POPULATION-BASED STUDIES OF HEALTH SERVICE UTILIZATION AND TREATMENT OUTCOMES OF ACTIVE AND LATENT TUBERCULOSIS PATIENTS IN QUEBEC, CANADA

by

Lisa Anne Ronald

MSc, Liverpool School of Tropical Medicine, 2005
MSc, University of British Columbia, 2001

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Department of Epidemiology, Biostatistics and Occupational Health

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LIST OF ABBREVIATIONS

Abbreviation	Definition
6H or 6INH	Six month treatment regimen of isoniazid
9H or 9INH	Nine month treatment regimen of isoniazid
4R or 4RMP	Four month treatment regimen of rifampin
AHFS	American Hospital Formulary Service
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral drug
BCG	Bacille Calmette-Guerin
CDC	US Centers for Disease Control
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DIN	Drug Identification Number (Health Canada)
EMB or E	Ethambutol
ED	Emergency department
FLQ	Fluoroquinolone
GIS	Guaranteed Income Supplement
GLY	Aminoglycoside
HR	Hazard ratio
HIV	Human Immunodeficiency Virus
ICC	Intraclass correlation
ICD	International Classification of Diseases
ICU	Intensive care unit
IGRA	Interferon-gamma release assay
INH or H	Isoniazid
IQR	Interquartile range
LOS	Hospital length of stay
LTBI	Latent tuberculosis infection
MAC	Macrolide
Med-ECHO	Maintenance et exploitation des données pour l'étude de la clientèle hospitalière
MD	Medical doctor
MDR-TB	Multi-drug resistant tuberculosis

NTM	Non-tuberculosis Mycobacteria
OR	Odds ratio
PAS	Para-acetylcylic acid
PZA or Z	Pyrazinamide
RA	Rheumatoid arthritis
RAMQ	Régie de l'assurance maladie du Québec
RCT	Randomized controlled trial
RFB	Rifabutin
RIF	Rifampin or rifabutin
RPT	Rifapentine
RMP	Rifampin
RR	Risk ratio, or relative risk, or rate ratio
SD	Standard deviation
SES	Socioeconomic status
TB	Tuberculosis
TST	Tuberculin skin test
WHO	World Health Organization
XDR-TB	Extensively drug resistant tuberculosis

THESIS ABSTRACT

INTRODUCTION: Treatment of latent tuberculosis infection (LTBI) is a key method of TB prevention in low TB-incidence countries such as Canada. Hepatotoxicity and low completion rates have been reported with the standard LTBI treatment regimen of 9 months of isoniazid (INH). But questions remain about the utility and cost-effectiveness of an alternative four-month regimen of rifampin (RMP) compared to INH. Estimates of completion rates, adverse event rates, and costs from clinical trials may have limited generalizability to the general population of patients treated for LTBI. The health resource use and costs attributable to development of active TB disease are also important considerations in economic evaluations of TB prevention programs. Previous estimates have generally been from single-site clinics, which can limit generalizability to general populations.

AIMS: 1) To review validated methods of identifying active TB and LTBI patients in health administrative databases; 2) to describe patterns and direct costs of health service utilization by active TB patients in Quebec and to estimate TB-attributable direct health system costs using data from the provincial health administrative database; 3) to evaluate predictors of hospitalization and hospital length-of stay during diagnosis and treatment of active TB patients; and 4) to compare completion rates, adverse event rates, and direct costs of treatment with INH and RMP regimens for LTBI in the general population.

METHODS: 1) Systematic literature review; 2) matched retrospective cohort study of health service utilization and direct costs of active TB patients compared to untreated patients using data from the provincial health administrative database; 3) retrospective cohort study of predictors of hospitalization and hospital length-of-stay in a clinical database of active TB cases in the Montreal health region; and 4) retrospective cohort study of LTBI treatment completion, drug-related adverse events, and direct costs using data from the provincial health administrative database

RESULTS: More than half of active TB patients were hospitalized during the TB episode of care, with hospitalizations accounting for more than 80% of direct health service use costs. The estimated per patient mean direct cost of health service use (including hospitalizations, ED visits, hospital procedures, physician billing, and drugs) for active TB patients during this episode of

care was $28,049 (95%CI: $25,896-$30,201) in 2011 Canadian dollars. Factors predictive of active TB patients in Montreal being initially hospitalized included being younger age (0-19 years) or older age (>65 years), having HIV, renal disease, one or more co-morbidities, smear-positive pulmonary TB, pulmonary or systemic TB-related symptoms, cavitary TB, miliary TB, and multi- or poly-TB drug resistance. Factors predictive of longer length of stay in-hospital included older age, HIV, renal disease, pulmonary smear-positive TB, having pulmonary symptoms, multi- or poly-TB drug resistance, and being admitted to a teaching hospital. Among LTBI patients, RMP-treated patients were on average older and had more co-morbidities than INH patients. LTBI treatment completion rates were significantly higher for 4RMP (53.5%) compared to 9INH (36.9%) after adjustment for confounders, RR=1.51 (95%CI: 1.31-1.75). Mean costs for TB drugs were higher for RMP patients than INH patients ($221 and $99, respectively), while mean costs for other health service use ($2823 and $2586, respectively) did not significantly differ after adjustment for age and co-morbidity level (adjusted cost ratio=0.87 (95%CI: 0.59-1.27).

