\alpha+\mu)(\gamma+\mu)(\xi+\mu)(\eta+\mu) - (1-\theta)\eta\xi[\tau\gamma(1-\delta)+\alpha(\mu+\gamma)] \tag{5.8}$$

5.2 The general framework of ABM

ABM is a computational model in which agents interact within a virtual computer environment to generate a dynamics resembling the underlying real-world phenomenon. Agents with a predetermined set of attributes communicate with each other and their surroundings according to some prescribed rules [127]. To structure their activities and interactions, agents are given attributes and basic behavioral rules. They can also change their behavior in reaction to interactions and experiences with other agents and their environment [127].

The main feature of an ABM is that it enables the creation of population-level phenomena from emerging localized properties, and could illustrate a more prevalent or distinct pattern from what may be observed based on the sum of individual behaviors alone. Consequently, ABM is known as a bottom-up approach, where actions at the micro level yield the dynamics at the macro level [128].

ABMs may include a range of characteristics and parameters that combine to influence how individual outcomes shape. The consequences of dynamics and continuing processes, such as ageing and community mobility, can also be explicitly incorporated into ABMs. These inter-connections, along with biological, behavioural, and social processes, form a comprehensive population level health system [129].

Autonomy, *heterogeneity*, *feedback*, and *stochasticity* are additional distinctive characteristics of ABMs. Their autonomous nature allows agents to decide for themselves how to respond to their environment and pre-programmed behavioural guidelines [130]. In an ABM, heterogeneity is represented by differences between agents and between elements present within the environment. These variables can exhibit a variety of static

and time-varying attributes [131, 127]. Feedback based on past experiences alters the trajectory of future reactions and can lead to unexpected changes in the behaviour of agents and their relation in the environment over time [132, 127]. Stochasticity and randomness affects how the framework evolves and behaves over time, which enables the model to develop in a probabilistic (as opposed to deterministic) manner [127].

Due to these characteristics, ABMs are more flexible than alternative approaches when considering relations that are affected by time and space. ABMs (and complex systems techniques in general) provide a wider range of computational solutions than standard analytic (equation-based) methodologies, with the opportunity to shed light on important public health issues [133].

An ABM is made up of three key components: 1) agents, 2) environment, and 3) a set of rules describing the relationship among agents and with the environment. On a simple level, agents can interact with one another within a given environment, and their activities are defined by a set of codified rules. By adhering to these rules, an agent makes a decision at any time step before the system advances to the next stage [134].

ABMs are increasingly being used in social and public health domains to simulate the transmission of infectious diseases and study public health management scenarios. Because interactions between people and their local settings result in population patterns of disease spread, ABMs are a suitable approach to understanding the transmission and control of infectious diseases [135].

The susceptible-infected-recovered (SIR) model introduced by Kermack and McKendrick [136] in the 1920s is a common foundation of ABMs for infectious disease transmission, whereby the flow within different compartments are controlled by a set of equations [136, 137]. Lacking from these typically aggregate, compartmental models, individual heterogeneities and complex network of interactions are accounted for in ABMs, offering new insights into infectious processes in a real-world context.

While ABMs are computational systems and may not provide algebraic solutions that can be analyzed similar to some equation-based models, they are founded upon mathematical concepts. A basic formulation of an ABM is described in the following section.

5.3 Mathematical formulation of ABM

A unique partial recursive function exists for each independent model that creates an ABM entity, and can be described as a computer program. Thus, an explicit collection of mathematical formulas (i.e., recursive functions) can theoretically be used to express an ABM [138, 139]. If the result of a system of equations depends on one or more of its previous results, the system is recursive (as opposed to simultaneous). In other words, it is possible to find the values of all state variables sequentially. The system is referred to as a Markov Chain and is considered memoryless if, in addition, the probability distribution of the next state only depends on the present state (and not the full history). As such, one can always describe an ABM as a Markov process [140]. In this section, outlining the formalism depicted by Shoukat et al [141], and using the notation introduced by Richiardi [139], I summarize the mathematical formulation of my ABM.

Consider an ABM, $\mathcal{A}$, with *m* agents that change over time. The model can be continuous or discrete. Here, describe the model at discrete times $t_1, t_2, ..., t_T$, with $t_k < t_{k+1}$; this time-step in my model is set to “week". Even if the underlying model runs in near continuous time, the model’s states can be sampled at discrete observation times. At any time, t, an agent $a_i \in \mathcal{A}$ is associated with the variable $\mathbf{x}_{(i,t)}$, which takes values in some finite field $\mathbb{F}$ and defines the attributes of agent a_i. Assuming the variables are quantitative in nature (i.e., real numbers) and can be codified in a finite set of possibilities, then $\mathbf{x}_{(i,t)} \in \mathbb{R}^n$ corresponds to an n-dimensional vector, depending on the number of characteristics we assign to each agent. The variable $\mathbf{x}_{(i,t)}$ represents the state of an agent. For instance, in my model, the vectors of age, health status, and household members associated with each agent are among the factors used to characterize the agents, making the collection of variables with a mix of numerical and codified elements. Equation 5.9 describes the evolution of the agent’s state variables over time using Richiardi’s model’s notation [139].

$$\mathbf{x}_{(i,t+1)} = f_i(\mathbf{x}_{(i,t)}, \mathbf{x}_{(i-,t)}, \alpha_i), \tag{5.9}$$

In this equation, f_i is an agent-specific update function (sometime referred to as transition function), which implements the agent’s Perception-Decision-Action (PDA)

cycle internally; α_i is a agent-specific parameters vector (some of these parameters could be stochastic); and $\mathbf{x}_{(i\_,t)}$ represents the state of all agents other than a_i. The set of update functions, f_i's, each of which for the agent a_i, defines the 'Data-Generating process' (DGP) of the framework. These functions may be complex, involving discontinuities, 'if-else' statements and fuzzy logic rules in their implementation. If each f_i is a polynomial, the model is known as a polynomial dynamical system and is in agreement with what derives from computational tools and theoretical results of computer algebra [142].

The full picture of system state at time t can be depicted by the collection $\mathbf{X}_t = [\mathbf{x}_{(1,t)}, \mathbf{x}_{(2,t)}, ..., \mathbf{x}_{(m,t)}]$, which is an $n \times m$ matrix of all individual states, where m is the number of agents, here the Nunavut population, and n is the dimension of the vector of characteristics. As such, the time evolution of the overall model is as follows:

$$\mathbf{X}_{t+1} = F(\mathbf{X}_t, \alpha) + \xi_t, \tag{5.10}$$

where α is an agent-specific vector of parameters, (such as the infectiousness, activation risk, etc.) and $\xi_t \in \mathbb{R}^{n \times m}$ is a matrix containing all stochastic elements of agents at time t. Since the DGP functions f_i may be nonlinear with stochasticity, the ABM may be represented by a more general map **F**:

$$\mathbf{X}_{k+1} = \mathbf{F}(\mathbf{X}_k, \alpha, \xi_k), \tag{5.11}$$

where ξ_t is a stochastic random matrix, and $(\mathbf{X}_0, \xi_0)$ is the initial condition of the system at t_0. We refer to equation 5.11 as the transition equation of the system. The ABM's Markov chain representation can be seen by taking a closer look at equation 5.11. However, in reality, these expressions might be convoluted and challenging to understand. In fact, the explicit set of functions f_i and, by extension, **F**, are not readily tractable mathematically. The transition functions in equation 5.11 are frequently expressed in closed form, simple, linear (or linearized), and with no (or a minimum degree of) heterogeneity in analytical frameworks.

Any aggregate of variables can be carried out by calculating the expected value over stochastic components. However, the definition of equation 5.11 has little or no limits in ABMs. The transition equation may not have an analytical form, as the state space of the framework can expand significantly (possibly with infinite states).

After the DGP has been described, one is interested in some aggregate or macro aspects of the model. Let h be a statistic function (i.e., a projection from **X** to **Y**) over the system state, and $\mathbf{y}_t$ a set of aggregate statistics at time t. Then:

$$\mathbf{y}_t = h(\mathbf{x}_{(1,t)}, \mathbf{x}_{(2,t)}, ..., \mathbf{x}_{(m,t)}) = h(\mathbf{X}_t) \tag{5.12}$$

The solution (i.e., shape and form) to equation 5.12 at each time t can always be calculated through backward iterations, which traces $\mathbf{y}_k$ back to the initial circumstances, regardless of the complexity and specification of each f_i. That is

$$\begin{aligned}
&\mathbf{y}_0 = h(\mathbf{X}_0), \\
&\mathbf{y}_1 = h(\mathbf{X}_1) = h(\mathbf{F}(\mathbf{X}_0, \alpha, \xi_0), \\
&\mathbf{y}_2 = h(\mathbf{X}_2) = h(\mathbf{F}(\mathbf{X}_1, \alpha, \xi_1) = h(\mathbf{F}(\mathbf{F}(\mathbf{X}_0, \alpha, \xi_0), \alpha, \xi_1)), \\
&\quad \vdots \\
&\mathbf{y}_k = h(\mathbf{F}(...\mathbf{F}(\mathbf{X}_0, \alpha, \xi_0), ...)))
\end{aligned} \tag{5.13}$$

Because of the stochastic ξ_t terms, it may be challenging to explain how this backward iteration process uniquely connects the value of $\mathbf{y}_t$ with its initial conditions. These random terms cannot be averaged out by expectations because the DGP functions in equation 5.11 and the statistic function h may be nonlinear. Therefore, Monte Carlo analysis is the only method that can reveal the relationship between the initial conditions $(\mathbf{X}_0, \xi_0)$ and the statistics **Y**. A distribution for **Y** could be obtained by running Monte Carlo simulations with various initial conditions and parameter values. The pseudo-random number generators (PRNG), which are the basis for Monte Carlo techniques, are deterministic algorithms by nature, given the initial value of the seed. Therefore, any stochasticity added to the model *via* a PRNG has a deterministic nature, allowing us to further investigate the ABM's formalization. The stochastic term ξ_k can be thought of a deterministic function of the seed and a determinant of the initial conditions. Defining $\mathbf{Z}_0 = \{\mathbf{X}_0, s\}$, equation 5.11 can be rewritten as:

$$\mathbf{X}_{k+1} = \mathbf{F}(\mathbf{Z}_0, \alpha) \tag{5.14}$$

and hence the statistic **Y** is given by:

$$\begin{aligned} \mathbf{X}_k &= \mathbf{F}(\mathbf{F}(...\mathbf{F}(X_0, \alpha, s))) = \mathbf{F}^k(\mathbf{Z}_0, \alpha), \\ \mathbf{Y}_k &= h(\mathbf{F}^k(\mathbf{Z}_0, \alpha)) \equiv g_k(\mathbf{Z}_0, \alpha). \end{aligned} \tag{5.15}$$

The “input-output transformation" function, which governs the ABM outcomes, is represented by equation 5.15. This function is a deterministic mapping of inputs (i.e., initial values and parameters of the system) onto outputs when the seed, the starting point of the PRNG, is fixed. Although this is an efficient mathematical representation, from a practical perspective, the precise form of the input-output transformation function is uncertain, and the empirical distribution of the underlying stochastic process is frequently derived by Monte Carlo simulations using various random seeds.

5.4 ABM formulation of TB dynamics

In this section, I illustrate the formulation of the ABM that describes the dynamics of TB transmission introduced by the deterministic form in equation 5.1.

It is well-known that the transmission process involves stochasticity. This includes but not limited to the contacts between individuals, disease-specific and biological factors, and environmental conditions. Here we develop an ABM, in which each agent represents a Nunavut resident, characterized by their health status as *Susceptible*, *Latent*, *Latent Treated*, *Active* and *Active Treated* each are codified as integer values of 0 = SUS, 1=LAT, 2=LATT, 3=ACT, 4=ACTT. Omitting other characteristics of each agent such as age and household composition (for the sake of simplicity at this stage and without loss of generality), an agent a is described by its internal state variable $x_a \in \{0, 1, 2, 3, 4\}$. For transitions between epidemiological statuses, either the occurrence of a successful Bernoulli event is required (such as disease transmission) or the desired time should be spent in the current status (such as treatment duration or time-to-identification).

Assuming a fully susceptible population, and introducing 10 infected agents as the initial condition, each iteration allows for agents to interact with their contacts, among which k interactions may be with infectious individuals, over a discrete time step, which is ‘a week’ in this case. If a susceptible individual interacts with an infectious agent, i.e., an active TB patient, disease transmission is determined using a Bernoulli trial.

Let $x_{a,t}$ be the internal state of a susceptible agent a at time t, and assume a interacts with k infectious agents simultaneously at time t. If b represents the transmission probability, the one-step transition probability of susceptible to latent (Figure 5.1) is given by:

$$P[x_{a,t+1} = LAT | x_{a,t} = SUS] = 1 - (1 - b)^k \tag{5.16}$$

If the transmission is successful, the susceptible individual becomes infected and enters the latent class at time $t + 1$. LTBI agents may remain in this stage for lifetime without developing active TB. They can also be diagnosed with TB test and treated to reduce the risk of developing active TB. Those who develop active TB are diagnosed and treated. Therefore:

$$\begin{aligned} P[x_{a,t+1} = ACT | x_{a,t} = LAT] &= \begin{cases} \alpha & \text{if } t > t_A \\ 0 & \text{otherwise} \end{cases} \\ P[x_{a,t+1} = LATT | x_{a,t} = LAT] &= \begin{cases} \tau & \text{if } t > t_I \\ 0 & \text{otherwise} \end{cases} \end{aligned} \tag{5.17}$$

Where α is the activation risk, t_A is the latency period, τ is the latent TB identification probability, and t_I is the time to identify a latent individual.

If an LTBI agent is diagnosed and treated, the transition to susceptible class depends on whether the treatment is successful:

$$\begin{aligned} P[x_{a,t+1} = SUS | x_{a,t} = LATT] &= \begin{cases} \delta & \text{if } t > t_T \\ 0 & \text{otherwise} \end{cases} \\ P[x_{a,t+1} = ACT | x_{a,t} = LATT] &= \begin{cases} 1 - \delta & \text{if } t > t_T + t_A \\ 0 & \text{otherwise} \end{cases} \end{aligned} \tag{5.18}$$

where δ is the probability of successful treatment, and t_T represents the treatment duration. Once the treatment duration is elapsed, the agent will return to the susceptible class with the probability δ. Otherwise, the individual will develop active TB at a randomly determined activation time, t_A.

Because all active patients are diagnosed at some point in time after becoming symp-

tomatic, there may be a delay involved in their diagnosis:

$$P[x_{a,t+1} = ACTT | x_{a,t} = ACT] = \begin{cases} 1 & \text{if } t > t_D \\ 0 & \text{otherwise} \end{cases} \tag{5.19}$$

Where t_D is the diagnosis delay. When an active TB is identified and treatment initiated, the regain of susceptible status depends on whether the treatment is successful. If treatment fails, there is a risk of relapse at some point following the completion of treatment:

$$\begin{aligned} P[x_{a,t+1} = SUS | x_{a,t} = ACTT] &= \begin{cases} \theta & \text{if } t > t_T \\ 0 & \text{otherwise} \end{cases} \\ P[x_{a,t+1} = LAT | x_{a,t} = ACTT] &= \begin{cases} 1-\theta & \text{if } t > t_T \\ 0 & \text{otherwise} \end{cases} \end{aligned} \tag{5.20}$$

where θ is the probability of successful treatment within the duration of the treatment regimen. It is worth stating that framework represented in this section is an abstract illustration of the ABM, and several functions such as if-else statements and Bernoulli trials are encapsulated in the actual computational model, depending on the demographic, age, social and biological factors as well as the scenarios under evaluation.

5.5 Model implementation

5.5.1 Structure

Each agent in the model, representing a resident of Nunavut, exhibit a time-dependent vector of variables, such as their demographics and health status. The age distribution of agents is derived from the most recent publicly available Canadian census data [118]. The model includes classes of health status to reflect the natural history of TB, as described in the compartmental structure. As a result of interaction among agents, the vector of attributes is updated over time. Given the stochastic nature of the process, 500 independent Monte-Carlo realizations were run to account for the range of possible outcomes evolving from micro-level events. The findings were then produced by averaging all realizations. The simulation code, written in Julia Programming Language, is accessible

at `https://github.com/Ellie-Abdollahi/TB`.

5.5.2 Contact patterns

Contact patterns shape how people interact on daily basis and are a major determinant of how infectious diseases spread through a population. Often, empirical contact data based on a contact matrix generated using negative binomial distributions is used to accurately describe key aspects of disease transmission, including estimating the relative risk of people in various classes [143]. The daily numbers of interactions within and between various age groups, which were sampled from negative binomial distributions, were included in the model. Daily contacts were summed up for every seven days, reflecting the simulation weekly time-step.

I took into account the possibility of both community and household transmission. The overall population was divided into households of sizes 1, 2, 3, 4, and 5+ individuals, matching the demographic composition of Nunavut reported in census data. Each agent was then assigned to a household randomly, considering no households of size 1 with an individual under 18 years of age. For households with five or more members, we fixed the maximum number of members to 15, and selected the exact size by sampling using a uniform distribution in the range 5 to 15. Note that this distribution was chosen due to the lack of data on the distribution of household sizes greater than 5 members.

In order to distinguish between the number of interactions within and outside households, I relied on the population-based research of social contacts in Canada that included the daily number of contacts occurring between and within age groups [144]. The mean and standard deviation were calculated from the same study and used to sample age-dependent contacts from a negative binomial distribution (Table 5.1). The percentage of contacts for everyday activities outside the agent's household was $\sim 60\%$ for children aged 0 to 4, $\sim 68\%$ for children aged 5 to 18, $\sim 76\%$ for adults 19 to 49, $\sim 66\%$ for older adults aged 50 to 64, and $\sim 59\%$ for those 65 years of age or older (Table 5.2) [144].

In order to take into account the community contacts, I divided the contacts for each agent with those outside the household into two categories: frequent contacts (such as interactions with coworkers or classmates) and casual or infrequent contacts with a short duration (e.g., during transportation or other daily activities). I then classified 80% of community contacts as frequent, which may happen repeatedly with some agents. The

Table 5.1: Contact matrix derived from empirical observations [144]. Daily number of contacts within and between these age groups were sampled from a negative binomial distribution and then aggregated to calculate weekly number of contacts.

Age group	0-4	5-19	20-49	50-65	65+	Mean no. of DC[a] (SD)[b]
0-4	0.33	0.15	0.37	0.12	0.04	10.21 (3.99)
5-19	0.04	0.49	0.35	0.08	0.04	16.79 (5.78)
20-49	0.04	0.16	0.56	0.16	0.07	13.79 (8.93)
50-65	0.04	0.11	0.43	0.26	0.16	11.27 (7.86)
65+	0.02	0.06	0.27	0.22	0.44	8.01 (3.21)

[a] Daily contacts
[b] Standard deviation

remaining encounters within the community were assigned randomly with other agents as casual contacts.

5.5.3 Natural history of TB

I incorporated the epidemiological statuses of susceptible, LTBI (non-infectious), and active TB (infectious), into the model. At the beginning of each simulation, I introduced 10 infectious agents in the model as initial conditions.

Contacts between susceptible and active TB agents could led to disease transmission, with a probability per contact. Since TB transmission from children is uncommon, I assumed that compared to adolescents and adults, active TB children under 12 years of age have a 95% lower risk of transmitting the disease [145].

The model included an age-dependent risk of progression to active TB disease for

Table 5.2: Age-stratified proportion of contacts occurring inside or outside of household.

Age group	% of contacts inside	% of contacts outside
0-4	40.45	59.55
5-19	31.91	68.09
20-49	24.04	75.96
50-65	33.58	66.42
65+	40.93	59.07

each infected agent in the LTBI stage during the course of the remaining life expectancy (since infection). This risk has been estimated to vary between 5% and 10% for untreated LTBI (see Section 2.1) [35, 146]. For those who progress to active TB, the length of LTBI duration can range from weeks (fast progression) to decades (slow progression), as was detailed in Section 2.1. As a means of accounting for this variability, I created a probability distribution for the average duration of LTBI based on the estimated Kaplan-Meier tuberculosis-free survival probabilities [31]. This duration for infected agents who will develop active TB was sampled from the distribution (using a Bernoulli random draw) with a probability of 45% within the first year of infection, 62% within the next two years, and 98% within the following twelve years [31].