CONCLUSION: This thesis provided real-world population-based data about health service use, direct costs, and treatment outcomes of active TB and treated LTBI patients over a ten-year period in the Canadian province of Quebec. Active TB disease was associated with a high health service use burden, with a large proportion of patients hospitalized. LTBI treatment completion rates were generally higher with the shorter-course 4RMP regimen compared to 9INH. TB drug costs were higher for RMP than INH, but costs for other health service use did not significantly differ after adjustment for age and comorbidity. Future studies should investigate the cost-effectiveness of using different LTBI regimens within the Quebec general population, among different co-morbidity and age groups.

FRENCH

ABRÉGÉ

INTRODUCTION: Le traitement de l'infection tuberculeuse latente (ITL) est une méthode clé de la prévention de la tuberculose dans les pays à faible incidence tuberculeuse, tels le Canada. L'hépatotoxicité et un faible taux d'achèvement ont été rapportés avec le traitement ITL standard de 9 mois à l'isoniazide (INH). Mais des questions demeurent sur le rapport coût-efficacité d'un

régime alternatif de quatre mois de la rifampicine (RMP) par rapport à l'INH. Les estimations des taux de réussite, des taux d'événements indésirables et des coûts des essais cliniques pourraient être généralisables à la population générale des patients traités pour la tuberculose latente. L'utilisation des ressources de santé et les coûts attribuables au développement de la tuberculose active sont également des considérations importantes dans les évaluations économiques des programmes de prévention de la tuberculose. Les estimations précédentes ont généralement porté sur des cliniques à site unique et la plupart ont été publiées aux États-Unis, ce qui peut limiter la généralisation aux populations canadiennes.

OBJECTIFS: 1) revoir les méthodes validées d'identifier les patients à tuberculose active et latente ITLdans les bases de données administratives sur la santé; 2) décrire les tendances et les coûts directs de l'utilisation des services de santé par les patients atteints de tuberculose active au Québec et estimer les coûts directs attribuables à la tuberculose en utilisant les données de la base de données de l'administration provinciale de la santé; 3) évaluer les facteurs prédictifs de l'hospitalisation et de la durée du séjour hospitalier pendant le diagnostic et le traitement des patients atteints de tuberculose active; et 4) comparer les taux d'achèvement et d'événements indésirables, et les coûts respectifs de traitement par les régimes thérapeutiques INH et RMP s pour la tuberculose latente dans la population générale.

MÉTHODES: 1) un examen systématique de la documentation; 2) une étude rétrospective de cohortes comparant l'utilisation des services de santé et les coûts directs des patients de tuberculose active par rapport aux patients non traités, à l'aide de données provenant de la base de données de l'administration provinciale de la santé; 3) une étude de cohortes rétrospective des facteurs prédictifs de l'hospitalisation et de la durée de séjour dans une base de données clinique des cas de tuberculose active dans la région de la santé de Montréal; et 4) une étude rétrospective de cohortes de l'ITL quant à l'achèvement du traitement, aux effets indésirables liés au médicament, et aux coûts directs en utilisant les données de la base de données de l'administration provinciale de la santé.

RESULTATS: Plus de la moitié des patients atteints de tuberculose active ont été hospitalisés durant la période de traitement, hospitalisations qui représentent plus de 80% des coûts directs de l'utilisation des services de santé. La moyenne estimée de l'utilisation des services de santé (y compris les hospitalisations, les visites à l'urgence, les procédures d'hôpital, la facturation des

médecins et des médicaments) pour les patients atteints de tuberculose active pendant cet épisode de soins était de 28 049$ (95% CI: 25,896$ -30,201$), en dollars Canadiens de 2011. Les facteurs prédictifs des patients atteints de tuberculose active à Montréal étant initialement hospitalisés incluent la jeunesse (de zéro à 19 ans) ou l'âge avancé (ayant dépassé 65 ans), ceux atteints du VIH, d'une maladie rénale ou d'une ou plusieurs co-morbidités, de la tuberculose pulmonaire à frottis positif, de symptômes pulmonaires ou systémiques liés à la tuberculose, la tuberculose cavitaire, la tuberculose miliaire, et la multi-résistance aux médicaments ou poly-tuberculose. Les facteurs prédictifs de la durée du séjour hospitalier comprenaient l'âge avancé, le VIH, la maladie rénale, la tuberculose pulmonaire à frottis positif, les symptômes respiratoires, la résistance multi-ou poly-médicaments contre la tuberculose, et le fait d'être dans un hôpital d'enseignement. Parmi les patients à tuberculose latente, les patients traités au RMP étaient en moyenne plus âgés et avaient plus de comorbidités que les patients au INH. Les taux d'achèvement du traitement au LTBI étaient significativement plus élevés pour 4RMP (53.5%) par rapport à 9INH (36.9%) après ajustement pour les facteurs confondants, RR = 1.51 (95%CI: 1.31-1.75). Le coût moyen des médicaments contre la tuberculose sont plus élevés pour les patients RMP que les patients INH (221$ et 99$, respectivement), tandis que les coûts moyens pour l'utilisation d'autres services de santé (2,823$ et 2,586$, respectivement) ne différaient pas de façon importante après ajustement pour l'âge et le niveau de co-morbidité (ratio ajusté des coûts = 0.87 (95%CI: 0.59-1.27)).

CONCLUSION: Cette thèse a fourni des données, basées sur une population générale, de l'utilisation des services de santé, des coûts directs et des résultats du traitement de la tuberculose active et latente chez les patients traités sur une période de dix ans dans la province canadienne du Québec. La tuberculose active a été associée à un lourd coût d'utilisation des services de santé, ayant une fréquence élevée de patients hospitalisés. Les taux d'achèvement du traitement ITL étaient généralement plus élevés avec le régime à court terme par rapport au 9INH. Le coût des médicaments contre la tuberculose était plus élevé pour la RMP que pour l'INH, mais les coûts d'utilisation des autres services de santé ne différaient pas de façon significative après ajustement pour l'âge et la comorbidité. Les études futures devraient examiner le rapport coût-efficacité de différents traitements de la tuberculose au sein de la population québécoise en général, entre les différents groupes d'âge et de co-morbidité.

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PREFACE AND CONTRIBUTION OF AUTHORS

Sections of this thesis have been written as multi-authored manuscripts for submission in peer-reviewed journals, as well as poster or seminar presentations. Details of the authors' contributions are provided where relevant.

Manuscripts in Progress

1. **Ronald, LA, *et al***. Validated methods for identifying tuberculosis cases in health administrative databases: A systematic review

2. **Ronald, LA, *et al***. Estimating the burden of tuberculosis treatment in the Quebec general population: A population-based study of health service use and costs

3. **Ronald, LA, *et al***. Predictors of hospitalization among active TB patients in Montreal, Quebec: A retrospective cohort study

4. **Ronald, LA, *et al***. Completion of treatment for latent tuberculosis infection in Quebec: A population-based study

   Authors' contributions: Lisa Ronald was responsible for the original ideas behind the manuscripts, analysis and writing the manuscripts. Dick Menzies and Mark FitzGerald provided guidance on all aspects of the studies and are the key editors of these manuscripts. Andrea Benedetti, Gillian Bartlett, Jean-François Boivin, and Kevin Schwartzman provided methodological guidance and editorial assistance on all manuscripts.

Conference Abstracts and Seminar Presentations

1. Ronald LA; Ling D; FitzGerald JM; Bartlett G; Schwartzman K; Boivin JF; Benedetti A; Menzies D. Validated methods for identifying tuberculosis cases in health administrative databases: A systematic literature review. 45th IUATLD World Conference on Lung Health. Barcelona, Spain. October 2014.

2. Ronald LA; FitzGerald JM; Bartlett G; Schwartzman K; Boivin JF; Benedetti A; Menzies D. Patterns and Direct Costs of Health Service Utilization by Tuberculosis Patients in Quebec, Canada: A Population-Based Study. 45th IUATLD World Conference on Lung Health. Barcelona, Spain. October 2014.

3. Ronald LA and Ling D. Alternative approaches to TB diagnostic and treatment research. Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute. Rounds seminar series, June 2014.

4. Ronald LA; FitzGerald JM; Bartlett G; Schwartzman K; Boivin JF; Benedetti A; Menzies D. Adherence to Treatment for Latent Tuberculosis Infection: A Population- Based Study Comparing Isoniazid and Rifampin Regimens. 17th Annual Meeting of the International Union of Tuberculosis and Lung Disease, North America Region. Vancouver, BC. March 2013.