I assumed that every agent with active TB is detected within a 1 to 4-week window after the onset of symptoms (Section 5.6.1), moving them from the untreated to the treated active TB class for the duration of treatment. Although all active TB agents are identified and treated, the contact-tracing scenario determines whether an LTBI (as a contact) is identified. Agents with LTBI identified using contact-tracing are also treated, reducing the risk of developing active TB (Figure 5.1).

5.6 Case-finding, treatment, and isolation of active TB

5.6.1 Diagnosis of active TB

Depending on the healthcare system capacity and other individual-level factors, there may be a time-lag between the onset of symptoms in active TB cases and diagnosis or the start treatment. Examples of delays in active TB diagnosis include the lack of particular attention to symptoms by patient and/or healthcare providers, a lack of appropriate infrastructure for implementing effective public health strategies, and restricted access to care and testing for TB patients [147].

As was described in Chapter 4, many of the aforementioned factors delaying timely diagnosis of active TB exists in Nunavut. While the is no data on exact timelines for case identification after develop active TB, communications with practitioners indicate that the lag-time can be as long as several weeks. I relied on a Canadian study suggesting an average of four weeks for the delay between the onset of symptoms and identification

of active TB patients [148]. Identification and treatment of TB patients is considered to be the cornerstone of control strategies, because contacts of undetected cases are continuously at risk of contracting TB infection.

I integrated time-to-identification (ToI) in my research to and assess the effect of delay in diagnosis on the annual incidence of TB in Nunavut. In the baseline scenario, I set the average ToI to 4 weeks and then considered additional scenarios in which the average ToI was reduced to 3, 2, and 1 week from the onset of symptoms. I assumed that an active TB treatment regimen started as soon as an active TB agent was diagnosed. Since there is a direct correlation between treatment and infectiousness, [149], I assumed that the infectiousness (and therefore transmissibility) of the disease was reduced by 50% after one week of treatment. Given the effectiveness of available drugs, I also assumed that active TB cases become non-infectious after two weeks of treatment, while the course of complete treatment may last for several weeks [149].

5.6.2 Treatment regimens for active TB

Effective treatment of active TB depends on early identification and the treatment regimen. Successful treatment can expedite recovery, reduce disease complications, and stop the spread of TB. Table 5.3 lists the two recommended treatment regimens for active TB in line with Canadian Tuberculosis Standards. TB manual developed for Nunavut, all cases of active TB are managed with directly observed therapy (DOT), using a treatment regimen in which Isoniazid (INH), Rifampin (RMP), Pyrazinamide (PZA), and Ethambutol (EMB) are taken every day for eight weeks as the initial phase, followed by a 4-month treatment using INH and RMP. The second treatment regimen is applied in specific cases of TB [11], and therefore not included in the scenario analyses.

5.6.3 Isolation

As was described in Chapter 2, TB as an airborne disease offers a considerable risk to those who are in close contact with an active case. The Nunavut TB manual recommends minimum of 2 weeks isolation of active TB patients to protect other from acquiring infection [11, 150]. In this research, all active TB patients are immediately isolated within their household for a period of two weeks. Therefore, throughout the isolation period,

Table 5.3: Standard regimens for treatment of active TB [12].

Regimen	Initial phase	Schedule	Drug	Second phase	Schedule per week
PZA/INH/ RMP/EMB	2 months	Daily	INH/RMP	4 months	3 times
INH/RMP/ EMB	2 months	Daily	INH/RMP	7 months	3 times

their interactions will be restricted to members of the same household. I simulated two additional scenarios in which TB patients are isolated out of their household for either 1 week or 2 weeks from the start of treatment.

It is important to note that patients under isolation will not be attending schools, meeting friends, or engaging in social events. When isolated out-of-home, they will be away from their household members. Those who are employed cannot not go to work, causing concerns over loss of income. These may hinder full compliance with in-home or out-of-home isolation [151]. Although the analysis here focuses on a maximum of two weeks isolation, not all active TB patients comply with isolation timelines and guidelines. To account for this, I simulated additional scenarios where only 80% of patients comply with in-home isolation.

5.7 Contact-tracing, testing, and treatment of LTBI

5.7.1 Contact-tracing

As highlighted in the Canadian TB standards, evaluation and follow-up with close contacts of active TB cases is the second priority to identify secondary cases and those who have recently acquired LTBI, and provide treatment to reduce the risk of progression to active TB. For this priority, the Canadian TB standards recommends identification of close contacts for active TB cases.

To implement contact-tracing, I divided the contacts of active TB agents into three categories (Section 5.5.2): (1) household members with the highest risk of contracting infection (high priority); (2) frequent non-household contacts, such as peers and coworkers

(medium priority); and (3) casual interactions during daily activities (low priority).

All simulations were run on the assumption that all members of the household for a diagnosed active TB case undergo an LTBI diagnostic testing. By taking into account the frequent contacts of an active TB agent in the four weeks prior to identification, scenario analyses extended the contact-tracing to the medium priority group. I made the assumption that there may be cognitive factors involved and therefore it may be less likely to recall past contacts with longer duration for identification in backward contact-tracing. Consequently, I set the probability of determining a frequent contact outside the household to 100%, 75%, 50%, and 25%, respectively, depending on whether the contact took place in the first, second, third, or fourth week prior to the identification of the active TB case.

Although systematic screening of contacts is one of the key components of TB control strategies, testing of all contacts may not be performed due to personal and health system barriers. These may consist of, but are not limited to: insufficient human resources, a lack of commitment and motivation on the part of both healthcare professionals and contacts, a lack of awareness of the necessity of screening contacts of TB patients, transportation issues and distance from the health centre, in addition to financial consideration, stigma, and discrimination [152, 153, 154]. If contacts are unaware of the reasons they have been asked for screening, they might believe that testing and treating the active TB would be sufficient and that there is no need to visit a health centre without exhibiting any symptoms. Furthermore, when people feel well, they would prioritize other tasks over attending a health facility and testing for TB [152, 154].

It is noted that not all identified contacts in Nunavut show a willingness to participate in TB testing [155]. Therefore, to address this issue, I examined various possibilities (i.e., 25%, 50%, 75%, and 100%) of frequent contacts of a diagnosed active TB case within the previous four weeks.

5.7.2 Testing for LTBI

According to the recommendations by the World Health Organization, a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) should be used to diagnose LTBI [44]. While IGRA is a more sensitive test than TST, in Nunavut, it is only employed at the discretion of the patient's physician, and TST is the recommended testing approach

Table 5.4: Standard regimens for treatment of LTBI [13].

Regimen	Duration	Schedule	Efficacy	Compliance	Source
INH/RMP	3 months	Twice weekly*	93%	95%	[54, 56]
INH	9 months	Daily	93%	86%	[159, 49]
INH	6 months	Daily	68%	75%	[160]
INH/RPT	3 months	Once weekly	68%	96%	[160, 161, 162]
RMP	4 months	Daily	63%	80%	[163, 164]

*DOT (directly observed therapy)

[11]. However, I included both TST and IGRA as LTBI testing methods in the model, with an estimated sensitivity of 77% for TST and 90% for IGRA. Thus, depending on the testing method, either 23% (using TST) or 10% (using IGRA) could be false negative if the individual was indeed infected with TB [45] (see Section 2.4).

Depending on the time elapsed since infection, there may not be adequate immune responses, resulting in a false negative test [156, 157]. To address this issue, I took into account the recommended eight-week window for conducting a second test for contacts of active TB cases. Thus, all household members in addition to the proportion of frequent contacts, depending on the scenario received a second test eight weeks after the first test. I assumed that all positive LTBI begin their course of treatment immediately after receiving a positive test result.

5.7.3 Treatment regimens for LTBI

As discussed in Section 2.5, the Canadian TB Standards recommend a number of treatment regimens for LTBI to reduce the risk of developing active TB and subsequent transmission to others. The main treatment regimen consists of daily administration of INH for nine months (9INH). A different regimen with a duration of 3 months and similar efficacy to 9INH has also been approved in an effort to increase the acceptance and completion rate of the treatment course [13, 158]. In Nunavut, the regimen of a weekly dose of INH and RMP for three months is being provided as DOT [54, 55]. I included 3HP as the LTBI treatment regimen in my research, assuming a relatively high compliance as a result of DOT, with a 93% efficacy and 95% completion rate [54, 55, 56].

5.8 Household size

As highlighted in Section 4.2 Inuit people in Canada are the group with the most housing disparities; their rates of overcrowding and significant home repair requirements are respectively 10 and 5 times higher than the national level [124]. In Nunavut, there are 3.8 persons per household on average, and over 30% of the households have more than five members [125, 165]. Together, the Northwest Territories Housing Corporation (NWTHC), the Canada Mortgage and Housing Corporation (CMHC), and the Nunavut Housing Corporation (NHC) intend to adopt joint approaches for the development of Inuit housing that is affordable and suitable, with the goal of meeting the territory's housing needs [166, 167].

Here, I made the assumption that by 2025, 1570 new homes will be built, and the average household size can be reduced to 3.3 in order to account for the problem of insufficient housing and assess the added effect of household size reduction on TB annual incidence. Since Poisson distribution presents an appropriate approach to develop models of household size distributions, I employed the Poisson distribution to rearrange the composition of households to achieve an average of 3.3 persons [168, 169]. Therefore, re-distributed the population of households with 5 or more individuals across new households using a Poisson distribution with a mean of 3.3.

5.9 Model calibration and simulation scenarios

The model was first calibrated to 10 years of TB incidence data from 2009 to 2018 in Nunavut [170], using the least-squares fitting method, to determine the transmission probability per contact (Figure 5.3). In the baseline scenario, all household members and 25% of frequent contacts of active TB cases were tested with TST. Identified active TB and LTBI cases were treated with drugs and schedules of regimen 1 outlined in Tables 5.3 and 5.4. After calibration, I simulated the model for 20 years, with a weekly time-step, to evaluate the impact of a combination of control measures and scenarios on reducing the annual TB incidence.

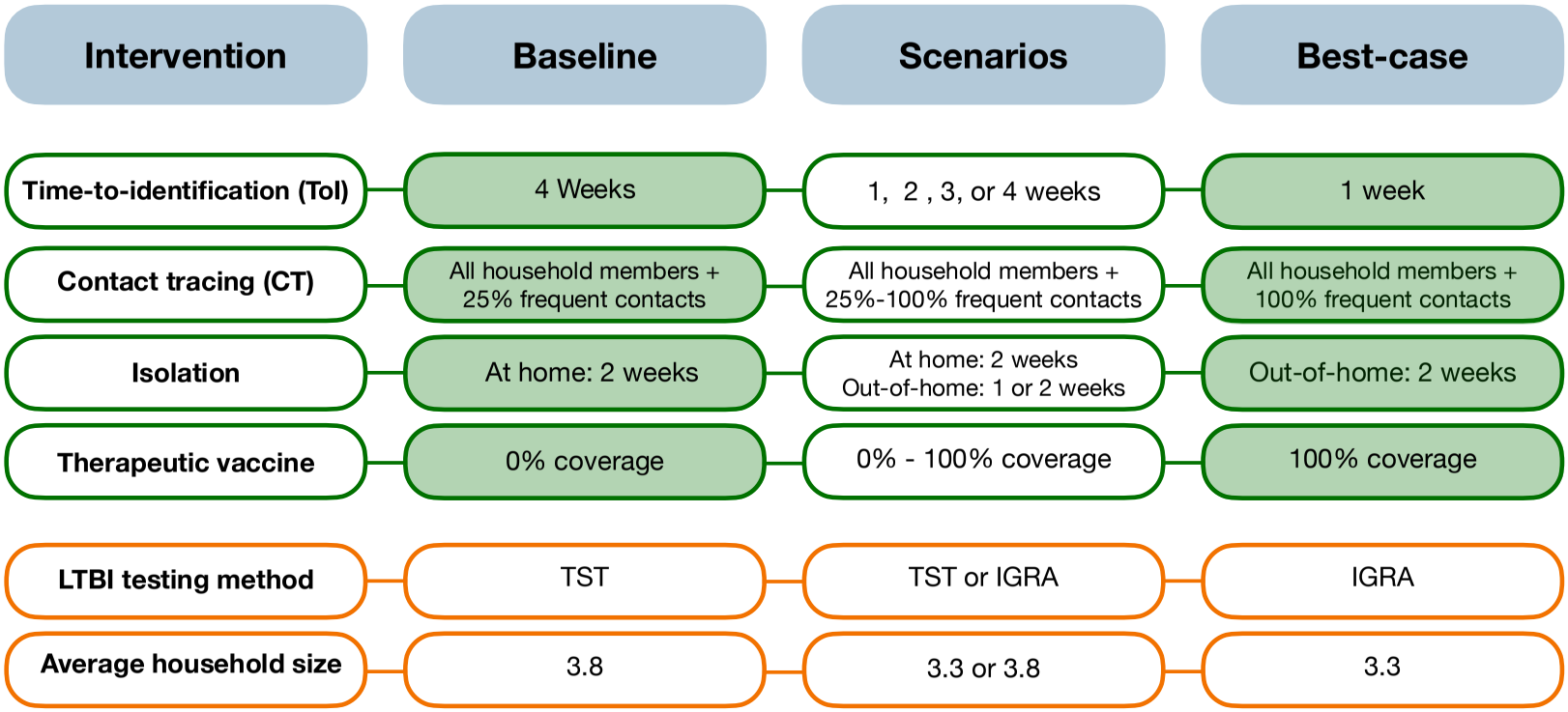

Figure 5.2: Simulated scenarios. The results of the baseline scenario and the best-case scenarios (highlighted scenarios) are presented in Chapter 6 and the findings for other scenarios are provided in the appendix. The scenarios involving the therapeutic vaccine are discussed in Chapter 7. TST: Tuberculin Skin Test, IGRA: Interferon-γ Release Assay

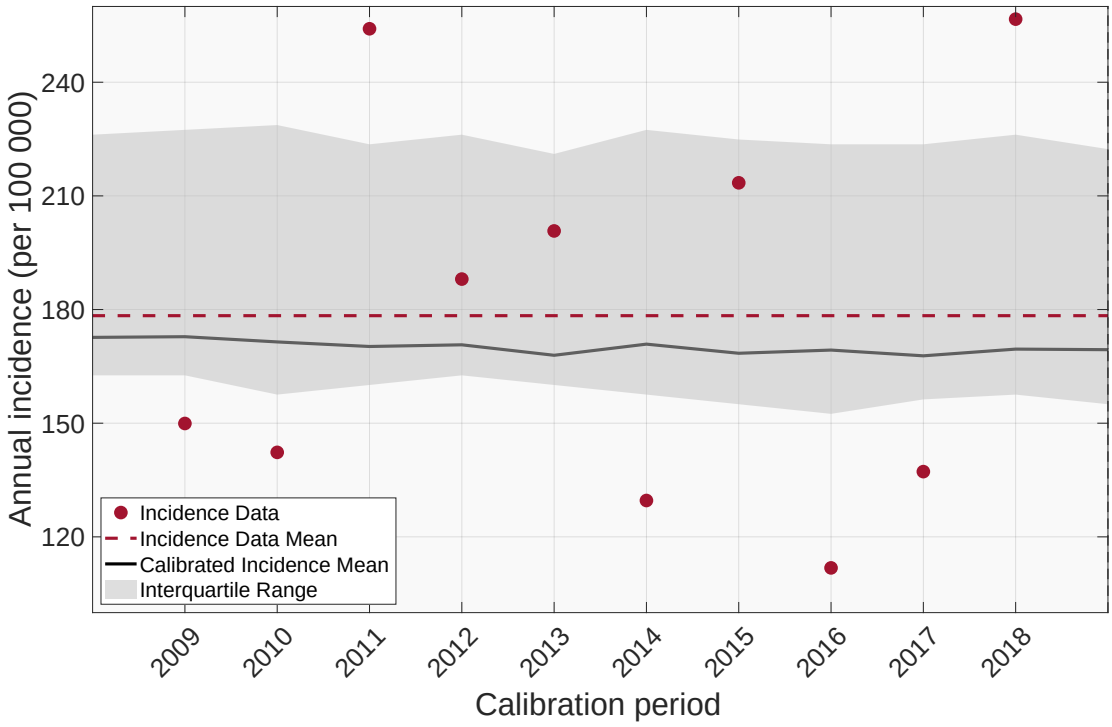

Figure 5.3: Calibrated incidence mean of 500 simulation and incidence data for calibration period

For each scenario, I assessed the percentage reduction in incidence from 2025 to 2040 by a 5-year increment compared to the reported incidence in 2018. The 95% credible intervals (CrI) were obtained using a bias-corrected and accelerated bootstrap method from 500 Monte-Carlo simulations. Figure 5.2 provides a summary of scenarios simulated in this dissertation using parameters in Table 5.5.

5.10 Sensitivity analysis

Sensitivity analysis is typically performed using the correlation-based approach, which involves selecting a type of correlation to use. Pearson correlation is used to measure the strength and direction of linear relationships, whereas rank (Spearman) correlation is used to measure the strength and direction of any monotone relationship. The latter is more suitable for biological models since nonlinear relationships are common. To

Table 5.5: Model parameters used for scenario simulations.

Description	Value	Source
Probability of TB transmission per contact	0.1750 (age > 12)	Calibrated to incidence data
	0.0086 (age ≤ 12)	
Risk of developing active TB without treatment*	0.02—0.4	[146, 35]
Effectiveness of LTBI treatment	93%	[54, 56, 13]
Probability of completing LTBI treatment regimen	0.95	[54, 55]
Success rate of active TB treatment	80.1% (age > 15)	[171]
	84.8% (age ≤ 15)	
Sensitivity of TST	77%	[45]

*age-dependent

account for the effects of other model parameters, partial correlation is often utilized to measure the sensitivity of the model output to a given parameter. As a result, the partial rank correlation coefficient (PRCC) is a popular choice for correlation-based sensitivity analysis. [172].

In this thesis, the partial rank correlation coefficient (PRCC) was used to determine the individual impact of each input parameter on the annual incidence reduction, regardless of any correlation between input variables [173]. To perform the sensitivity analysis, I utilized the 100 replications of each parameter generated during the uncertainty analysis to calculate the PRCCs.

Chapter 6

Results

Implementing and calibrating the model in the Julia language, I simulated it to project the annual incidence of TB through 2040 under various time-to-identification (ToI), contact-tracing (CT), out-of-home Isolation, testing methods, and household size scenarios. The extent to which these interventions, individually or combined, are expected to decrease TB are quantified in the years 2025, 2030, 2035, and 2040. Scenarios in which elimination is achievable are then identified. In this chapter, I first examine the baseline scenario, followed by an evaluation of each intervention at their best-case level. Lastly, I present the outcomes for the scenario where the level of isolation compliance is at 80% (instead of 100%).

6.1 Baseline scenario

For the 20-year simulation period from 2020 to 2040, the baseline scenario assumed a 25% CT rate, a 4-week ToI for active TB cases, a TST testing method, with all active TB patients being home-isolated for two weeks from the start of treatment. Comparing this to the 10 year calibration timelines, I discovered that maintaining interventions at the baseline would result in a small, 2% increase in the incidence of TB by 2025 and 5% increase in the annual incidence by 2040 (Appendix, Figure A.1, Table A.1).

In addition to quantifying the effect of best-case scenario for each intervention, I simulated the model to project the effect of combining interventions. The results of various scenarios of interventions are discussed in the Appendix.

6.2 Best-case scenarios of interventions

In the first set of simulations, I considered the best-case scenario for each intervention, while keeping the other interventions at their corresponding level in the baseline (Figure 5.2). The best-case scenarios were 1 week for ToI, 100% contact-tracing and testing of frequent contacts in addition to all household members, and 2 weeks out-of-home isolation of all active TB patients from the start of treatment.