5. Ronald LA; FitzGerald JM; Menzies D. Adherence to Treatment for Latent Tuberculosis Infection in Quebec: A Population-Based Study. Centre for Clinical Epidemiology and Evaluation, Vancouver Coastal Health Research Institute. Rounds seminar series, June 2012.

6. Ronald LA; FitzGerald JM; Boivin JF; Bartlett G; Schwartzman K; Benedetti A; Menzies D. Identifying Tuberculosis Cases in a Canadian Health Administrative Database: A Feasibility Study. 16th Annual Meeting of the International Union of Tuberculosis and Lung Disease, North America Region. San Antonio, Texas. February 2012.

7. Ronald LA; FitzGerald JM; Menzies D. Treatment of Active Tuberculosis and Latent TB Infection in Quebec: A Population-Based Study and Cost-Effectiveness Analysis. Respiratory Epidemiology and Clinical Research Unit Seminar, Montreal Chest Institute, Quebec, February 2011.

CHAPTER 1: INTRODUCTION AND THESIS OBJECTIVES

Tuberculosis (TB) rates have stabilized globally in recent years, following a dramatic resurgence in the previous two decades[1]. Still, an estimated one-third of the world's population is infected with a latent form of infection with *Mycobacterium tuberculosis* (LTBI), and the total number of new cases and deaths attributable to TB continue to increase as the global population grows[1]. In Canada, TB control programs will continue to face the challenge of diagnosing, treating and preventing TB in diverse patient populations.

Treatment of LTBI is considered a key method of TB prevention in low-TB incidence countries such as Canada. However, the potential benefits of LTBI treatment must be balanced against the risk of adverse events, the likelihood of treatment completion, and costs. Controversy remains about when to screen and treat patients for LTBI and which treatment regimens to use. With the standard LTBI treatment regimen of 9 months of isoniazid (INH), hepatotoxicity and low adherence have been reported[3-5]. Treatment with more costly, short-course regimens has been proposed[6, 7]. A four month regimen of Rifampin (RMP) is a recommended alternative, and randomized controlled trial results suggest higher adherence and a better safety profile with RMP than the standard INH regimen[8, 9]. However, while implementing short-course RMP as a new standard is promising, there are still outstanding questions. First, while a 3 month regimen of RMP showed better efficacy than no treatment in one clinical trial[10], the four month regimen of RMP is currently undergoing a randomized clinical trial and efficacy of this regimen compared to INH is not yet known. Second, most previous studies of RMP have been clinical trials or retrospective single-site observational studies, which may overestimate adherence rates occurring in 'real-world' settings with more diverse patient populations and provider types. Third, RMP is more expensive than INH and the cost-effectiveness of switching to RMP remains uncertain[6].

Cost-effectiveness analyses of LTBI treatment are highly dependent on model inputs, including TB reactivation rates, rates of completion and efficacy of LTBI treatment, adverse drug-related event rates, costs of LTBI treatment, and costs related to the development of active TB[11]. Few prior studies of TB-related health service utilization, costs, and treatment outcomes have been conducted in a Canadian setting. Health administrative databases offer a near-complete capture of health service use in the general population[12-15], and can provide data to evaluate LTBI treatment outcomes in jurisdictions where no LTBI registries exist. A better understanding of

LTBI treatment outcomes and of TB-related health service utilization and costs in a large and diverse Canadian population, using data from a provincial health administrative database, will aid health planners to forecast the health service needs of TB patients, to more effectively target prevention, and to develop more realistic estimates of the cost-effectiveness of TB prevention programs.

This thesis builds on a CIHR-funded project to evaluate the cost-effectiveness of LTBI treatment in Quebec. The primary objectives of this thesis are:

1) To review validated methods for identifying TB patients in health administrative databases, and to identify cohorts of active TB patients and LTBI patients in the Quebec provincial health administrative database;
2) To describe patterns and direct costs of health service utilization among active TB patients in the general Quebec population using data from the provincial health administrative database, and to estimate direct costs of TB-attributable health service utilization
3) To identify predictors of hospitalization and hospital length-of-stay during diagnosis and treatment of active TB patients
4) To compare completion rates, drug-related adverse event rates, and direct costs of health service utilization of INH and RMP regimens for LTBI treatment in the general Quebec population

This manuscript-based thesis is organized into seven chapters. A comprehensive literature review was first undertaken (Chapter 2) to review the epidemiology, diagnosis and treatment of active tuberculosis and LTBI; to identify the risks and benefits of LTBI treatment, including a summary of studies comparing adherence, adverse event rates, and potential cost-effectiveness between INH and RMP regimens; and to summarize evidence about active TB health service utilization and costs. I conclude Chapter 2 with the rationale, objectives and hypotheses for the four studies that constitute my thesis.

My initial study, outlined in Chapter 3, is a systematic literature review of validated definitions for identifying TB patients in health administrative databases. Several previously published studies have attempted to validate methods for identifying patients with active TB using diagnostic codes, drug prescriptions, and other data available in such databases. This review summarizes and discusses these published validated definitions.

In my second study (Chapter 4), I apply lessons learned from Chapter 3 to identify cohorts of treated active TB and LTBI patients in the Quebec provincial health administrative database. Chapter 4 details the methods I used to identify the cohorts, including a description of the health administrative database, definitions of the study follow-up and TB drug treatment periods, and application of decision rules to identify active TB and LTBI patients. Chapter 4 concludes with a description of patterns and direct costs of health service utilization by active TB patients in Quebec over a ten-year period, and an estimation of TB-attributable direct costs.

In my third study (Chapter 5), I evaluate more detailed clinical, social, and demographic predictors of hospitalization and hospital lengths of stay of patients with active TB in one Quebec health region (Montreal) using data from a comprehensive clinical database of patients with confirmed active TB in Montreal.

In my final study (Chapter 6), I evaluate and compare treatment completion rates, drug-related adverse event rates, and direct costs of health service utilization for the two LTBI regimens, INH and RMP, in the Quebec general population, using the LTBI cohort that I identified in Chapter 4. This database provides near-complete capture of all TB drug prescriptions filled in the province, and thus provides a data source for evaluating LTBI treatment completion rates and outcomes in the general population.

Finally, in Chapter 7, I provide an integrated discussion of the four studies and suggest directions for future research.

CHAPTER 2: LITERATURE REVIEW

2.1 TB EPIDEMIOLOGY, PATHOLOGY, DIAGNOSIS, AND TREATMENT

2.1.1 Global TB Epidemiology

TB remains a major cause of morbidity and mortality worldwide. According to WHO estimates, there were approximately 8.7 million new active TB cases and 1.4 million TB-related deaths globally in 2011[1]. More than 80% of TB cases occur in twenty-two high-burden countries, predominantly in Asia, Sub-Saharan Africa, and Eastern Europe [16]. Incidence rates in 2011 were 163 new TB cases/100,000 population in high-burden countries, and 125/100,000 globally[1]. An estimated one-third of the world's population are also infected with latent (asymptomatic) TB infection (LTBI) [16].

The global epidemic of human immunodeficiency virus (HIV) has had a major impact on TB epidemiology [17]. Described by some as 'a deadly human syndemic'[18] and 'the perfect storm'[19, 20], HIV has altered patterns of TB epidemiology, and created new challenges for TB diagnosis and treatment [18]. Of the active TB cases in 2009, an estimated 18% of all TB-associated deaths and 12% of new TB cases were associated with HIV co-infections [1]. This is a proportionate increase from 2005, when an estimated 13% of TB-related deaths and 8% of new TB cases were HIV-positive . TB is also a leading cause of death among HIV-positive patients, accounting for up to half of all deaths among AIDS patients worldwide [22].

A further major challenge to TB control programs globally is the increasing number of TB strains that are resistant to one or more first-line, and even second-line, TB drugs. Worldwide, it is estimated that slightly more than 3% of all new TB cases are multi-drug resistant (MDR-TB), which is defined as resistance to INH and RMP, the two main first-line TB drugs . This proportion is almost one-third of all new TB cases in some settings in the former Soviet Union . Extensively drug resistant TB (XDR-TB) has emerged since 1999 and has been confirmed in 58 countries. XDR-TB is resistant to INH, RMP, a second-line fluoroquinolone, and at least one injectable second-line drug [17, 24].

In Canada, the incidence of TB is lower than in TB-endemic countries: between the years 2000 and 2010, there were 18,157 reported TB cases in Canada, with approximately one-sixth of these cases reported in Quebec. In 2010, there were 1577 new and retreatment active TB cases in Canada, with an incidence rate of 4.6 cases/100,000 population. An estimated 9% of TB cases are co-infected with HIV in Canada [26, 27]; INH resistance is currently detected in up to 8% of TB cases, while MDR-TB is found in 1% of cases [28]. Rates of TB in Canada also vary disproportionately among different population subgroups - the majority of TB cases (66% in 2010) occur in foreign-born patients, compared to 21% in Canadian-born aboriginal and 12% in Canadian-born non-aboriginal patients. In 2010, incidence rates were 13.3 cases/100,000 in foreign-born patients, 26.4 cases/100,000 in Canadian-born aboriginal patients, and 0.7/100,000 in Canadian-born non-aboriginal patients. Further, while TB incidence in the Canadian-born non-aboriginal population has been declining over the past 2 decades, rates among the foreign-born and aboriginal populations remain higher and have not experienced the same declines [28]. Outbreaks of TB in Canada and the US are also often clustered among the urban homeless and other marginalized populations, highlighting the social and economic aspects of TB [29-31]. Predominantly a disease of poverty , TB is often associated with such risk factors as overcrowded and poorly ventilated housing, incarceration, homelessness, drug abuse, malnutrition, and poor healthcare access [32, 33].