In the absence of a therapeutic vaccine, the results (Figure 6.1) show that with a 1-week ToI, a 50% reduction in the annual TB incidence could be achieved between 2025 and 2030. However, this reduction is not attainable by applying the best-case scenario of any other intervention alone. Figure 6.2 illustrates timelines for the reduction of annual TB incidence, indicating a 43% decline by 2025 and 63% by 2030, compared to year 2020. Inclusion of 2 weeks of out-of-home isolation along with 1-week ToI would accelerate TB reduction, making the first goal of action plans feasible by achieving 57% reduction by 2025. A combination of best-case scenarios for all interventions would also lead to at least 90% reduction of annual TB incidence between 2025 and 2040. It is worth noting that when active TB patients are identified within 1 week and initiate treatment with isolation, the effect of contact-tracing is markedly reduced.

6.3 Isolation compliance

As discussed in Section 5.6.3, active TB patients may not fully comply with complete isolation. To account for this, I simulated additional scenarios with an 80% compliance rate for patient isolation. The results, presented in Figure 6.3 and Table 6.1, show that reduced compliance leads to a 5.7% increase in the annual TB incidence relatively quickly compared to the baseline. In the best-case scenario of 1-week ToI and 100% contact-tracing for frequent contacts, timelines of achieving 50% reduction are further delayed, yet still possible before 2030 reaching 52%. This reduction is $\sim$11% lower than the same scenario where all active patients fully comply with 2 weeks isolation (Figure 6.3 and Table 6.1). When all active patients are isolated out-of-home, the difference in reduction of incidence between 80% and 100% compliance rates is $\sim 30\%$ at 2025 and this difference is $\sim$33% at 2030 (Tables A.3 and 6.1, Figure 6.3).

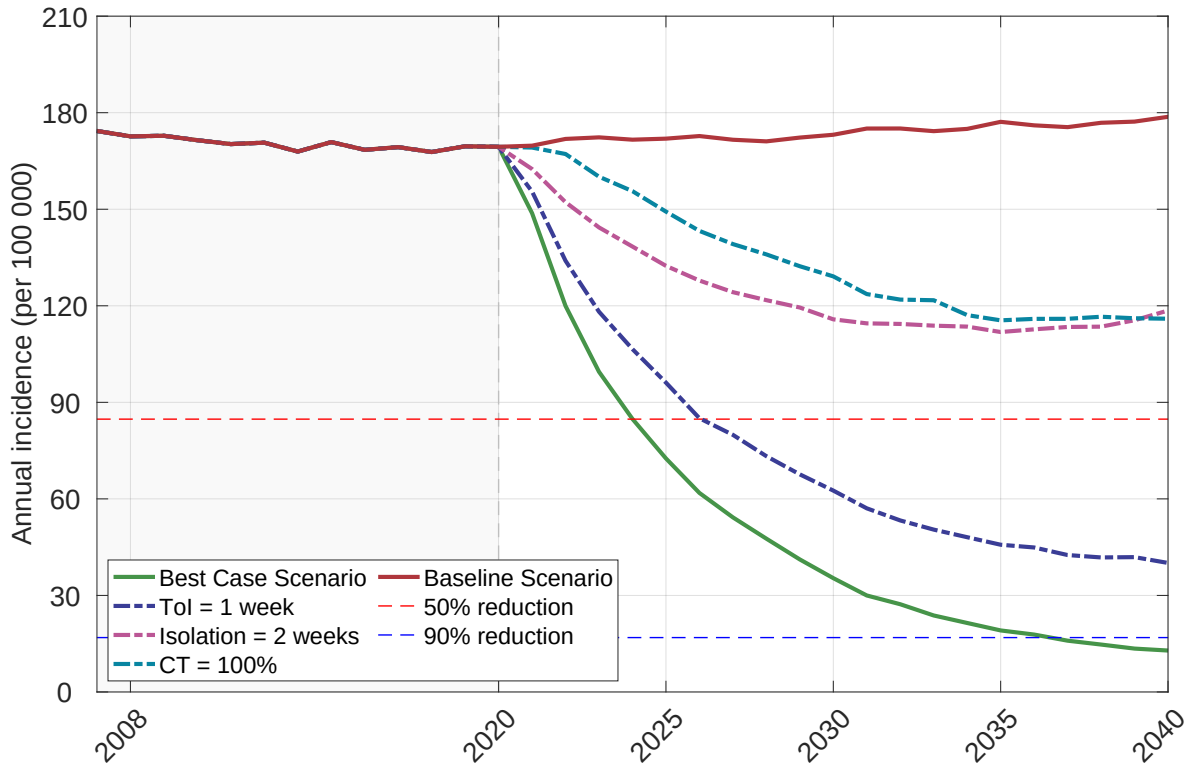

Figure 6.1: Projected annual incidence of TB per 100,000 population for the baseline and best-case scenarios of each intervention, when ToI is 1 week, contact-tracing is set to 100% of frequent contacts, and active TB patients are isolated out-of-home for two weeks. Compliance with isolation was set to 100%.

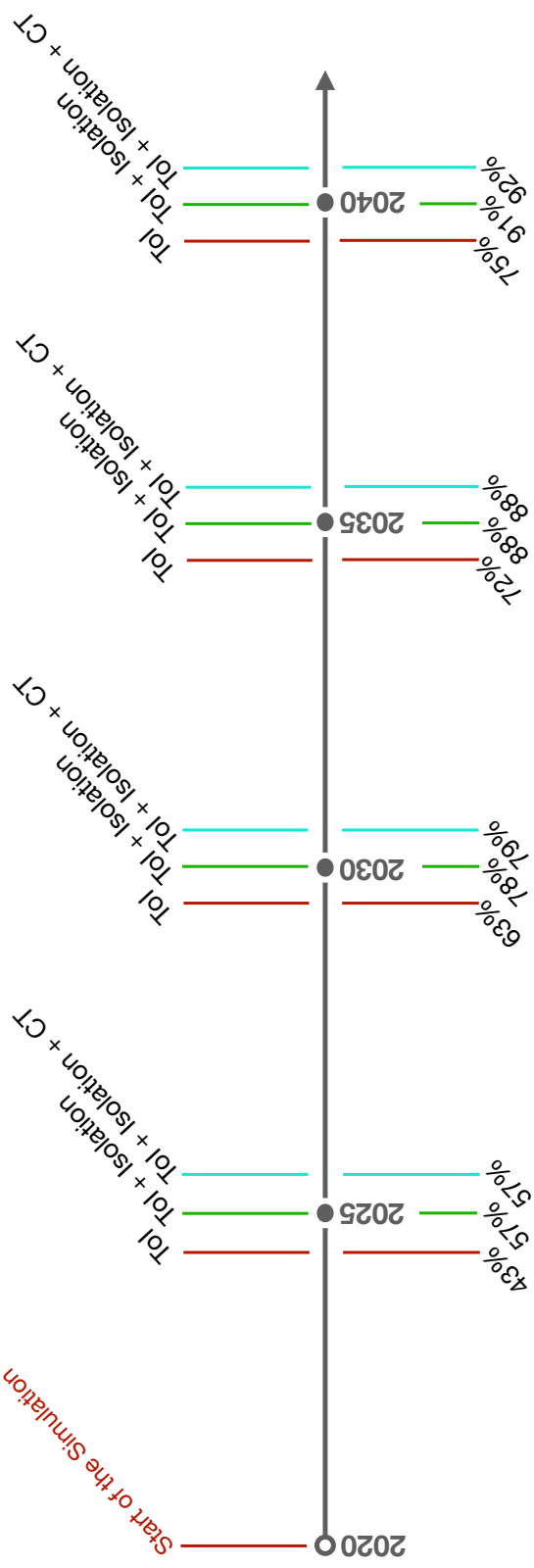

Figure 6.2: Projected timelines of incidence reduction for the best-case scenario of each intervention: 1 week ToI, 100% contact-tracing of frequent contacts, and two weeks out-of-home isolation for active TB patients from the start of treatment. For the best-case scenario of any intervention, other interventions remained fixed at the same level as the baseline. Compliance with isolation was set to 100%.

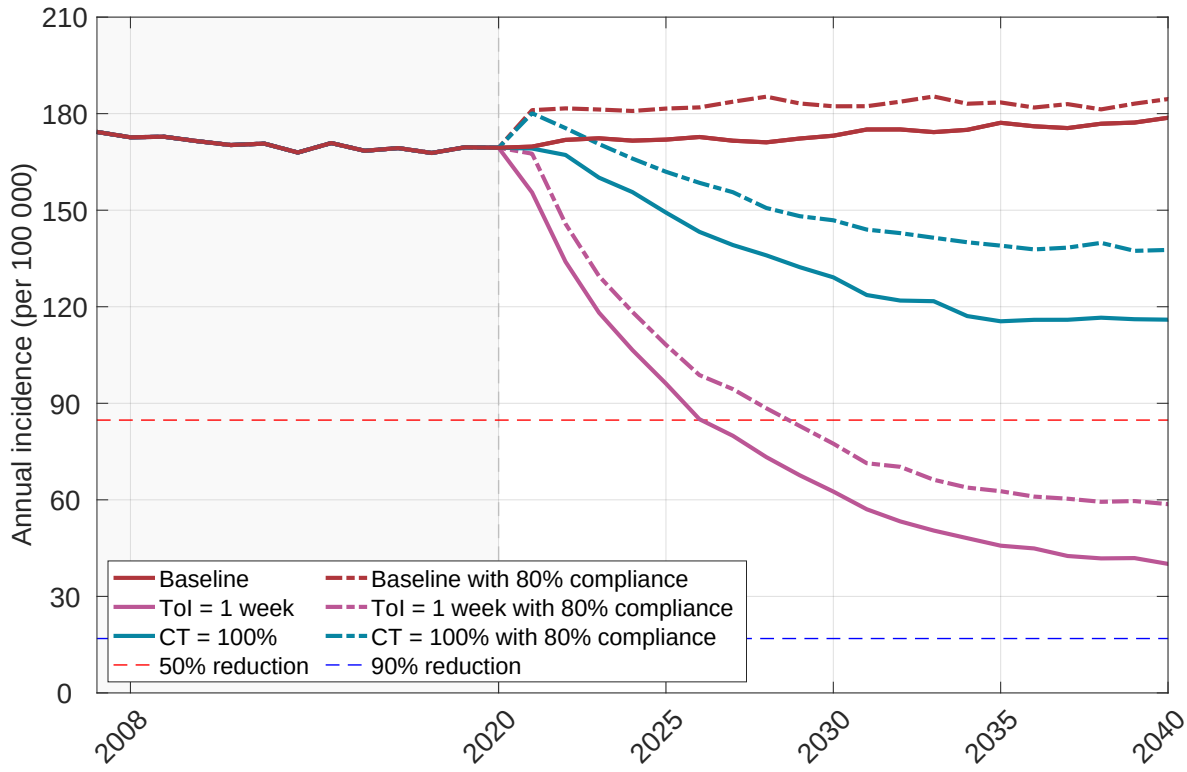

Figure 6.3: Projected annual incidence of TB per 100,000 population for the baseline and best-case scenarios of each intervention, when ToI is 1 week, contact-tracing is set to 100% of frequent contacts, and active TB patients are isolated out-of-home for two weeks. Solid and dashed curves correspond to 100% and 80% compliance rate for isolation, respectively.

6.4 Sensitivity analysis

I conducted a one-way probabilistic sensitivity analysis using the partial rank correlation coefficient (PRCC) to evaluate the impact of each control variable on the overall uncertainty of results for the reduction of incidence. In this analysis, each parameter was varied independently across its domain. The PRCC analysis is displayed in Figure 6.4 representing various combinations of ToI, isolation of active TB patients, contact-tracing, average household size, LTBI testing method. Figure 6.4 illustrate the relative importance of each control variable in reducing TB incidence.

As shown in Table 6.2, a positive value of PRCC indicates that increasing the value of the corresponding control variable leads to a high reduction in the incidence of TB.

Table 6.1: Projected reduction of incidence (%) in simulated scenarios of contact-tracing rates and ToI, with 80% compliance rate for active TB isolation from the start of treatment

	CT*	25%		100%	
ToI	Year	Mean	95% CrI	Mean	95% CrI
4 weeks	2025	-7	(-13, -1)	4	(-1, 9)
	2030	-7	(-14, -1)	13	(8, 18)
	2035	-8	(-15, -2)	17	(12, 22)
	2040	-8	(-14, -1)	18	(13, 23)
1 week	2025	36	(32, 39)	35	(30, 38)
	2030	54	(51, 56)	54	(51, 57)
	2035	63	(60, 65)	62	(60, 64)
	2040	64	(62, 67)	64	(62, 66)

*CT: contact-tracing.

Therefore, increasing ToI will significantly negatively affect TB incidence reduction. This analysis also reveals that there is a positive association between the reduction of TB incidence and enhancement in contact-tracing level and isolation. In contrast, the effect of reducing average household size or replacing TST with IGRA was found to be minimal compared to other interventions.

Table 6.2: PRCC analysis of control variables.

Control variable	PRCC	95% CI	P-value
ToI	-0.431	(-0.445, -0.418)	< 0.001
Isolation	0.218	(0.204, 0.233)	< 0.001
Contact-tracing	0.076	(0.061, 0.090)	< 0.001
LTBI testing Method	0.016	(0.001, 0.031)	0.034
Average Household Size	-0.031	(-0.046, -0.017)	< 0.001

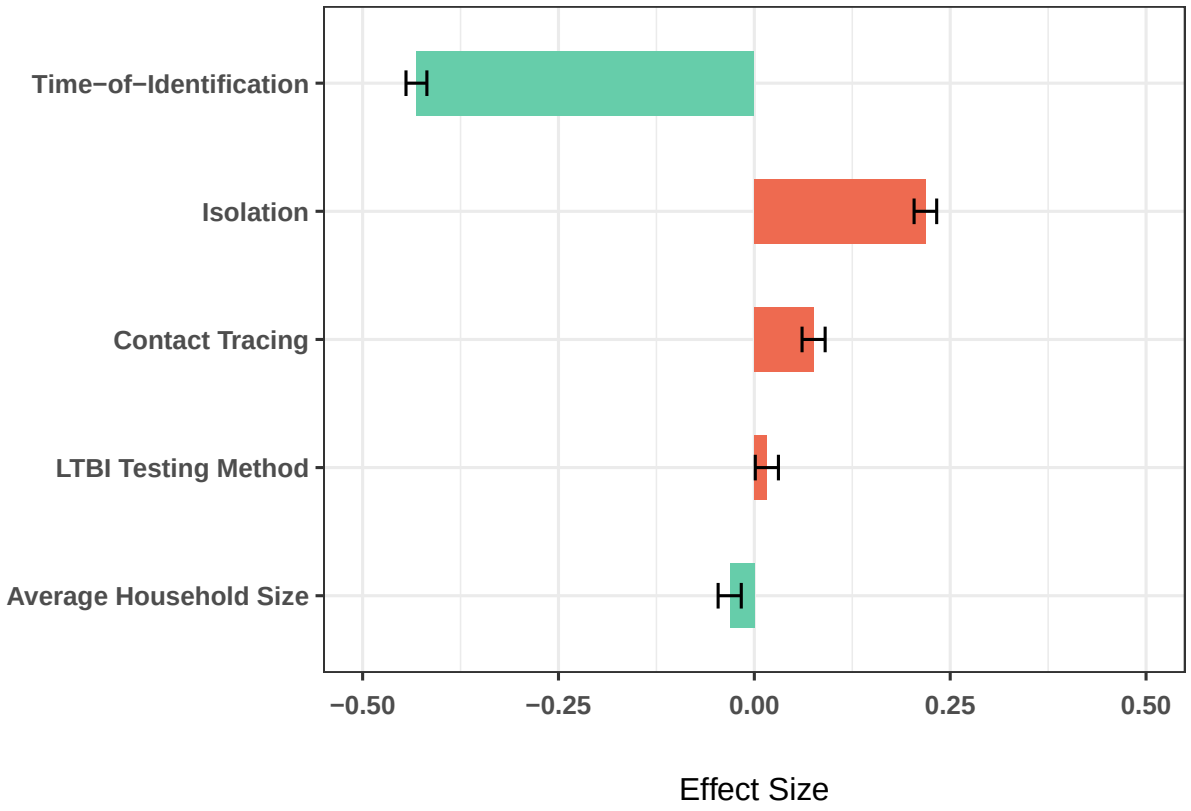

Figure 6.4: Partial rank correlation coefficient (PRCC) for different interventions with response variable as reduction of TB incidence.

Chapter 7

Therapeutic Vaccines

Vaccination has been one of the most effective approaches to controlling many infectious diseases. Despite the historical use of Bacillus Calmette-Guérin (BCG) vaccine, TB is still one of the top ten leading causes of mortality worldwide. The most common form of disease and its transmission mode, pulmonary TB, is not preventable by the BCG vaccine. This has instigated numerous research activities to generate new TB vaccines [174]. The TB vaccine pipeline has advanced significantly over the past ten years, and several vaccines are being investigated for their clinical efficacy against Infection, disease, and Recurrence [175].

Therapeutic vaccines are designed to alleviate the symptoms and complications of a disease or condition, rather than preventing the initial infection or disease onset. Unlike traditional, prophylactic vaccines that aim to stimulate the immune system to provide protection against specific pathogens, therapeutic vaccination refers to the administration of an immunomodulatory agent, in the presence of an existing disease, with the goal of enhancing outcomes, reducing the duration of treatment, or preventing relapse, as seen in tuberculosis (TB) cases. The vaccine is employed as a means to modulate the immune response and improve the overall management of the condition [176, 177].

In contrast to prophylactic vaccination [176, 178], therapeutic vaccination serves as adjunctive treatment of TB with the aim of reducing recurrence rates in active TB cases, improving the effectiveness of treatment regimens within potentially shorter timelines. To enhance the effectiveness of pharmacological treatment, therapeutic vaccination against TB aims to activate immune responses [179]. While therapeutic vaccines are expected

to play an important role in TB elimination efforts, very few studies have evaluated their public health impact using mathematical modelling. For other vaccine types, modeling studies suggests that vaccination against the disease would have a greater and more rapid effect on controlling *M.tb* spread than vaccination against TB infection [180, 105]. This chapter focuses on TB therapeutic vaccination, which is offered, along with treatment, to active TB patients to enhance treatment effects and reduce the rates of recurrence [178].

Currently, a number of therapeutic vaccine candidates including attenuated and inactivated entire organisms, fragmented mycobacteria, adjuvanted protein subunit molecules, and DNA vaccines are being investigated [180, 181, 182].To examine the impact of a therapeutic vaccine on the incidence of TB in Nunavut, I expanded a previous framework [105] within the ABM developed in this dissertation. In Section 7.1, I provide an overview of TB vaccines under clinical trial. Then, mathematical modelling studies on novel TB vaccines will be reviewed in Section 7.4. In Sections 7.5 and 7.6, I expand the ABM and simulate it to illustrate the outcomes of TB vaccination along with treatment regimens.

7.1 TB vaccines in clinical trial

7.1.1 Inactivated vaccines

Inactivated vaccines incorporate either whole bacteria that are inactivated or their cleavage fragments that have been created using physical or chemical techniques. These vaccines have shown to be effective at regulating the development of TB because they can trigger cellular immune responses to protect against extracellular pathogen infection. However, inactivated vaccines have some drawbacks. For example, they achieve a lower preventative protection, unable to induce a cytotoxic T cell response, may generate a short protective duration, and are required to be administered in high doses *via* numerous inoculations.

Nevertheless, inactivated vaccines are beneficial in terms of administration, production, and safety. Currently, only two inactivated TB vaccines (Utilins and Mycobacterium Vaccae) have progressed to clinical stage, while five inactivated TB vaccines are in research [182].