2.1.2 TB transmission and disease

TB is caused by infection with the bacterium *Mycobacterium tuberculosis* [17]. Transmission is primarily through respiratory droplets, and transmission risk is highest for persons with active TB who have a high bacillary load detected in sputum samples, cavitation on chest radiographs, and cough [28, 34]. 'Close and prolonged contact' is generally considered necessary for TB transmission. However, evidence of transmission with casual contact has been shown to occur [34]. It is generally estimated that a person with smear-positive active TB will infect approximately 10 people annually, on average, but this depends on the prevalence of sources of infection in the community [32]. Annual rates of TB infection are usually reported to be approximately 1-2% in developing countries and 0.1-1% in developing countries[32].

Two forms of TB may be described - the first is active TB and the second is latent TB infection (LTBI). Active TB is the symptomatic and infectious form of disease. Active pulmonary TB is

often characterized by chronic cough of at least 3 weeks' duration, fever and night sweats, and weight-loss. LTBI, in contrast, is asymptomatic and non-infectious [28]. In the majority of infected individuals (estimated to be approximately 90%), the infection will not progress to active TB. Rather, it remains dormant as asymptomatic LTBI throughout life; approximately 10% of those with latent infection will reactivate to develop active TB disease at some time [28]. Risk factors for reactivation of LTBI infection to active TB are generally associated with a reduction in immune function, with HIV co-infection being the strongest documented risk factor for reactivation [35]. Other documented risk factors for reactivation include diabetes, solid organ transplantation, head and neck cancers, silicosis, chronic renal failure, gastrectomy and immunosuppressive therapy e.g. anti tumour necrosis factor agents, corticosteroids [35] . The risk of developing active TB is considered highest within the first two years of infection [36]. A 10% lifetime risk of reactivation is estimated for individuals with no major immune suppression; with HIV co-infection in the absence of anti retroviral therapy, this can increase to a 10% annual risk of reactivation [35].

Active TB can occur in any organ system of the body, but most disease occurs in the lungs - a reflection of the primary transmission mode of TB. In Canada, respiratory TB is estimated to account for 70% of new TB cases, while extra-pulmonary TB accounts for the remainder [28]. HIV infection can change the pattern of active TB. However in persons with concomitant HIV infection, smear-negative and extra-pulmonary or miliary TB (a disseminated form of TB that can simultaneously infect many organ systems) are more frequently seen [17]. Similarly in young children, a higher proportion of disseminated TB and central nervous system TB is typically seen, as well as an accelerated progression from infection to disease [28].

TB case fatality rates remain high even in low-incidence countries such as Canada. In 2004, an estimated 11% of patients with active TB in Canada died during treatment, with 20% of these directly attributable to TB and 40% with TB as a contributory cause [28]. TB-related death rates higher than 20% have been reported in hospitalized populations with immune-suppression and multiple co-morbidities [37, 38]. Among TB patients requiring admission to intensive care units, higher mortality rates have been observed [39]. TB-related tissue damage can also lead to long-term morbidity [40]. In patients with pulmonary TB, for example, permanent changes in lung structure [41] and reduced lung function [42] have been observed after the completion of treatment [41].

2.1.3 Active TB Diagnosis and Treatment

2.1.3.1 Role of active TB diagnosis and treatment in TB control programs

The major priority of TB control worldwide is the identification and complete treatment of active TB [28]. In the US and Canada, detection is primarily passive (ie. after symptomatic presentation), although some active screening programmes exist, e.g. for new immigrants, contacts of individuals with active TB, and high-risk populations living in congregate settings such as prisons and homeless shelters [28, 43, 44]. Currently, immigration applicants, refugees, and individuals applying to stay in Canada as a temporary visitor for a period of longer than 6 months and coming from specific high incidence countries, are required to undergo a chest x-ray as part of an immigration medical examination[28]. Applicants with active TB are generally required to prove adequate treatment for active TB (that they are not infectious) before they are allowed entry into Canada, while individuals with inactive TB and risk factors for reactivation (e.g. radiographic scarring) may be monitored by provincial/ federal authorities [28].