7.1.2 Utilins

Fast-growing *Mycobacterium phlei* thrives at temperatures between 28°C and 52°C. Utilins is widely utilised as a therapeutic vaccine or immunomodulator in China after receiving a new drug certificate from the Chinese Food and Drug Administration [182]. Evidence to date has demonstrated that Utilins generated effective therapeutic benefits in the treatment of pulmonary TB, verruca vulgaris [3], atopic dermatitis [4], non-small cell lung cancer, recurrent respiratory tract infections, malignant pleural effusion [5], and condyloma acuminatum [6]. Additionally, according to multiple studies [182, 187], elderly pulmonary TB patients or those with new smear positive pulmonary TB who received the Utilins vaccine along with anti-TB medications experienced significantly higher sputum-negative conversion rates, foci absorption rates, and cavity closure rates than the control group, which consisted of people who received the anti-TB vaccine alone [182].

7.1.3 Mycobacterium vaccae

Mycobacterium Vaccae (M. vaccae), also known as SRL-172, is a non-pathogenic species that is frequently found in soil. M. vaccae shares several antigens with *M.tb* and other non-tuberculous mycobacteria. Multiple studies have assessed the immuno-therapeutic potential of oral and injectable M. vaccae products for the treatment of TB, leprosy, or other conditions, like cancer and depression [188].

In a study of mouse model immunization with a low-dose, heat-inactivated M. vaccae, it was shown that the vaccinated population exhibited a diminished mycobacterial load following challenge with *M.tb* [189]. In a trial assessing the immuno-therapeutic impact of M. vaccae on MDR-pulmonary TB, sputum-negative conversion rates in patients treated with chemotherapy and M. vaccae for 6 months reached 43% [190]. This rate was significantly higher than the conversion rates of 21% observed among those who were treated

[3] Also known as a common wart, is a skin growth caused by the human papillomavirus (HPV). [183]

[4] Also known as eczema is characterized by itchy, red, and dry skin. It is a chronic inflammatory skin condition and it is prevalent in people of all ages, although it is most frequently observed in infants and young children [184].

[5] A condition where fluid accumulates in the pleural space (the space between the lungs and the chest wall) due to the spread of cancer to the pleura, which is the thin layer of tissue that lines the chest wall and covers the lungs [185].

[6] Also known as genital warts, is a sexually transmitted infection caused by the human papillomavirus (HPV) [186].

with chemotherapy alone. A meta-analysis revealed that M. vaccae supplementation to chemotherapy for TB patients who had never been treated enhanced sputum conversion and X-ray appearance [191].

A phase III randomised double-blinded placebo-controlled clinical research found that M. vaccae vaccine significantly reduced the risk of TB infection in HIV-infected participants who had received a childhood BCG vaccination [192]. Other studies have investigated the effectiveness of M. vaccae in the prophylactic treatment of TB patients who were latently infected, revealing that the incidence of TB in the M. vaccae treatment group was 0.30% (2/660), while the incidence in the group receiving chemotherapy (isoniazid-treated) was 0.61% (4/660) [182]. These rates were both significantly lower than the incidence rate in the control group, which was 3.48% (23/660). Although there was no remarkable reduction in the level of TB between the chemotherapy group and the M. Vaccae treatment group, the latter group had a reduced adverse rate [182].

7.1.4 RUTI

Another possible TB vaccine, known as RUTI, uses detoxicated cell fragments from *M.tb*. This candidate has undergone numerous animal tests to determine its safety and effectiveness. Pre-clinical research revealed that RUTI could improve immune responses in animal models and reduce bacterial loads. Healthy adult volunteers were used in phase I clinical research to assess the immune responses and safety profile six months after subcutaneous inoculation. The vaccine efficacy has been established, and studies on RUTI have shown that it leads to a specific immune response that targets *M.tb*. To evaluate the RUTI protection when administered either prophylactically or immediately following an infection, another animal trial was conducted, demonstrating that RUTI was as effective as BCG vaccination, indicating that newly infected individuals could receive RUTI. Consequently, immunisation via RUTI may have the potential for use as both immunotherapy and TB prophylaxis [188, 193].

7.1.5 Mycobacterium smegmatis vaccine

A non-pathogenic, rapidly expanding mycobacterium is M. smegmatis. More than 2000 homologous genes, along with an unusual cell wall structure are shared between M.

smegmatis and *M.tb*. An effective acellular M. smegmatis vaccine has been shown to have protective effects on guinea pigs infected with *M.tb* [194, 182].

7.1.6 MIP/Mw

A non-pathogenic, rapidly proliferating strain of non-tuberculous mycobacteria is known as *Mycobacterium indicus pranii* (MIP) or *Mycobacterium w* (Mw). Studies have found that the killed MIP vaccine, which was initially developed for leprosy, can also help prevent TB in mice and guinea pigs [195]. Phase III, multi-centric clinical trials in pulmonary TB patients assessing the efficacy and safety of MIP in TB patients have shown that MIP is safe with no side effects, and can aid in clearing mycobacterium [195].

7.2 TB subunit vaccines

Subunit vaccines typically contain multiple immunoactive components that have been identified and purified from *M.tb*, for instance, proteins, myolic acids, polypeptides, and glycolipids. This type of vaccine can produce immunological protection or be used as immunotherapy when combined with an adjuvant. The subunit vaccine is generally used as therapeutic or improved vaccination. Seven options are currently being tested in clinical trials, including AEC/BC02, BCG-PSN, Mtb72F, Hybrid 1, H4:IC31 (AERAS-404), H56:IC31 (AERAS-456), and ID93+GLA-SE [182]. The TB subunit vaccines exhibit several advantages, including low cost, high yield, purity, and safety, recurrent usage, and lasting immunological memory of effector T cells through increased immunisation. These properties make this type of vaccination ideal for protecting individuals from contracting TB. However, in comparison to BCG vaccination, the TB subunit vaccines have several drawbacks, such as a shorter duration of immunogenicity, low levels of immune memory, and the need for adjuvants. Ongoing effort aim to address these shortfalls [182].

7.3 DNA vaccines

By injecting genetically modified DNA that causes the synthesis of a target antigen, DNA vaccines can offer protection against disease. There may be advantages to TB

DNA vaccines over traditional immunisations, including therapeutic DNA vaccines and improved preventive DNA vaccines. They are safe and more efficient [181]. However, DNA vaccines need to overcome several challenges during clinical studies and later industrial applications. First, although immune responses can be brought on by the microproteins generated by DNA vaccines in vivo, they may not be as strong as those generated by live vaccinations. Second, ongoing studies indicate that the protective efficacy of DNA vaccines is not superior to BCG. Third, DNA vaccines can cause inoculators to generate anti-DNA IgG, which could increase the risk of developing autoimmune diseases. The only DNA vaccine presently undergoing clinical testing is GX-70 [182].

7.4 Review of TB vaccine modeling

Mathematical models play a fundamental role in the investigation of the potential epidemiological effects of various future vaccination profiles and delivery methods. Recent years have seen a growth in the production of models evaluating the potential impact of future TB vaccines; however, very few have examined this impact for therapeutic vaccination at the population level. This is partly because therapeutic vaccines are still in the development stage and clinical data are limited. Furthermore, the effects of therapeutic vaccines may be linked to the characteristics of TB patients [105].

In the absence of such data, mathematical models can provide crucial insights for the formulation of target product profiles to guide the development of vaccine candidates with the greatest population-level impact. Such models can also provide information that could be used to streamline support for research and development of successful vaccine candidates. The earliest BCG-based TB vaccine model was introduced in the 1960s [196], with a substantial gap to the modelling TB vaccines in 1998 when novel TB vaccine profiles were discovered [196]. In this section, I briefly discuss some of the recent modelling studies that were designed to assess the epidemiological effects of therapeutic vaccination against TB.

The performance of a vaccine may be affected by the diversity of *M.tb* strains. Cohen et al. [197, 86] found that while vaccines hold great promise for enhancing TB control, the expected advantages of mass vaccination may be undermined if strain replacement occurs with *M.tb* variants that are not effectively targeted by vaccines.

Elad et al. quantified the impact of vaccine effectiveness, period of vaccine-induced immunity, and vaccination coverage rates on the cumulative percentage of infections and TB cases prevented using differential equation frameworks to make comparisons between the potential public health effects of mass vaccination campaigns using either pre- or post-exposure vaccines [85]. In a compartmental model with vaccination, Ayinla et al. [96] investigated the effect of vaccination programs, diagnosis, and treatment of TB. Their findings demonstrated that TB would still be endemic for low vaccination rates under 20%. Another compartmental deterministic model has been proposed, incorporating therapeutic vaccine and accounting for key biological, clinical, and epidemiological elements of TB [105]. The prevalence of active TB cases sharply decreased when therapeutic vaccine was implemented, and the extent of the decline depended on the coverage and the efficacy of the vaccine in reducing the frequency of reactivation.

To predict the combined efficacy of a potential therapeutic vaccine like RUTI with a conventional anti-TB therapeutic strategy, Russo et al. [107] used an innovative computational modelling called Universal Immune System Simulator (UISS). The UISS-TB outcomes were found to be in good agreement with clinical trial findings, suggesting that RUTI vaccine may facilitate a partial recovery of infected lung tissue [107, 108].

Of the various mathematical models that have been studied, none have employed agent-based frameworks to evaluate the impact the therapeutic vaccines undergoing clinical trials. I extended the ABM presented in Chapter 5 and incorporated a prospective therapeutic vaccine in the model to quantify the reduction of TB incidence in the population study of Nunavut.

7.5 Therapeutic vaccination model

As described in Section7.1, significant progresses have been made in the development of TB therapeutic vaccines, leading to a number of candidates that are currently in clinical evaluation. Several observations support the technical viability of developing a therapeutic vaccination for TB; however, the immunological mechanisms of *in-vivo* control and elimination of *M.tb* remain unclear [198].

The key public health objectives for therapeutic vaccination include:(i) increasing the proportion of patients who are successfully treated; (ii) decreasing the rate of recurrence

following completion of a treatment regimen; and (iii) lowering the number of medications needed to treat TB caused by both drug-sensitive and drug-resistant *M.tb* strains, as well as the duration of a treatment regimen [178]. Since drug-resistance remains an insignificant challenge in Indigenous populations (2.9) with a rate of only 2% among treated patients [73], my primary focus was on the first two public health goals for therapeutic vaccines.

Recurrence of disease, which can be caused by relapse or reinfection, refers to the development of active TB after the completion of a treatment regimen. Reducing recurrence rates is beneficial not only to the patient, but also to the overall population health by decreasing the risk of *M.tb* transmission to others [178]. In addition to enhancing the effect of treatment, therapeutic vaccines are expected to reduce the risk of relapse due to the presence of residual as viable mycobacteria after the treatment has ended. This could be accomplished by immunization during the course of treatment [178].

Before extending the ABM developed for evaluating TB interventions, I will describe a compartmental model for the inclusion of therapeutic vaccination [105].

7.5.1 Compartmental model

Section 5.1 discussed a compartmental model which is extended here to include vaccination for a proportion of TB active patients under treatment. In this extended model, the vaccine is given as an adjuvant to the treatment regimen for TB patients. This of the model is labeled as A_{TV}. The model in equation 5.1 is then extended to the following form:

$$\begin{aligned}
\frac{dS}{dt} &= \mu N - \beta AS + \delta\gamma L_T + \theta\eta A_T + [1-(1-\epsilon)(1-\theta)]\lambda A_{TV} - \mu S \\
\frac{dL}{dt} &= \beta AS - (\tau+\alpha+\mu)L + (1-\theta)\eta A_T + (1-\epsilon)(1-\theta)\lambda A_{TV} \\
\frac{dL_T}{dt} &= \tau L - (\gamma+\mu)L_T \\
\frac{dA}{dt} &= \alpha L + (1-\delta)\gamma L_T - (\xi+\mu)A \\
\frac{dA_T}{dt} &= (1-p)\xi A - (\eta+\mu)A_T \\
\frac{dA_{TV}}{dt} &= p\xi A - (\lambda+\mu)A_{TV}
\end{aligned} \tag{7.1}$$

Similar to 5.1, β represents the transmission rate, α is the rate of developing active tuberculosis (TB), and τ is the rate of diagnosis and treatment of latent TB infection (LTBI). The rates of successful treatment completion, the fraction of successfully treated LTBI, diagnosis and treatment of active TB, treatment completion in active TB, and the fraction of successfully treated active TB patients are denoted by γ, δ, ξ, η and θ, respectively. Both death and birth rates are represented by μ, which is used to maintain a constant population size. Adding the vaccine compartment, ϵ represents the vaccine efficacy and p represents the proportion of active patients who receive vaccine in conjunction with the treatment. The model diagram with vaccination is illustrated in Figure 7.1.

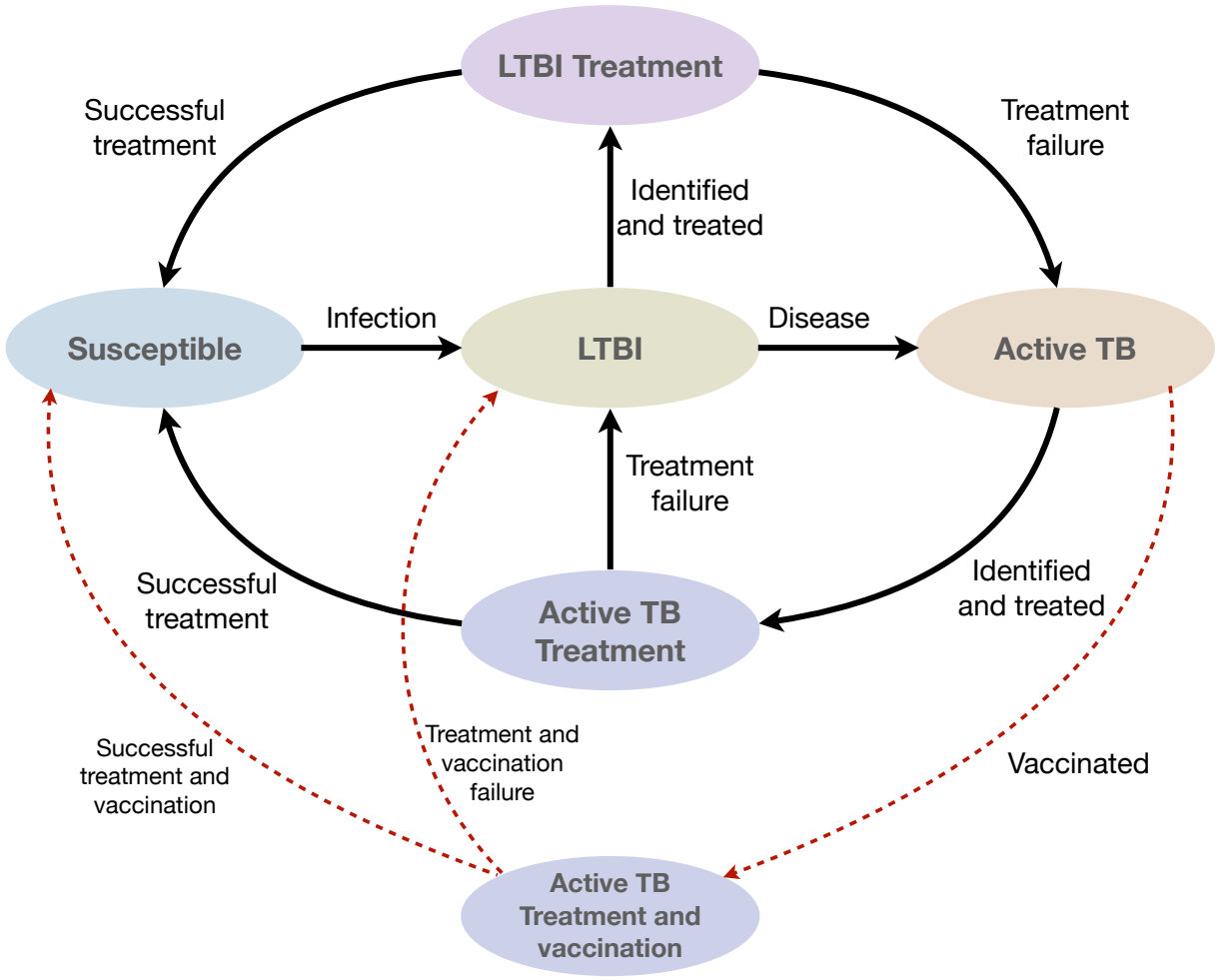

Figure 7.1: Modified schematic structure of the model for the transmission dynamics and treatment of TB, with therapeutic vaccination.

7.5.2 Reproduction number

Applying the next generation matrix method as discussed in Section 5.1.1 gives:

$$\mathcal{F} = \begin{pmatrix} \beta AS \\ 0 \\ 0 \\ 0 \\ 0 \end{pmatrix}, \qquad \mathcal{V} = \begin{pmatrix} -(\tau+\alpha+\mu)L + (1-\theta)\eta A_T + (1-\epsilon)(1-\theta)\lambda A_{TV} \\ \tau L - (\gamma+\mu)L_T \\ \alpha L + (1-\delta)\gamma L_T - (\xi+\mu)A \\ (1-p)\xi A - (\eta+\mu)A_T \\ p\xi A - (\lambda+\mu)A_{TV} \end{pmatrix} \tag{7.2}$$

Thus,

$$F = \begin{pmatrix} 0 & 0 & \beta S & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix} \tag{7.3}$$

and

$$V = \begin{pmatrix} \tau+\alpha+\mu & 0 & 0 & -(1-\theta)\eta & -(1-\epsilon)(1-\theta)\lambda \\ \tau & \gamma+\mu & 0 & 0 & 0 \\ \alpha & -(1-\delta)\gamma & \xi+\mu & 0 & 0 \\ 0 & 0 & -(1-p)\xi & \eta+\mu & 0 \\ 0 & 0 & -p\xi & 0 & \gamma+\mu \end{pmatrix} \tag{7.4}$$

Considering the largest eigenvalue of the matrix $\rho(FV^{-1})$ gives the effective reproduction number

$$R_e = \frac{N\beta(\eta+\mu)(\gamma+\mu)[\alpha(\gamma+\mu)+\gamma\tau(1-\delta)]}{\det(V)} \tag{7.5}$$

where

$$\begin{aligned} \det(V) = (\tau+\alpha+\mu)&[(\gamma+\mu)(\xi+\mu)(\eta+\mu)(\gamma+\mu)] \\ &- [\tau(1-\delta)\gamma + \alpha\xi(\gamma+\mu)(1-\theta)][p(\eta+\mu)(1-\epsilon) + (1-p)(\gamma+\mu)\eta)] \end{aligned} \tag{7.6}$$

7.5.3 ABM with therapeutic vaccination

To extend the ABM model of TB treatment and include vaccination, I assumed that active TB patients receive the vaccine in addition to the treatment, with coverage of 25%, 50%, 75%, or 100%. All patients who are under treatment for active TB disease were considered for therapeutic vaccination. Even when treatment is successful, recurrence could still occur due to reinfection or from the inadequate elimination of the original infecting organism. I assumed that vaccine reduces both the rate of recurrence and the rate of treatment failure by 50% for those who are vaccinated compared to unvaccinated patients[178].

7.6 Results

I assumed that a therapeutic vaccine would be available in 2025 for vaccination of TB patients. in the absence of clinical efficacy data, I assumed that a therapeutic vaccine would reduce the recurrence and treatment failure rates by 50%. Incorporating a therapeutic vaccine with these attributes into the model, the goal of a 50% reduction in the incidence of TB can be attained in additional scenarios, with greater reductions compared with the scenarios without vaccine. However, even with a therapeutic vaccine, TB elimination (i.e., less than one incidence per million population) is not achievable by 2040. Under the best-case scenario of interventions and 100% vaccine coverage of TB patients, the reduction of TB incidence was estimated to be 96% in 2040 (Figure 7.2).

In the absence of a therapeutic vaccine, the annual incidence was projected to increase by 5% by 2040 in the baseline scenario. However, when the therapeutic vaccine is implemented in the baseline scenario with 100% coverage of diagnosed TB patients, a 25% decrease in the incidence of TB can be achieved by 2040.

As shown previously by the model projections, neither contact-tracing nor isolation alone could achieve the 50% reduction goal, even under the best-case scenarios. However, with 100% coverage of vaccination, 50% reduction of TB incidence is attainable even if isolation and contact-tracing measures are maintained at their baseline level (Figure 7.2). The magnitude of this reduction is 53% by 2035, which is $\sim$20% higher than the projected reduction without vaccination.

Similarly, with a 100% vaccination coverage and two weeks out-of-home isolation, a

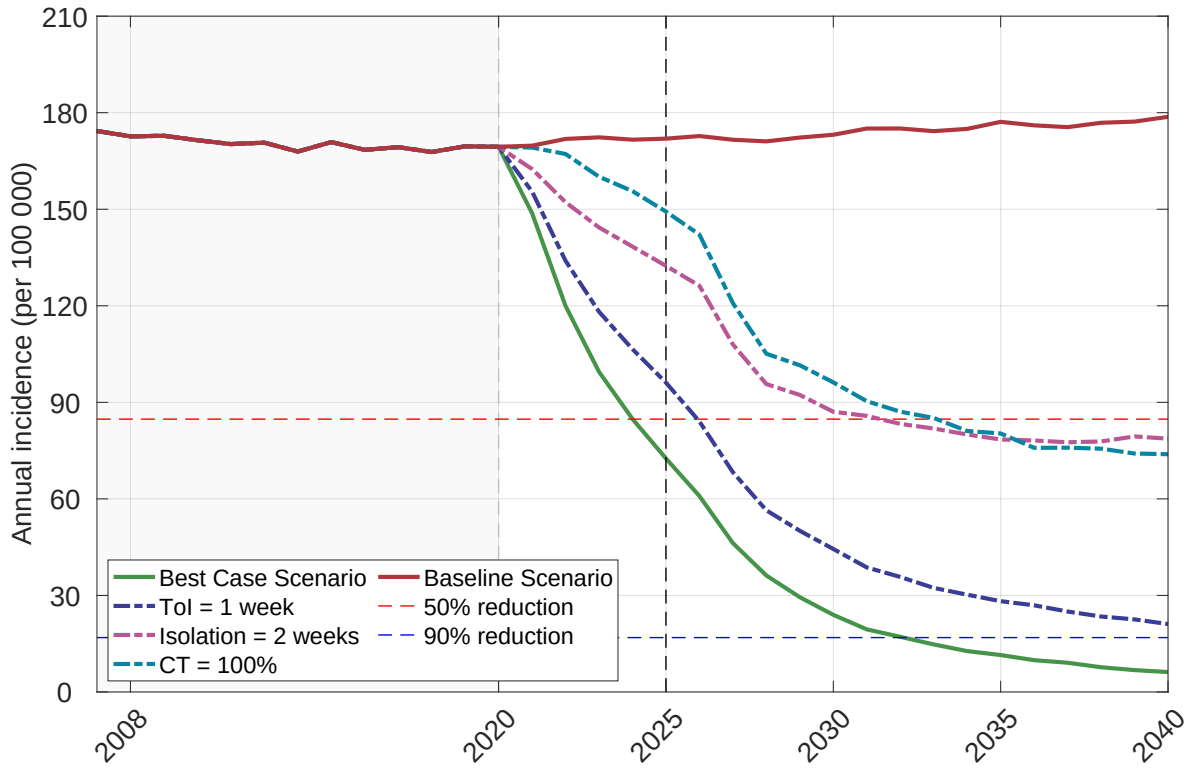

Figure 7.2: Projected annual incidence of active TB per 100,000 population, for the baseline and best-case scenario of each intervention (i.e., when ToI is 1 week, contact-tracing level is 100% and patients are isolated out of home for two weeks) with 100% coverage of vaccination for TB patients.

reduction of $\sim$54% in the annual TB incidence is achieved by 2035 (Figure 7.2), while this reduction is projected to be $\sim$34% (Figure 6.1) in the absence of vaccination. When all interventions are set to their best-case, an additional 7% reduction of TB incidence can be achieved by 2030 with vaccination compared to the scenario without vaccination (Figures 7.3 and 7.2).

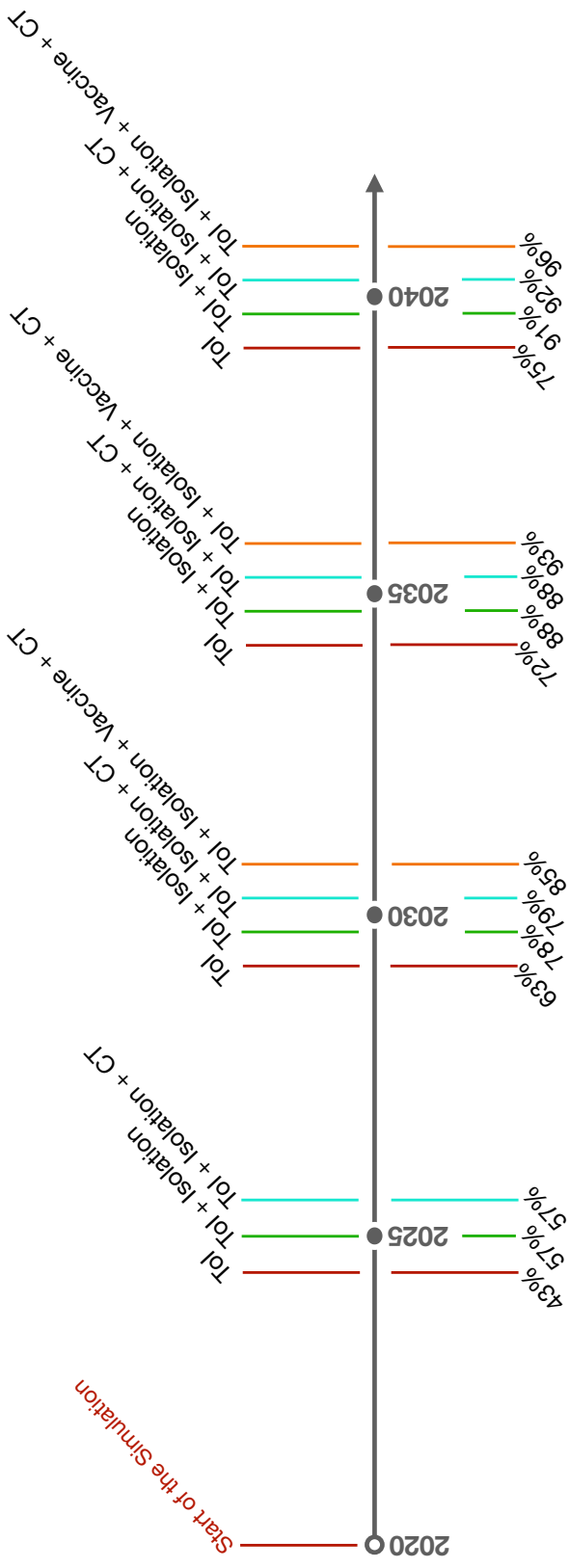

Figure 7.3: Projected timeline for the reduction of TB incidence using the best-case scenario of each intervention with ToI of 1 week, contact-tracing level of 100% and out-of-home isolation TB patients for two weeks.

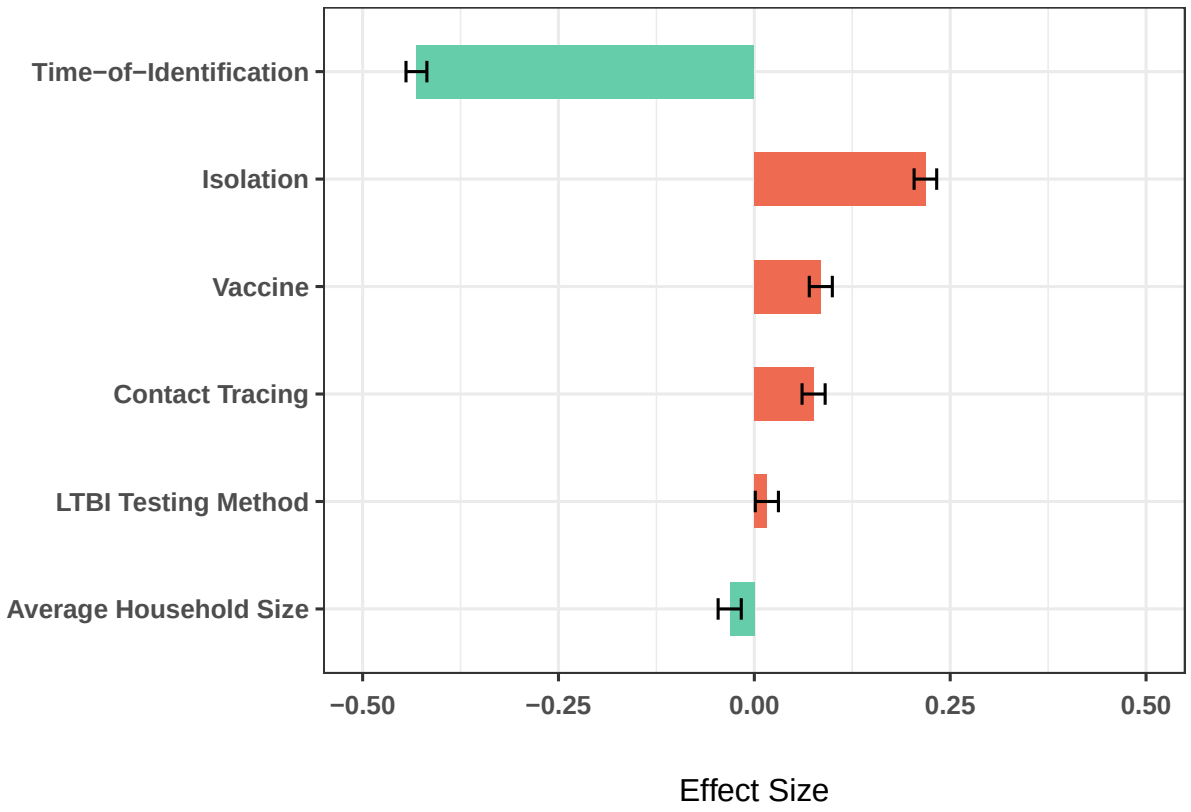

Figure 7.4: Projected annual incidence of active TB per 100,000 population, for the baseline and best-case of each intervention (i.e., when ToI is 1 week, contact-tracing level is 100%, and patients are isolated out of home for two weeks) with 100% vaccination coverage of TB patients.

By combining all interventions at their best-case scenario, along with vaccination of 100% coverage of TB patients, the incidence of TB is reduced by 85%, 95%, and 96% by 2030, 2035, and 2040, respectively (Figure 7.3). The sensitivity analysis also confirms the positive impact of vaccination on reducing the annual TB incidence (Figure 7.4).

As discussed in chapter 6, the reduction of TB incidence will be smaller if compliance with two weeks isolation is lower than 100%, which also holds true with vaccination. For instance, maintaining all other interventions at their baseline level and if only 80% of patients adhere to isolation at home, with 100% vaccination coverage, the incidence is projected to increase by $\sim$15% in 2030 compared to the scenario where all patients comply with home-isolation for two weeks. This difference between 100% compliance and 80% compliance remains the same over time and in 2040 the difference is $\sim$14%.

Table 7.1: Partial rank correlation analysis.

Intervention	PRCC	95% CI	P-value
Time-to-identification	-0.431	(-0.445 , -0.418)	0.000
Isolation	0.218	(0.204 , 0.233)	0.000
Vaccination	0.085	(0.070 , 0.100)	0.000
Contact-tracing	0.076	(0.061 , 0.090)	0.000
LTBI testing method	0.016	(0.001 , 0.031)	0.034
Average household size	-0.031	(-0.046 , -0.017)	0.000

(Figures 7.5, red curve and 7.2).

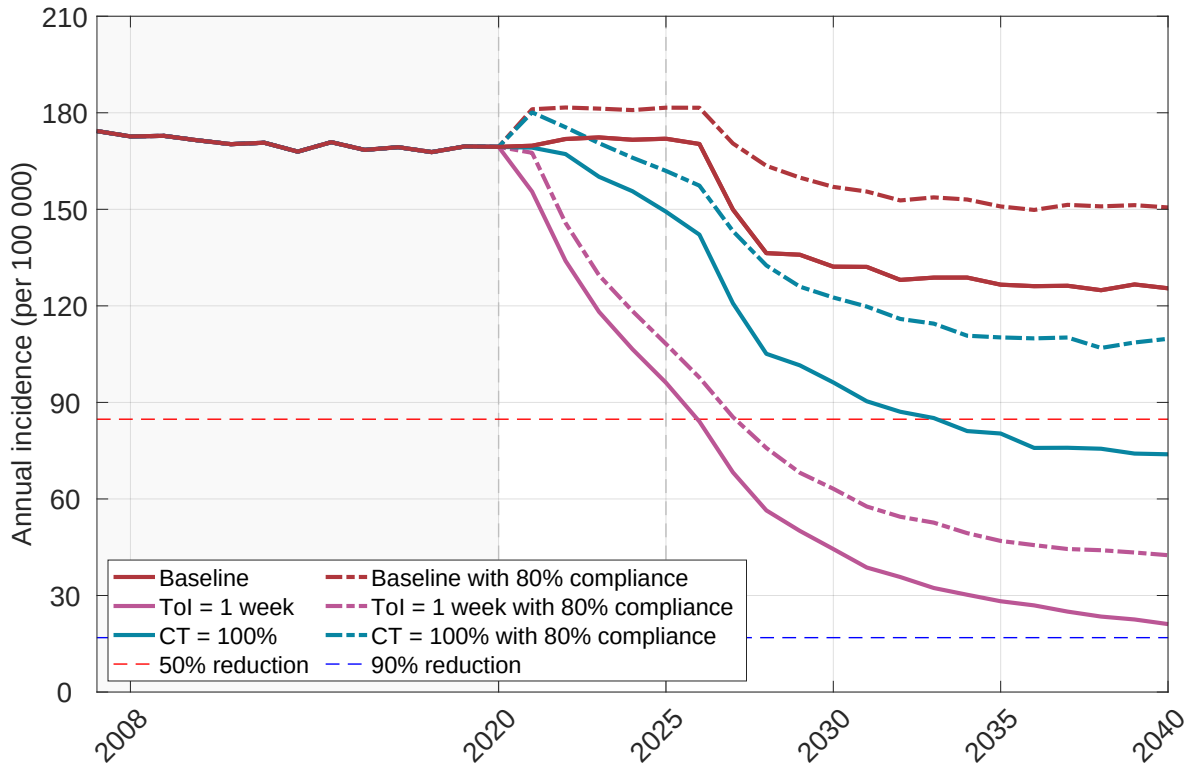

Figure 7.5: Projected annual incidence of active TB per 100,000 population, with 80% rate of compliance with isolation at home, and 100% vaccination coverage of TB patients.

Table 7.2: Reduction of TB incidence (%) in simulated scenarios of best-case and baseline level of contact-tracing rates and time-to-identification, with 80% compliance rate of isolation at home, and 100% vaccination coverage of TB patients.

	CT*	**25%**			**100%**		
ToI	Year	Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	-7	-14	-1	4	-2	10
	2030	7	2	13	28	23	32
	2035	11	5	16	35	31	39
	2040	11	6	16	36	32	40
1 week	2025	36	32	40	35	31	39
	2030	63	61	65	63	60	65
	2035	72	71	74	71	70	73
	2040	74	73	76	74	72	76

*CT: contact-tracing.

Chapter 8

Discussion

In this dissertation, I developed an agent-based simulation model to investigate the effect of currently available interventions and a future therapeutic vaccine on reducing the incidence TB in the Inuit population of Nunavut. My objective was to determine whether goals set in action plans for TB elimination can be achieved, and what level of interventions are required to accelerate these goals within the expected timelines.

This thesis employs an innovative agent-based framework that can be adapted to any population setting, to address a critical gap in the literature regarding the evaluation of TB intervention strategies and the extent to which each action in the TB elimination framework in Indigenous populations contributes to reducing TB incidence. A distinctive feature of this thesis is its explicit definition of timelines for TB incidence reduction, focusing on Nunavut-specific interventions and their combinations. Furthermore, One of the key novelties of this thesis is the way the household structure and contact patterns within the framework is shaped. The findings of this study provide valuable insights into the impact of each TB control strategy on the reduction of TB cases in the coming years, projecting incidence reduction until 2040.

The results of this investigation, based on parameterization that reflects TB management in northern Canadian population, indicate that TB elimination is not achievable by 2030 under the most plausible scenarios. However, reducing the annual TB incidence by 50% can be achieved by under a combination of interventions. The findings show that despite the significance of early detection and treatment of active TB patient, a 50% reduction of TB incidence is still not feasible by 2025 under the spectrum of scenarios

simulated in this dissertation.

8.1 Time-to-identification and contact-tracing

Identification of both active TB cases and their contacts who may be infected as LTBI is critically important in the cascade of care. While significant efforts have been invested in eliminating TB in Nunavut, the success remains hampered by multiple factors [199], including a protracted time lag between case diagnosis and treatment, limited access to diagnostic resources and services, inadequate resources for contact-tracing, and delayed initiation of treatment. Given the significance of case findings, achieving elimination goals will depend on the expansion of accessibility to more precise diagnostic services and laboratory capacity.

My study emphasises the value of contact-tracing among frequent contacts in the community. A wide range of potential obstacles may correlate with limited, low rates of contact-tracing for active TB patients. For instance, inadequate human resources, a lack of commitment and motivation among healthcare professionals and contacts, transportation and distance from laboratory and healthcare centres, limited awareness of the importance of screening, as well as financial considerations, stigma, and discrimination [152, 153, 154].

8.2 Out-of-home isolation

The findings show similar outcomes for a 1-week and 2-week out-of-home isolation periods with a high level of contact-tracing and a maximum of 1-week delay in active TB case diagnosis after the onset of symptoms. Not all patients exhibit similar levels of infectiousness or disease severity after becoming active, and thus, isolation cannot be based on a predetermined treatment duration. The isolation period instead may depend on the evidence of clinical and bacteriologic improvement and the efficacy of the treatment regimens. Isolation may continue until there is full confidence that the patient is no longer contagious [200, 201].

Implementing short-term out-of-home isolation could be an effective strategy for preventing onward transmission of TB within households and its further spread in the

community. However, this strategy faces numerous challenges, including high costs and substantial resources that are required for maintaining isolation facilities, in addition to potential harmful consequences, including those that affect employment, caregiving and support structures, mental health, and access to education.

Hospitalization is the most expensive component of TB control programs within the healthcare system. Delays in diagnosis and start of treatment may lead to a more severe disease, necessitating hospitalization with prolonged stay. Early detection and treatment could prevent severe disease and the risk of hospitalization. This could be facilitated through campaigns to raise awareness of the disease with preventative initiatives.

Infection-control measures, medical stabilisation and direct observation of TB patients are among the advantages of hospitalization [202]. Furthermore, extended inpatient treatment may be utilised to ensure treatment completion for patients who are homeless or living in communal settings, have mental or substance addiction problems, or struggle with daily life activities [203, 204]. TB hospitalizations, however, involves the risk of nosocomial transmission to healthcare staff and other at-risk patients [202, 203]. Additionally, hospitalizations account more than 50% of TB treatment costs, inflicting substantial economic burden in the healthcare system [205, 203].

8.3 Testing method

The analyses in this dissertation shows that the difference in reduction of TB incidence using TST and IGRA is unremarkable. The application of IGRA as a testing tool in Nunavut remote settings is currently facing great challenges, including transferring samples to a distant laboratory and lengthy processing times. While IGRA is a more sensitive test that can increase detection rates and, thereby, is expected to contribute to a further reduction in TB incidence, repeated TST testing contacts within 8 weeks provides comparable outcomes.

8.4 Reduction of household size

The findings presented in dissertation are in line with other research evaluating the effect of household sizes on the incidence of TB in Indigenous populations [112, 199].