In Canada, active TB is a notifiable disease, thus it is mandatory for all physicians and laboratories to report confirmed cases of active TB to the relevant public health authority [46]. Confirmed cases can include both laboratory-confirmed cases, as well as clinically-confirmed cases, where there is evidence of active TB but no culture results are available, diagnosed either pre- or post-mortem . Reporting is required for all cases diagnosed in Canada, whether treatment is started or not, among Canadian citizens, permanent residents, or refugees. For temporary residents of Canada, reporting is only required if treatment is started in Canada . Treatment of active TB once diagnosed is also mandatory in Canada. Although detention warrants are not often enacted, refusal by patients to complete treatment for active TB can result in detention according to Canadian public health law [47]. Thus, public health notification and treatment of active TB is considered fairly complete in Canada [46]. Notification of HIV co-infections among TB patients, however, may not be complete within TB surveillance systems [27, 46].

Timely and accurate diagnosis and treatment of active TB is critical [33, 48, 49]. Differentiating active TB from LTBI is also important, as misdiagnosis can lead to insufficient treatment and the development of drug resistance [50, 51]. A low index of suspicion among healthcare workers and

failure to recognize clinical symptoms as being potentially due to TB can lead to delays in starting treatment, inappropriate treatment, development of drug resistance (in cases where treatment given is inadequate), worse health outcomes, and ongoing transmission within the community [33, 52-55]. More accurate diagnosis and treatment, and better health outcomes, for example, are found for TB patients treated in hospitals and by healthcare workers with greater TB-related experience [53, 54, 56-59].

2.1.3.2 Active TB diagnosis: methods

Diagnosis of active TB is based on clinical symptoms, imaging, pathology, and microbiologic confirmation--based on presence of acid-fast bacteria (AFB) in smears, and/or subsequent positive mycobacterial culture [60]. Diagnosis based on clinical presentation of active TB disease can be challenging, ranging from classic to asymptomatic presentation [28]. Older children and adults, for example, may be more likely to present with classic symptoms [28], while in many young children and seniors, the clinical presentation may be varied or asymptomatic and without the typical adult-type symptoms [52, 61]. Chest radiography is also used initially to identify pulmonary TB. However, poor sensitivity, specificity and inter-rater reliability are limitations [49, 60].

AFB smears are used widely in many world regions to diagnose TB. AFB smear microscopy is a rapid, relatively low-cost method for diagnosis, but known limitations to standard smear microscopy include reduced sensitivity in children and patients with HIV or extra-pulmonary TB; by definition, patients with smear-negative TB are missed by smear microscopy [48, 62, 63]. Newer fluorescent and fluorescent light-emitting diode (LED)-microscopes improve testing sensitivity [62]. However, the high initial capital cost to purchase equipment, particularly of standard fluorescent microscopy, remains one issue for implementation in many settings [62, 63]. Lastly, culture, both solid and liquid media, is the gold standard for active TB diagnosis in developed countries [28, 49]. However, culturing mycobacteria can take several weeks, leading to possible delays in the diagnosis [28]. The newest technology available is the GeneXpert® cartridge-based test employing nested PCR, that requires minimal handling and provides high sensitivity and specificity for detection of active TB and RMP resistance within two hours [64].

Waiting for drug susceptibility testing results can also lead to further delays in the initiation of an effective regimen in patients whose isolates are drug resistant. At a minimum, in Canada, it is recommended that all isolates should be tested for resistance to the first-line TB drugs INH, RMP, pyrazinamide, and ethambutol, and testing for resistance to second-line TB drugs is also recommended when a treatment regimen is failing, or when resistance to one or more first-line drugs is encountered [28]. Drug susceptibility testing using conventional methods can take 6-8 weeks, or even longer if solid media are used; more rapid drug susceptibility testing methods have reduced the time for results (to within 10 days), but are more labour-intensive [17]. Lastly, for detecting RMP resistance, the newest technology (GeneXpert) can provide accurate test results within two hours [64].

2.1.3.3 Active TB treatment: recommended regimens

Once active TB is diagnosed, treatment is divided into two phases [65]. The initial phase typically consists of four first-line TB drugs daily in the first two months: INH, RMP, ethambutol, and pyrazinamide; and with a fully sensitive organism the continuation phase consists of two drugs (INH and RMP), either daily or thrice-weekly for 4 additional months [66] (see Appendix 1 for a summary table of recommended TB treatment regimens). During the initial phase, multiple drugs with bactericidal and/or sterilizing activity are combined to kill rapidly replicating bacteria; RMP and pyrazinamide, the two most active sterilizing drugs available allow treatment duration to be shortened [65].