While it provides no measurable effect on reducing the incidence of TB, a lower average household size can help reduce secondary household transmission, and improve the social determinants of health. According to molecular study, only 8%–19% of TB transmission takes place within households or via established social contacts [206]. This relatively low rate of transmission compared to community transmission of TB could be explained by the fact that once a secondary household member is infected, any subsequent infectious contact (that occur frequently within household members) before the patient recovers from the disease are wasted in the chain of transmission.

8.5 Therapeutic vaccines

Traditional platforms were primarily focused on creating prophylactic vaccines that would be administered to newborns. However, recent advances in vaccine technologies have provided alternative types of vaccines that can be useful in different situations, even after infection and during treatment of TB patients. For instance, a post-exposure therapeutic vaccine can be administered after infection to increase the effectiveness of drug treatment [188].

Although these vaccines may have distinct mechanisms and targets against TB, they share a common public health objective with regard to outcome measures and efficacy. These objectives are 50% or greater efficacy in reducing the rate of recurrent TB after a standard course of drug treatment and/or 50% or greater reduction in treatment failure at the end of drug treatment [178]. My research findings show that even with the availability of vaccination, the elimination goals may not be achieved without efforts to reduce the time-to-identification of active TB patients, and improve contact-tracing.

8.6 Study limitations

As with any modelling research, there are limitation in the use of agent-based models. While the requirement of vast computational capacity may not be a limiting factor with advancement and wider availability of computing power, these models require significant amount of information and data for parameterization. In the absence of data pertaining to

the characteristics of individuals and different components of the system, simpler models may be a prudent approach for evaluating interventions in disease epidemiology.

It is important to highlight the limitations of this research and their impact on the interpretation of the results. I assumed that individuals who had frequent interactions in the community belong to a group of peers (such as coworkers or classmates) and utilised a negative binomial distribution to sample the within-group contacts using the age-specific contact distribution. It was also assumed that 80% of community encounters frequently occur within each group, with the remaining 20% being classified as casual contacts. As contact patterns play a fundamental role in TB transmission dynamics [207, 94], the model parametrization could be improved by additional household and community data on the network of interactions.

Although only age-specific risks of disease activation were considered, other factors such as pre-existing conditions like diabetes, HIV, renal disease, cancer, as well as smoking, may significantly impact the likelihood of acquiring active TB. For instance, the prevalence of tobacco use in Nunavut is about six times greater than the national average, with a two-fold increased risk of TB activation compared to never-smokers [208, 209, 210]. Notwithstanding these limitations, the quantitative analyses present meaningful insights that can inform TB elimination initiatives in the Inuit populations.

While therapeutic vaccine platforms reviewed in this dissertation (Section 7.1) have different efficacy, I assumed vaccination would be 50% effective at both preventing relapse and reducing treatment failure. As clinical stages of vaccine development progresses, a more effective vaccine may become available; thus new analyses are warranted to assess its impact on reducing TB incidence. Such analyses may also evaluate the effect of vaccination on re-infection or prevention of primary infection.

For treatment and management of TB patient, the model presented here did not consider hospital admission. Hospitalization plays an important role in management of TB in severe patients; however, it also increases the possibility of nosocomial transmission to medical personnel and other vulnerable patients. The World Health Organization estimates that for every 100 hospitalised patients, seven that live in developed countries, and 15 that live in developing countries contract at least one of the infection acquired in a healthcare environment during their stay [211]. One of these infections is TB, presenting a major public health concern [212]. Since hospitalization was not explicitly modelled

here, the transmission that could occur within a healthcare setting was not taken into consideration.

8.7 Future work

Although a wide range of interventions and treatment regiments were investigated, analysis of the associated costs were beyond the scope of this research. Future work may include cost-effectiveness of such interventions to determine optimal resources allocation and utilization. The adoption of each of these interventions may depend on their cost-effectiveness in specific population settings such as northern communities, which have limited resources, a face social and geographic barriers.

The World Health Organization (WHO) has recommended the same-day diagnosis and treatment initiation of TB to address treatment delays [213]. This approach aims to reduce the time interval between TB diagnosis and treatment initiation. In order to achieve this goal, rapid diagnostic tools are crucial to provide quick results and minimize diagnostic delay, which refers to the time gap between sample collection and TB diagnosis [213, 214].

One such diagnostic tool is Xpert® Mycobacterium tuberculosis and rifampicin (Xpert® MTB/RIF, Cepheid, Sunnyvale, CA), commonly known as GeneXpert. It is a simple, rapid, and accurate method for detecting TB in sputum specimens [215]. However, it remains unclear how cost-effective GeneXpert would be compared to other testing methods or interventions aimed at reducing diagnosis delays among indigenous population.

The TB vaccine candidate pipeline includes various types of vaccines designed to either prevent infection or prevent the development of the disease. The availability of a preventive vaccine could potentially contribute to the reduction of TB incidence, but this aspect also requires further evaluation [216].

Finally, the presence of competing priorities and demand for other health care may affect management and control TB. For instance, most affected countries, including Canada, many routine healthcare services were interrupted or faced significant challenges during the COVID-19 pandemic [217].

The pandemic overwhelmed services related to pulmonology, infectious disease, and microbiology. Most available resources were allocated to the fight against COVID-19,

halting the majority of TB screening programs in public areas, shelters, and drug rehabilitation facilities. The number of TB cases diagnosed since the start of the pandemic has decreased. COVID-19 also posed additional challenges for patients in accessing basic care, causing further delay in diagnosis of active TB and initiation of treatment. Economic and social burdens resulted from the pandemic have been significant. The World Health Organization estimated that a 3-month lockdown and a 10-month protracted recovery could result in 6.3 million additional TB cases and 1.4 million additional TB fatalities between 2020 and 2025. These estimates are based on the effect that the COVID-19 pandemic has had on the TB control responses [218, 219].

In Canada, LTBI treatment initiation rates were reduced by 30% to 66%. During the COVID-19 pandemic, In Montreal and Toronto, treatment rates of active TB patients declined by 16% and 29%, respectively, weakening the strategies for TB eradication [217, 219]. Personnel from the Stop-TB Canada initiative were required to work on COVID-19-related concerns, which led to a disruption in active case finding, contact-tracing, LTBI management, and reduced the quality of TB care. Diagnosis delays with patients presenting a more advanced stages of TB disease were also reported [220]. Additional research is warranted to determine how the COVID-19 pandemic has affected the timelines and milestones set in action plans for TB elimination in Indigenous populations.

Appendix A

Simulation Scenarios

This Appendix presents the outcomes of various scenarios for time-to-identification (ToI), contact-tracing (CT), isolation, reduction of average household size, and testing method (Figure 5.2). Chapters 6 and 7 provided details of analyses for the baseline and best-case scenarios of each intervention. This appendix illustrates combination of various scenarios not covered in previous chapters. First, I present the results of scenarios without vaccination. Then, scenarios with vaccination are discussed.

A.1 Time to identification

To assess the impact of a time delay in diagnosis of active TB patients, I evaluated the annual incidence of active TB cases by reducing the ToI from the baseline of 4 weeks to a minimum of one week. I projected that the annual incidence would decline by $\sim$11%, $\sim$25%, and $\sim$43% by 2025 when the ToI is 3 weeks, 2 weeks, and 1 week, respectively, compared to the baseline scenario.

If at least 75% of frequent contacts were tested and those identified with LTBI were treated, identification of active TB patients within two weeks would enable a 50% reduction of TB incidence by 2035. Further reduction of ToI to one week after the onset of symptoms would accelerate the time to reach the goal of 50% reduction in TB incidence between 2025 and 2030, even if only 25% of frequent non-household contacts were tested. This reduction was estimated to be $\sim$63% by 2030 (Figure A.1A4).

A.2 Contact-tracing

When compared to the baseline scenario of 25% CT, I projected that increasing CT to 50%, 75%, and 100% of frequent contacts would decrease the annual incidence of active TB cases by $\sim$3%, $\sim$8%, and $\sim$12% in 2025, and by $\sim$6%, $\sim$16%, and $\sim$24% in 2030, respectively. These estimates show that the impact of CT becomes less pronounced as the ToI decreases (Figure A.1). For example, in the baseline scenario with a 4-week ToI on average, an increase in CT from 25% to 100% of frequent contacts would result in a reduction of only $\sim$36% by 2040. However, the effect of contact-tracing decreases when the ToI is one week and the difference in the incidence reduction between 100% CT and 25% CT would be under 2% at any point with a 1-week ToI.

This is a direct effect of early TB case detection and a two-week home isolation period, which would prevent transmission to frequent community contacts and therefore decrease the need for a high level of CT. I also projected that the average reduction in TB incidence would be $\sim$63% by 2030, $\sim$73% by 2035, and $\sim$77% by 2040, assuming active TB cases were detected within 1-week of symptom onset, and the CT rate was exceeded 25% of frequent contacts (Figure A.1).

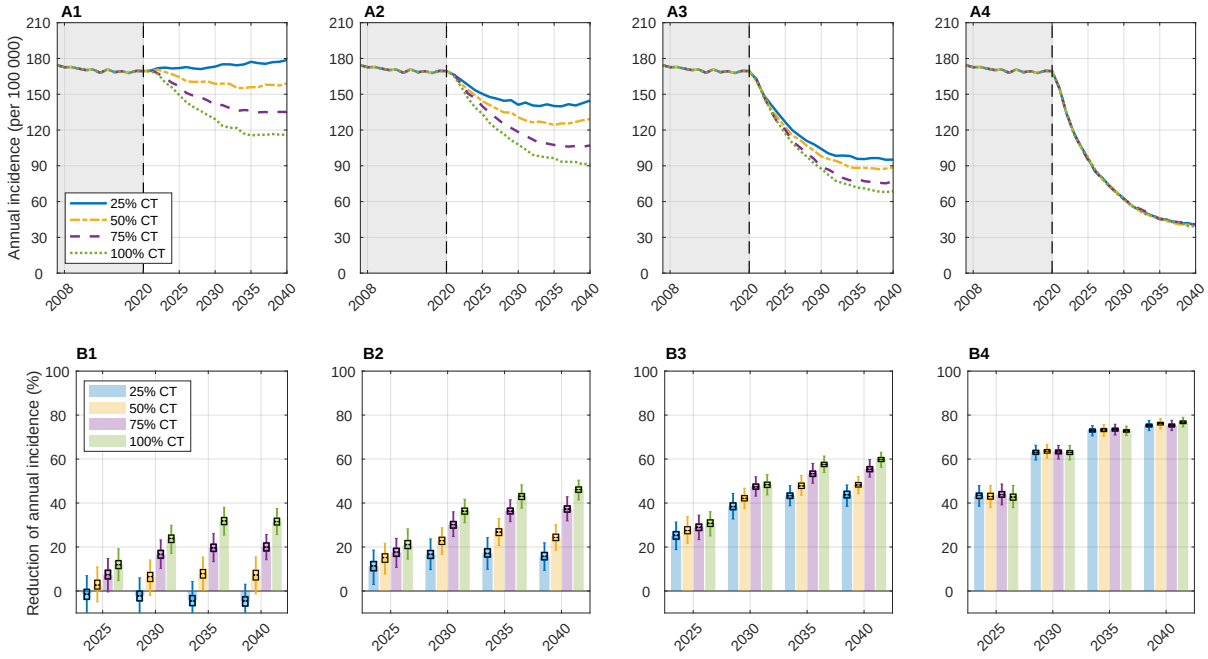

Figure A.1: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different contact-tracing (CT) rates and an average household size of 3.8. ToI was set to 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

Table A.1: Reduction of incidence (%) in simulated scenarios of different contact-tracing rates compared to the baseline scenario with average household size of 3.8. The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	CT*	**25%**			**50%**			**75%**			**100%**		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	-1	-8	5	3	-4	9	7	2	13	12	6	18
	2030	-2	-9	5	6	0	12	17	11	21	24	19	28
	2035	-4	-11	3	8	2	13	20	14	24	32	27	36
	2040	-5	-11	1	7	1	13	20	16	25	32	27	36
3 weeks	2025	11	5	17	15	9	21	18	12	23	21	16	26
	2030	17	11	23	23	18	27	30	26	34	36	32	41
	2035	17	12	23	27	22	31	36	33	40	43	39	47
	2040	16	11	21	24	20	29	37	33	41	46	43	50
2 weeks	2025	25	20	29	28	23	32	29	24	33	31	26	35
	2030	38	34	42	42	38	46	47	44	51	48	45	52
	2035	43	40	47	48	44	51	53	50	57	58	55	60
	2040	44	40	47	48	45	51	55	52	58	60	57	62
1 week	2025	43	39	46	43	40	47	44	40	47	43	39	46
	2030	63	60	65	64	61	66	63	61	66	63	61	65
	2035	73	71	75	73	71	75	73	72	75	73	71	75
	2040	75	73	77	76	74	78	75	73	77	77	75	78

*CT: contact-tracing.

A.3 Isolation

As a means of determining the impact of out-of-home isolation which eliminates contacts with household members, I evaluated scenarios in which the active TB patients were isolated in a setting for either one week or two weeks (Section 5.6.3).

For a 1-Week out-of-home isolation, the results show that a decrease of $\sim$13% in the incidence of TB can be achieved by 2025 compared to the baseline scenario in which patients self-isolate at home for 1-week. By 2040, the reduction of TB incidence would reach $\sim$17%. The incidence decreases by $\sim$26% by 2025, and if combined with the shortest possible diagnosis delay of one week, the target of 50% reduction in TB incidence would be achievable by 2025. The magnitude of the reduction is 53%.

By increasing the CT level to 100% and setting ToI to 4 weeks, a 50% reduction of TB incidence can be achieved by 2035. This indicates that, as observed in earlier scenarios, contact-tracing alone is inadequate and shorter diagnosis delay would be required to accomplish the target goal by 2025. When the ToI does not exceed one week, the effect of contact-tracing is diminished. The extent of incidence reduction could reach $\sim$87% by 2040 (Figures A.2, A.2).

For a two-week isolation, the results indicated there will be an additional $\sim$9% reduction of TB incidence can be achieved by 2025 compared to one-week isolation scenario, and a total reduction of $\sim$22% compared to the baseline scenario. However, the goal of 50% incidence reduction would still not be attainable in any of the scenarios involving two-week out-of-home isolation if ToI exceeds 1 week. With 100% CT and TOI of 1 week, the reduction of TB incidence is projected to reach 57% by 2025. In this scenario, TB incidence would be reduced by $\sim$92% by 2040 (Figures A.3, A.3).

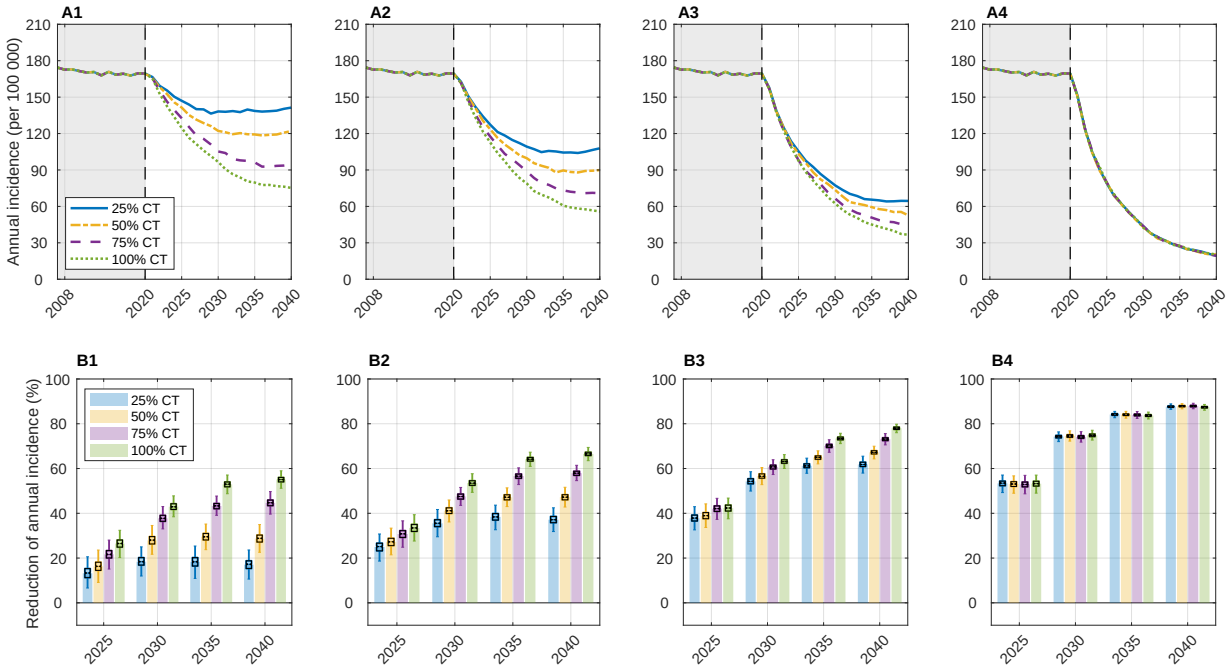

Figure A.2: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different contact-tracing rates and an average household size of 3.8, when the active TB patient is out-of-home isolated for 1 week. ToI: 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP). CT: contact-tracing.

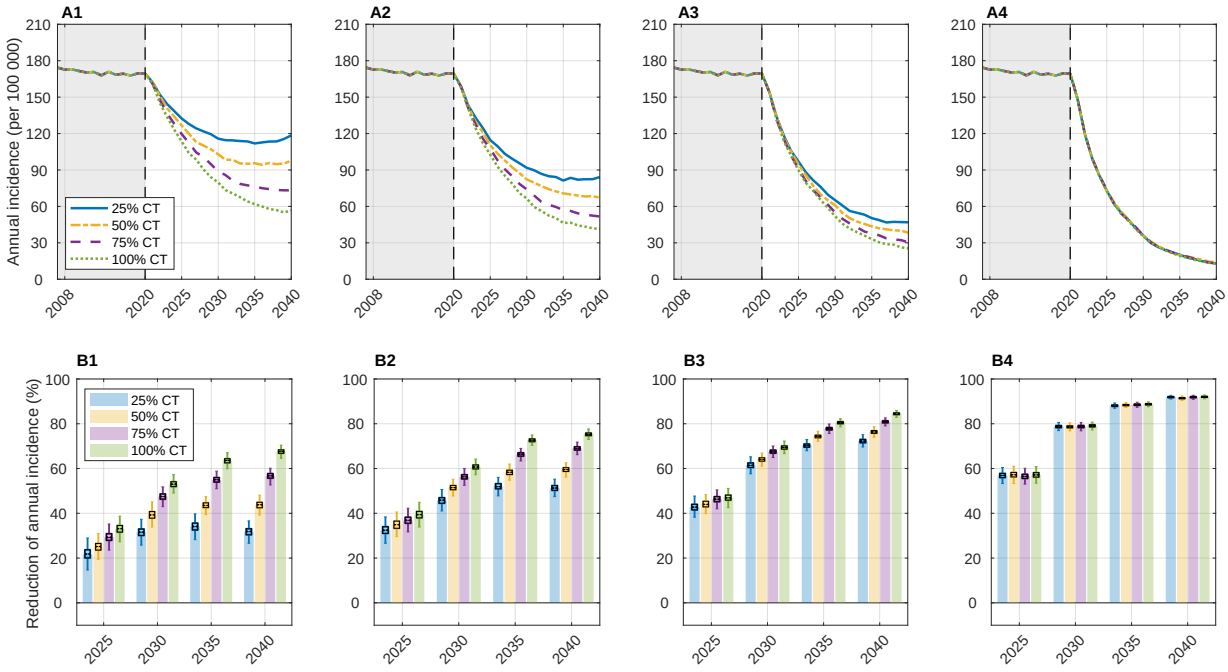

Figure A.3: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different contact-tracing rates and an average household size of 3.8, when the active TB patient is isolated out of home for 2 weeks. ToI: 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP). CT: contact-tracing.

Table A.2: Reduction of incidence (%) in simulated scenarios of different contact-tracing rates, with average household size of 3.8 and 1 week out-of-home isolation of active TB patients. The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	CT*	**25%**			**50%**			**75%**			**100%**		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	13	7	19	16	11	21	22	17	27	26	22	31
	2030	18	13	24	28	23	33	38	34	41	43	39	46
	2035	18	13	24	30	26	34	43	40	47	53	50	56
	2040	17	12	22	29	24	33	45	41	48	55	52	58
3 weeks	2025	25	20	30	27	23	32	31	26	35	33	29	38
	2030	36	31	40	41	37	45	48	44	51	53	50	56
	2035	38	34	42	47	43	50	57	54	60	64	62	66
	2040	37	33	41	47	44	51	58	55	61	67	64	69
2 weeks	2025	38	34	42	39	35	43	42	38	45	42	38	46
	2030	54	51	57	57	54	59	61	58	63	63	61	66
	2035	61	59	64	65	63	67	70	68	72	73	72	75
	2040	62	59	65	67	65	69	73	71	75	78	77	79
1 week	2025	53	50	56	53	50	56	53	50	56	53	50	56
	2030	74	73	76	75	73	76	74	72	76	75	73	76
	2035	84	83	85	84	83	85	84	83	85	84	82	85
	2040	88	87	89	88	87	89	88	87	89	87	86	88

*CT: contact-tracing.

Table A.3: Reduction of incidence (%) in simulated scenarios of different contact-tracing rates, with average household size of 3.8 and 2 weeks out-of-home isolation of active TB patients. The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	CT*	**25%**			**50%**			**75%**			**100%**		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	22	17	27	25	20	29	29	25	34	33	29	37
	2030	32	27	36	39	35	43	47	44	50	53	50	56
	2035	34	30	38	44	40	47	55	52	58	63	61	66
	2040	32	27	36	44	40	47	57	54	59	68	65	70
3 weeks	2025	32	28	37	35	31	39	37	32	41	39	35	43
	2030	46	42	50	51	48	54	56	54	59	61	58	63
	2035	52	49	55	58	55	61	66	64	69	73	71	74
	2040	51	48	54	60	57	62	69	67	71	75	74	77
2 weeks	2025	43	39	46	44	41	48	46	43	49	47	43	50
	2030	61	59	64	64	62	66	68	65	70	69	67	72
	2035	70	68	72	74	73	76	78	76	79	80	79	82
	2040	72	70	74	76	75	78	81	79	82	84	83	86
1 week	2025	57	54	60	57	54	60	56	54	59	57	54	60
	2030	79	77	80	79	77	80	79	77	80	79	78	80
	2035	88	87	89	88	87	89	88	88	89	89	88	90
	2040	92	91	93	91	91	92	92	91	93	92	91	93

*CT: contact-tracing.

A.4 Testing method

The timelines and the magnitude of TB incidence reduction did not alter significantly when the IGRA was implemented as a testing method for detection of LTBI. In most scenarios, the additional reduction of TB incidence compared to TST method was less than ∼2%. When the ToI was set to one week, the difference between outcomes of TST and IGRA testing methods was negligible (Figure A.4, Table A.4).

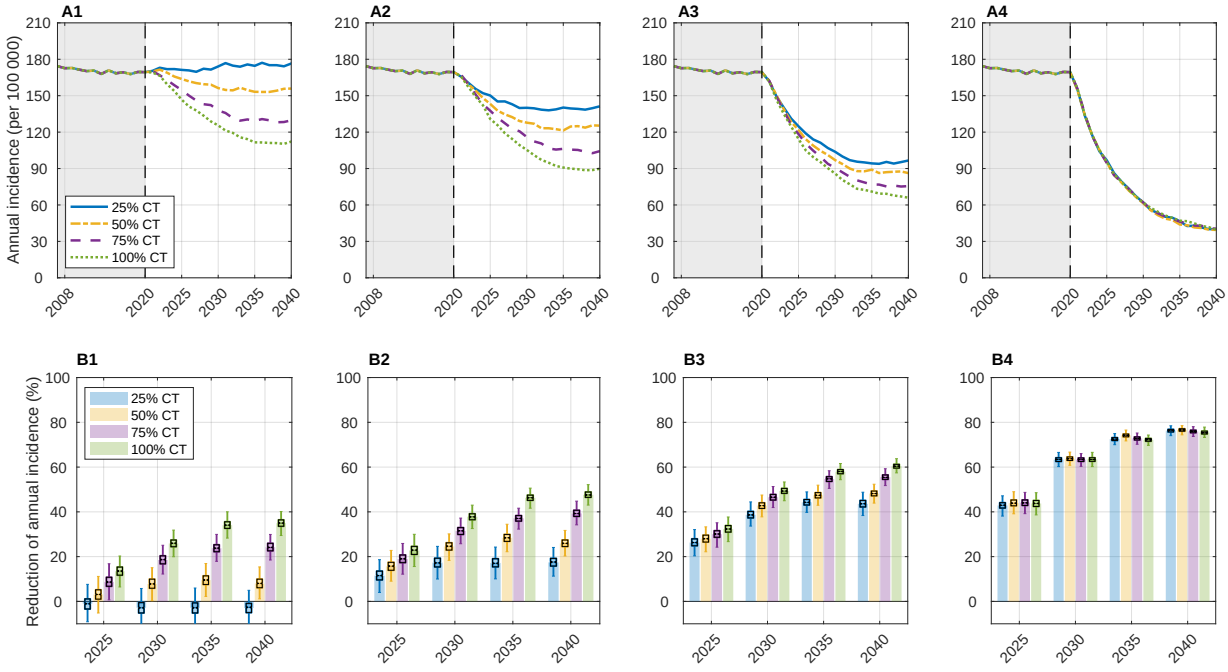

Figure A.4: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different contact-tracing rates and an average household size of 3.8, when testing method is IGRA. ToI: 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP). CT: contact-tracing.

Table A.4: Reduction of incidence (%) in simulated scenarios of different contact-tracing rates, with average household size of 3.8, when the testing method is IGRA. The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	CT*	**25%**			**50%**			**75%**			**100%**		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	-1	-7	5	3	-3	9	9	3	15	13	8	19
	2030	-3	-10	4	8	2	14	19	13	23	26	21	30
	2035	-3	-9	4	10	4	15	24	19	28	34	29	39
	2040	-3	-9	3	8	2	14	24	20	29	35	31	39
3 weeks	2025	12	6	17	16	10	21	19	14	24	23	18	27
	2030	17	12	23	25	20	29	32	28	36	38	34	42
	2035	17	12	22	28	24	34	37	33	41	46	43	50
	2040	17	12	22	26	21	30	39	35	43	48	44	51
2 weeks	2025	26	21	31	28	24	32	30	25	34	32	28	37
	2030	39	34	43	43	39	46	47	43	50	49	46	53
	2035	44	41	48	47	44	51	55	52	58	58	55	61
	2040	44	40	47	48	44	51	56	53	58	60	58	63
1 week	2025	43	39	46	44	40	47	44	41	48	44	40	47
	2030	63	61	65	64	61	66	63	61	66	63	61	66
	2035	73	71	74	74	72	76	73	71	75	72	70	74
	2040	76	74	78	77	75	78	76	74	78	75	74	77

*CT: contact-tracing.

A.5 Reduction of average household size

It is expected that government investments in housing infrastructure would result in reduced crowding and a lower average household size. Assuming this averaged decreases from 3.8 to 3.3 in 2025, the results show a maximum of ∼2% additional reduction in the annual TB incidence (Figures A.5, A.5). This outcomes is in line with earlier research, suggesting that a minimal impact of lowering household size on TB incidence rates [112, 206, 221].

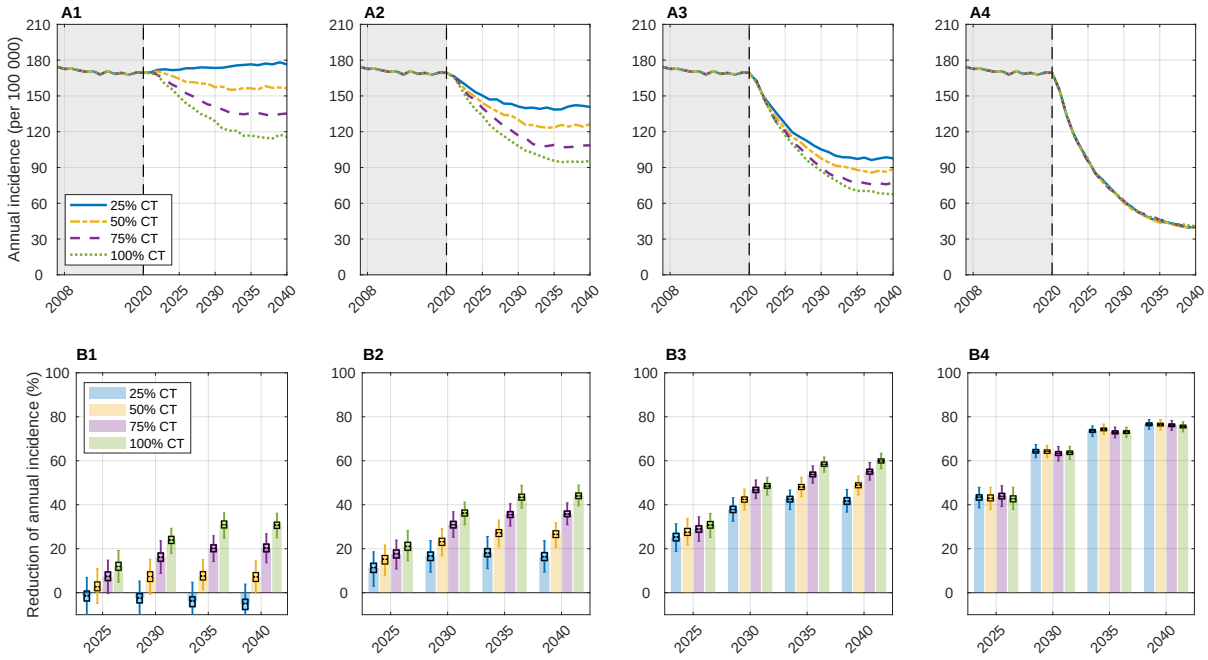

Figure A.5: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different contact-tracing rates and an average household size of 3.3. ToI: 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP). CT: contact-tracing.

Table A.5: Reduction of incidence (%) in simulated scenarios of different contact-tracing rates, with average household size of 3.3. The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	CT*	25%			50%			75%			100%		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	-1	-8	5	3	-4	9	7	2	13	12	6	18
	2030	-1	-9	4	7	2	13	16	11	21	24	19	28
	2035	-4	-10	3	8	2	13	20	15	25	31	26	35
	2040	-3	-12	1	7	1	13	20	16	25	31	26	35
3 weeks	2025	11	5	17	15	9	21	18	12	23	21	16	26
	2030	17	11	22	23	19	28	31	27	35	36	32	40
	2035	18	13	24	27	22	32	36	32	40	43	40	47
	2040	16	11	21	27	22	31	36	32	40	44	41	48
2 weeks	2025	25	20	29	28	23	32	29	24	33	31	26	35
	2030	38	34	42	42	38	46	47	43	50	49	45	52
	2035	43	39	46	48	45	52	54	51	57	58	56	61
	2040	42	38	45	49	46	52	55	52	58	60	57	63
1 week	2025 2025	43	39	46	43	40	47	44	40	47	43	39	46
	2030	64	62	67	64	62	67	63	61	65	64	61	66
	2035	74	72	75	74	72	76	73	71	75	73	71	75
	2040	77	75	78	76	74	78	76	74	78	76	74	77

*CT: contact-tracing.

A.6 Vaccination augmented with contact-tracing

Increasing vaccination coverage from 25% to 100% resulted in ∼22% reduction of TB incidence by 2030 under the baseline scenario, in which 25% of frequent contacts are tested and the active TB cases are detected within a week. With vaccination, the timelines for achieving a 50% decrease in TB incidence is shortened, and expected between 2025 and 2030. By 2030 when vaccination coverage is minimum of 75% and ToI is two weeks. (A.6 A.6).

In contrast to the results observed for masking the effect of CT when implementing a rapid ToI, the effect of vaccination remains measurable, but less pronounced. When the ToI is 4 weeks, increasing vaccination coverage from 25% to 100% will result in an additional ∼21% reduction of TB incidence by 2040. This reduction is ∼28% with a 1-week ToI (A.6 A.6). When CT is at 25% with ToI under one week, the highest reduction achieved by 2040 is projected to be ∼80%, ∼82%, ∼84%, and ∼87% for 25%, 50%, 75%, and 100% vaccination coverages, respectively.

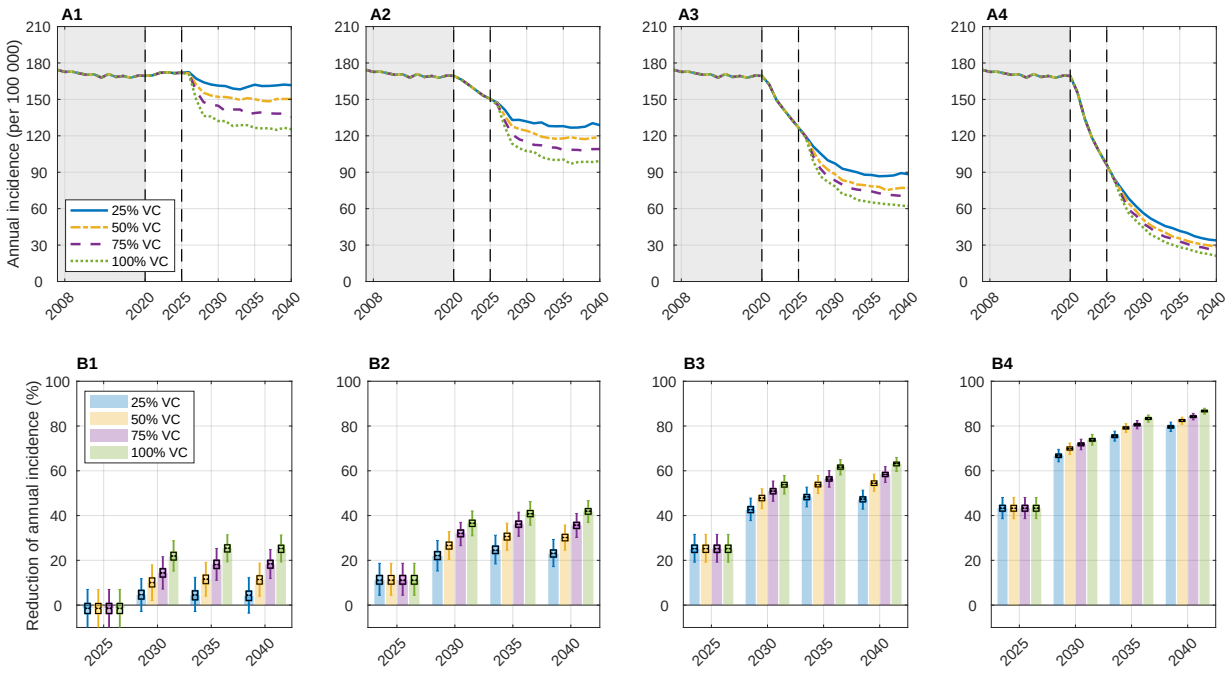

Figure A.6: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different vaccine coverages and an average household size of 3.8, when 25% of frequent contacts are tested. ToI: 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP). VC: Vaccine Coverage.

Table A.6: Reduction of incidence (%) in simulated scenarios of different vaccine coverages, with average household size of 3.8 and 2 weeks out-of-home isolation of active TB patients, and with 25% contact-tracing. The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	VC*	25%			50%			75%			100%		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	-1	-8	5	-1	-8	5	-1	-8	5	-1	-8	5
	2030	5	-2	11	10	4	16	14	9	20	22	17	27
	2035	4	-2	11	12	6	17	18	13	24	25	20	31
	2040	4	-1	10	11	5	17	18	13	23	25	21	30
3 weeks	2025	11	6	17	11	6	17	11	6	17	11	6	17
	2030	22	17	27	27	22	31	32	28	36	37	32	41
	2035	25	19	30	31	25	35	36	32	40	41	36	45
	2040	23	18	27	30	26	34	36	31	39	42	38	46
2 weeks	2025	25	20	30	25	20	30	25	20	30	25	20	30
	2030	43	39	46	48	44	51	51	48	54	54	50	57
	2035	48	45	52	54	51	57	56	53	60	62	59	64
	2040	47	44	51	54	52	57	58	56	61	63	61	65
1 week	2025	43	40	47	43	40	47	43	40	47	43	40	47
	2030	67	64	69	70	68	72	72	70	74	74	72	76
	2035	75	74	77	79	78	81	81	79	82	83	82	85
	2040	80	78	81	82	81	84	84	83	85	87	86	88

*VC: vaccine coverage.

The timelines for achieving the 50% reduction goal did not vary when CT was increased to 100%. In contrast to 25% CT, a 2-week ToI is not a necessary requirement for attaining this goal. In addition, ToI is required to remain under 3 weeks with vaccination of at least 75% of TB patients to attain the goal by 2030. The magnitude of this reduction is ∼54%. By 2040, this reduction is projected to reach ∼87% if ToI is under one week, all TB patients are vaccinated, and their contacts are tested (Figures A.9 A.9).

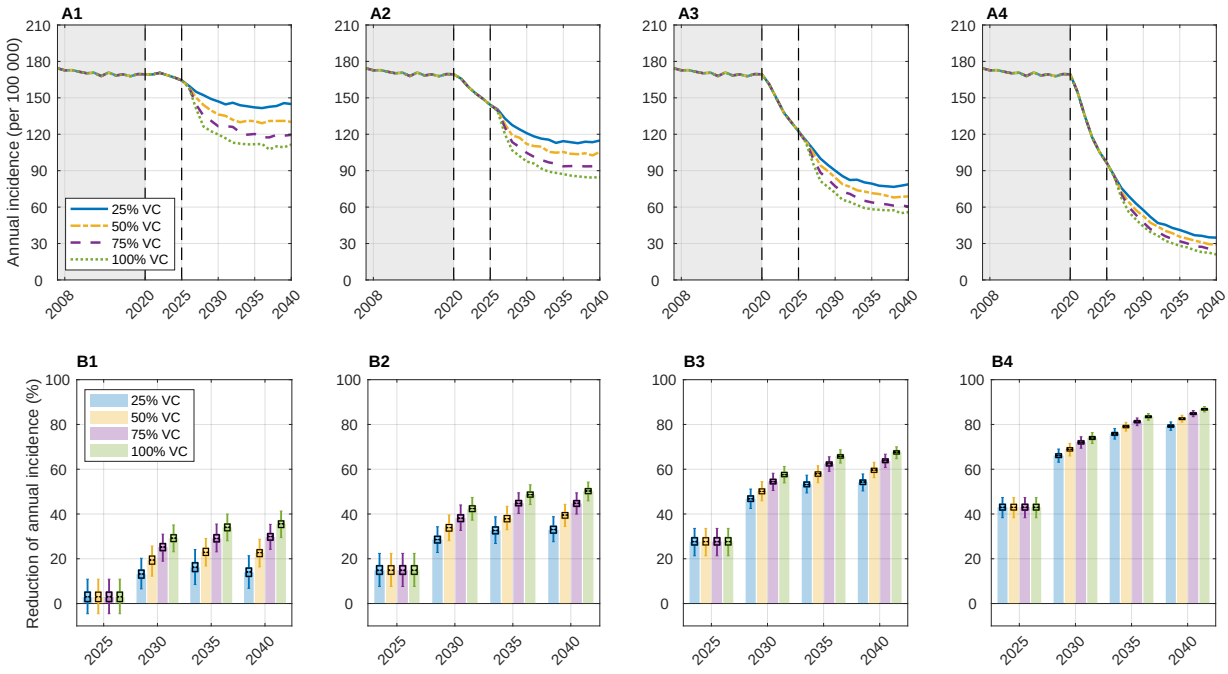

Figure A.7: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different vaccine coverages and an average household size of 3.8, when 50% of frequent contacts are tested. ToI: 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP). VC: Vaccine Coverage.

Table A.7: Reduction of incidence (%) in simulated scenarios of different vaccine coverages, with average household size of 3.8 and 2 weeks out-of-home isolation of active TB patients, and with 50% contact-tracing. The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	VC*	**25%**			**50%**			**75%**			**100%**		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	3	-3	9	3	-3	9	3	-3	9	3	-3	9
	2030	13	7	19	19	14	25	25	21	30	29	25	34
	2035	16	11	22	23	18	29	29	24	34	34	30	39
	2040	14	9	19	23	18	28	30	26	34	35	31	39
3 weeks	2025	15	10	20	15	10	20	15	10	20	15	10	20
	2030	29	24	33	34	29	38	38	34	42	42	39	46
	2035	33	28	37	38	34	42	45	41	49	49	45	52
	2040	33	29	37	39	35	43	45	41	48	50	47	53
2 weeks	2025	28	23	32	28	23	32	28	23	32	28	23	32
	2030	47	43	50	50	47	53	54	51	57	58	55	61
	2035	53	50	56	58	55	61	62	60	65	66	63	68
	2040	54	51	57	60	57	62	64	61	66	68	65	70
1 week	2025	43	39	47	43	39	47	43	39	47	43	39	47
	2030	66	64	68	69	67	71	72	70	74	74	72	76
	2035	76	74	77	79	77	81	81	80	83	83	82	85
	2040	79	78	81	83	81	84	85	84	86	87	86	88

*VC: vaccine coverage.

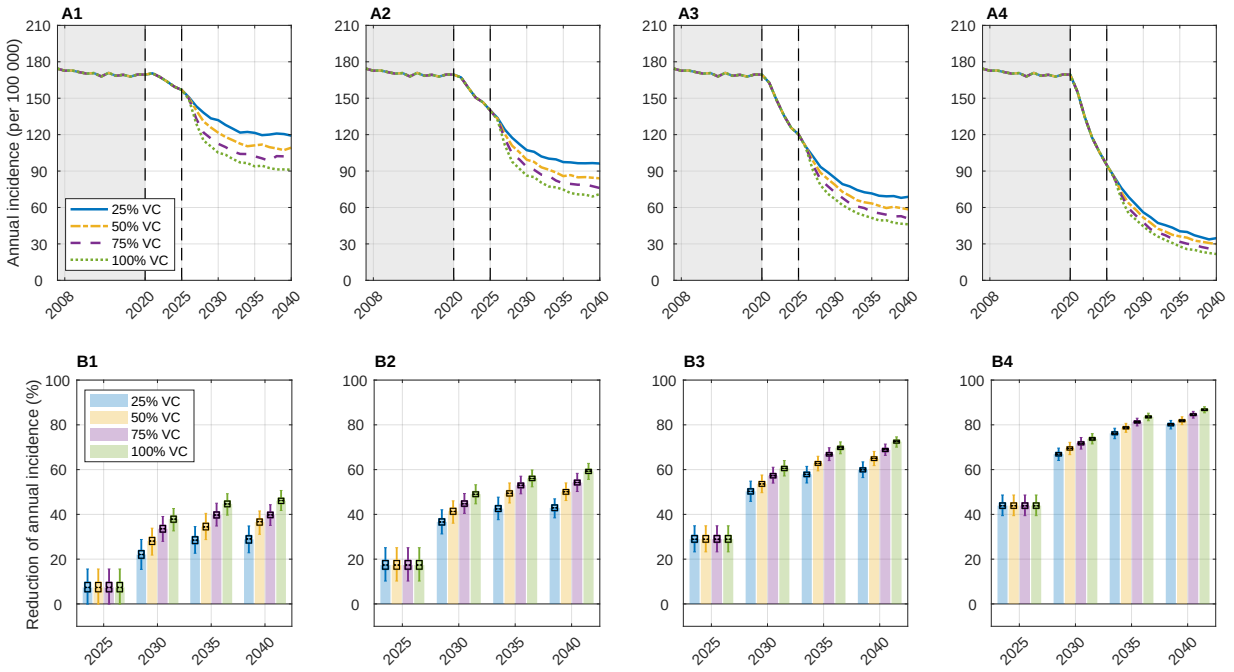

Figure A.8: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different vaccine coverages and an average household size of 3.8, when 75% of frequent contacts are tested. ToI: 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP). VC: Vaccine Coverage.

Table A.8: Reduction of incidence (%) in simulated scenarios of different vaccine coverages, with average household size of 3.8 and 2 weeks out-of-home isolation of active TB patients, and with 75% contact-tracing. The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	VC*	25%			50%			75%			100%		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	7	1	13	7	1	13	7	1	13	7	1	13
	2030	22	17	27	28	23	33	34	29	38	38	34	42
	2035	28	24	33	35	30	39	40	36	44	45	41	48
	2040	29	24	33	37	32	40	40	36	43	46	42	49
3 weeks	2025	17	12	22	17	12	22	17	12	22	17	12	22
	2030	37	33	41	41	38	45	45	41	48	49	46	52
	2035	43	39	46	49	46	53	53	50	56	56	53	59
	2040	43	39	46	50	47	53	54	51	57	59	57	62
2 weeks	2025	29	24	34	29	24	34	29	24	34	29	24	34
	2030	50	47	54	54	50	57	57	54	60	61	58	63
	2035	58	55	61	63	60	65	67	65	69	70	67	72
	2040	60	57	62	65	62	67	69	67	71	72	71	74
1 week	2025	44	40	47	44	40	47	44	40	47	44	40	47
	2030	67	64	69	69	67	72	72	70	74	74	72	75
	2035	76	75	78	79	77	80	81	80	83	84	82	85
	2040	80	79	81	82	80	83	85	83	86	87	86	88

*VC: vaccine coverage.

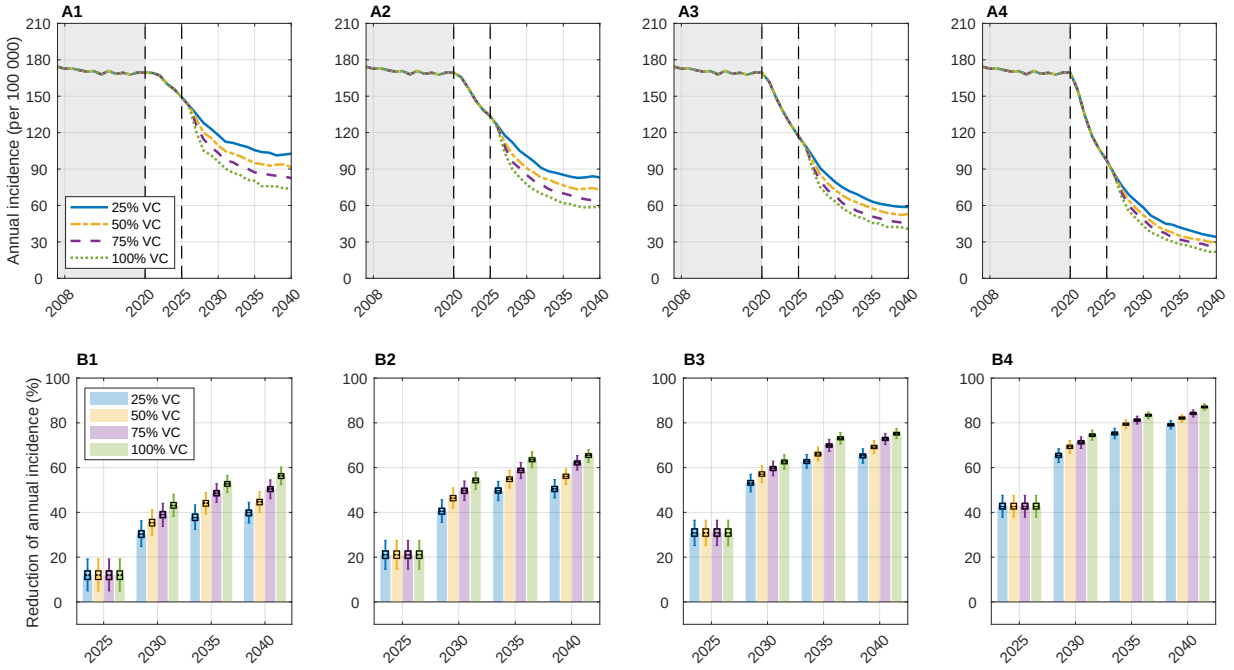

Figure A.9: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different vaccine-coverage rates and an average household size of 3.8, when 100% of frequent contacts are tested. ToI: 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP). VC: Vaccine Coverage.

Table A.9: Reduction of incidence (%) in simulated scenarios of different vaccine coverages, with average household size of 3.8 and 2 weeks out-of-home isolation of active TB patients, with 100% contact-tracing. The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	VC*	25%			50%			75%			100%		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	12	6	17	12	6	17	12	6	17	12	6	17
	2030	30	26	35	35	31	40	39	35	43	43	39	47
	2035	38	34	42	44	40	48	49	45	52	53	50	56
	2040	40	36	44	45	41	48	50	47	53	56	53	59
3 weeks	2025	21	16	26	21	16	26	21	16	26	21	16	26
	2030	41	37	44	46	43	50	50	46	53	54	51	58
	2035	50	46	53	55	52	58	59	56	62	64	61	66
	2040	50	47	54	56	54	59	62	60	64	65	63	68
2 weeks	2025	31	27	35	31	27	35	31	27	35	31	27	35
	2030	53	50	56	57	54	60	60	57	62	63	60	65
	2035	63	60	65	66	64	69	70	68	72	73	71	75
	2040	65	63	68	69	67	71	73	71	75	75	73	77
1 week	2025	43	39	46	43	39	46	43	39	46	43	39	46
	2030	65	63	68	69	67	71	71	69	73	74	73	76
	2035	75	74	77	79	78	81	81	80	83	83	82	85
	2040	79	78	81	82	81	83	84	83	85	87	86	88

*VC: vaccine coverage.

A.7 Vaccination augmented with out-of-home isolation

With a 1-week out-of-home isolation, a 50% decrease in TB incidence can be achieved with 75% CT and 100% vaccination coverage, even if the TOI remains at 4 weeks on average. Reducing CT would require shorter ToI. When CT is increased to 100%, the incidence of TB in 2040 is projected to reduce by $\sim$94% with a 1-week ToI (A.11 A.10).

The reduction of TB incidence can exceed 50% before 2030 if out-of-home isolation increased to two weeks with a 4-week ToI, 50% CT, and 100% vaccination coverage of TB patients. Increasing CT level to 100% is projected to decrease annual TB incidence by $\sim$66% by 2030. in this scenario, rapid identification of active TB cases within 1 week of symptom onset is projected to reduce the annual TB incidence by $\sim$96% by 2040. This provides only a marginal improvement of $\sim$2% with similar interventions but 1 week out-of-home isolation, suggesting that increasing CT would reduce the effect of out-of-home isolation.

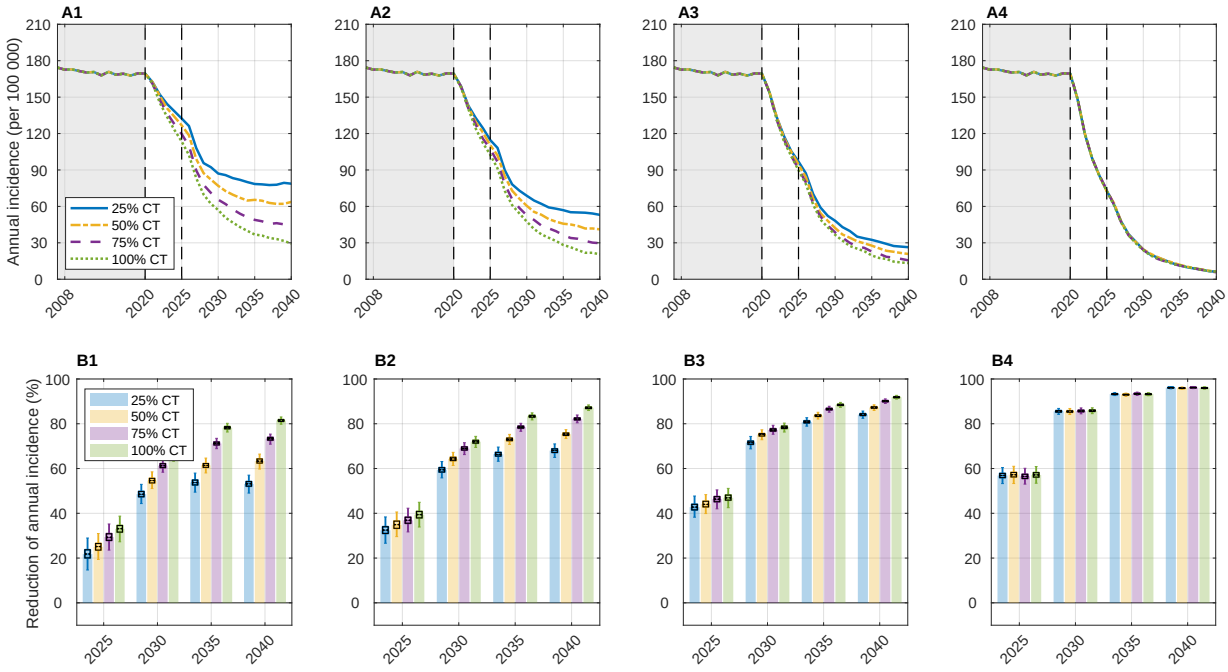

Figure A.10: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different contact-tracing rates and an average household size of 3.8, when the active TB patient is isolated out-of-home for 2 week and 100% of active patients are vaccinated. ToI: 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP). CT: contact-tracing.

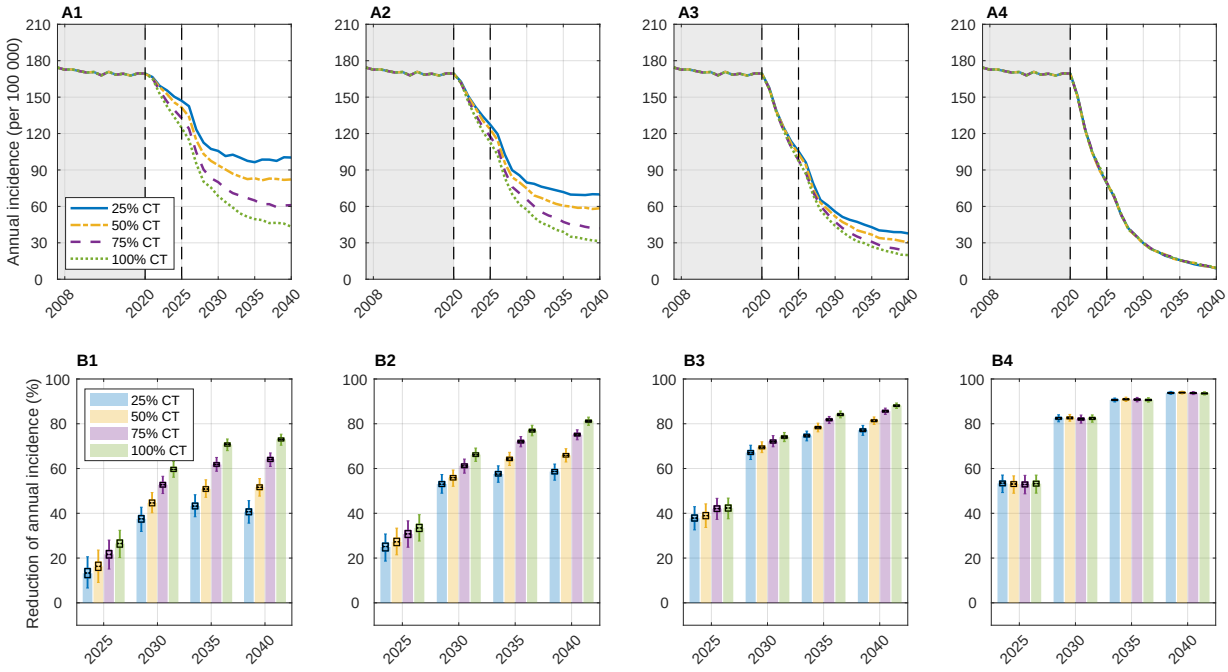

Figure A.11: Projected annual incidence of active TB per 100,000 population (A1-A4) and reduction of annual TB incidence (B1-B4) with different contact-tracing rates and an average household size of 3.8, when the active TB patient is isolated out-of-home for 1 week and 100% of active patients are vaccinated. ToI: 4 weeks (A1,B1), 3 weeks (A2,B2), 2 weeks (A3,B3), and 1 week (A4,B4). The treatment regimen for active TB was set as a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP). CT: contact-tracing.

Table A.10: Reduction of incidence (%) in simulated scenarios of different contact-tracing rates, with average household size of 3.8 and 1 week out-of-home isolation of active TB patients, when the vaccine coverage is 100% The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	CT*	**25%**			**50%**			**75%**			**100%**		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	13	7	19	16	11	21	22	17	27	26	22	31
	2030	38	33	42	45	41	48	53	50	56	60	57	62
	2035	43	40	47	51	48	54	62	59	64	71	69	73
	2040	41	37	45	52	48	55	64	62	66	73	71	75
3 weeks	2025	25	20	30	27	23	32	31	26	35	33	29	38
	2030	53	50	56	56	53	59	61	59	64	66	64	68
	2035	58	55	60	64	62	67	72	70	74	77	75	79
	2040	59	56	61	66	64	68	75	73	77	81	80	83
2 weeks	2025	38	34	42	39	35	43	42	38	45	42	38	46
	2030	67	65	69	69	67	71	72	70	74	74	72	76
	2035	75	73	76	78	77	80	82	80	83	84	83	85
	2040	77	75	79	81	80	83	86	85	87	88	87	89
1 week	2025	53	50	56	53	50	56	53	50	56	53	50	56
	2030	82	81	84	83	81	84	82	81	83	82	81	84
	2035	91	90	91	91	90	92	91	90	92	91	90	91
	2040	94	93	94	94	93	94	94	93	94	94	93	94

*CT: contact-tracing.

Table A.11: Reduction of incidence (%) in simulated scenarios of different contact-tracing rates, with average household size of 3.8 and 2 weeks out-of-home isolation of active TB patients, when the vaccine coverage is 100%. The treatment regimen for active TB was set a combination of daily INH/RMP/EMB for 2 months followed by 4 months of INH/RMP. The treatment regimen for LTBI was set a combination of directly observed isoniazid and rifapentine for 3 months (3HP).

	CT*	**25%**			**50%**			**75%**			**100%**		
ToI	Year	Mean	95% CrI		Mean	95% CrI		Mean	95% CrI		Mean	95% CrI	
4 weeks	2025	22	17	27	25	20	29	29	25	34	33	29	37
	2030	49	45	52	55	52	57	61	59	64	66	64	68
	2035	54	51	57	61	59	64	71	69	73	78	77	80
	2040	53	50	56	63	61	66	73	71	75	81	80	83
3 weeks	2025	32	28	37	35	31	39	37	32	41	39	35	43
	2030	59	57	62	64	62	66	69	67	71	72	70	74
	2035	66	64	69	73	71	75	78	77	80	83	82	84
	2040	68	66	70	75	74	77	82	81	84	87	86	88
2 weeks	2025	43	39	46	44	41	48	46	43	49	47	43	50
	2030	72	69	74	75	73	77	77	76	79	78	77	80
	2035	81	79	82	84	82	85	87	86	87	88	88	89
	2040	84	83	85	87	86	88	90	89	91	92	91	92
1 week	2025	57	54	60	57	54	60	56	54	59	57	54	60
	2030	86	84	86	85	84	86	86	85	87	86	85	87
	2035	93	93	94	93	92	94	93	93	94	93	93	94
	2040	96	96	97	96	96	96	96	96	97	96	96	96

*CT: contact-tracing.

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