In all cases, multiple-drug treatment for active TB throughout the course of the treatment is essential to avoid the development of drug resistance [65]. However, variations on this standard treatment regimen may be used - for instance, where pyrazinamide is not used, or with pulmonary disease and positive cultures after 2 months of treatment, the treatment duration should be extended [67]. Also, any regimen not including INH and RMP throughout its full course should be extended for at least 12 months [65]. Drug resistance further complicates and lengthens the course of treatment [68]; second-line TB drugs, such as fluoroquinolones and aminoglycosides may be substituted for first-line TB drugs. However, these drugs are more costly and may have more side effects [17, 66, 68].

Treating patients with HIV-related TB presents additional challenges. The standard regimen is recommended for TB patients in most cases, regardless of HIV status [17, 66]. Patients who have active TB and who are co-infected with HIV, however, may require treatment with alternative drugs to RMP (such as another rifamycin drug, rifabutin) due to drug interactions between RMP and many anti-retrovirals [66, 69]. Rifabutin has less potential for enhancing metabolism of anti-retrovirals; however, rifabutin is more expensive [69]. Lastly, the co-administration of anti tuberculosis and antiretroviral drugs involves high pill burdens [66, 70], and side effects of TB drugs are more commonly reported among TB patients with HIV infection [71]. Anti-retroviral and TB drugs share many of the same side effects, resulting in challenges in the differentiation of effects due to antiretroviral versusTB drugs [69, 70].

2.1.3.4 Side effects of TB drugs

Side effects of TB drugs, in general, can complicate the course of treatment, and may require the withdrawal and reinstatement of different drugs [72]. Drug-related side effects during TB treatment can also lead to increased morbidity [72], and are associated with reduced health-related quality of life among TB patients [73]. Serious adverse events, particularly hepatotoxicity, have been reported among individuals taking first-line TB drugs [71, 72, 74-76]. In a Montreal study based at one large referral hospital, rates of major adverse events were reported to be 0.55 per 100 person-months [71]. Other studies have reported rates of as high as 23% [77] to 30% [72] of all active TB patients having a major treatment-related adverse event while taking up to four first-line TB drugs concurrently. Factors such as older age, more co-morbidities, and a hepatitis history have all been associated with an increased risk of major TB-drug related adverse events [71, 72, 76, 77]. Hepatotoxicity is a particular concern. While mild drug-induced liver injury can be asymptomatic, severe hepatic injury can be life-threatening and may require a liver transplant for survival [76, 78].

Attributing adverse events to specific TB drugs can be a challenge due to the multidrug nature of TB treatment, and to concomitant treatment for other conditions, such as HIV [49, 50]. As well, it can be challenging to identify the specific drug causing liver injury, since many cases are idiosyncratic and not dose-dependent. Liver toxicity can be asymptomatic, or can involve a range of symptoms including fever and malaise, jaundice, rash and pruritis [76, 78]. Further, there are generally no reliable tests for diagnosing drug-induced liver injury. Causality assessment is

generally made through consideration of such factors as timing of drug exposure and adverse event onset, nature of the drug, other possible explanations for liver disease. [76, 78]. Use of regimens containing pyrazinamide, in particular, has been associated with an increased risk of hepatitis, as well as other adverse reactions such as rash, arthralgias, and gastrointestinal complications [60, 72, 75, 77]. A meta-analysis of active TB treatment regimens, for example, found that adding pyrazinamide to regimens of INH and RMP increased the risk of hepatotoxicity from 0.8% to 2.6% of active TB patients [75]. INH has also been shown to be associated with hepatitis, leading to elevated serum aminotransferases and, in severe cases, jaundice [76, 78]. Ethambutol is known to cause optic neuritis, and RMP has been associated with pruritis, gastrointestinal adverse reactions, and hepatitis, among other potential side effects [60, 66, 78].

2.1.4 LTBI Diagnosis and Treatment

2.1.4.1 Role of LTBI diagnosis and treatment in TB control programs

The targeted screening and early treatment of LTBI among individuals at highest reactivation risk is considered a key method of TB prevention in low-TB incidence countries, primarily for the individual benefit of preventing a serious illness, but also with the public health objective of reducing the reservoir of individuals who may reactivate and infect others in the community [35, 36, 60, 80]. However, most clinic-based studies of LTBI treatment programs report low rates of adherence at all stages of the process. This includes failure to participate in initial screening, failure to return for tuberculin skin test (TST) reading or failure to show up for medical evaluation of a positive test, and non-adherence, both by physicians who did not prescribe treatment even when indicated, and by patients who refused to start or complete treatment [60]. In most jurisdictions, LTBI is not a notifiable infection to public health authorities, and thus there is no population-based surveillance of LTBI prevalence, treatment patterns or outcomes for LTBI treatment.

It is generally agreed that LTBI treatment should be targeted towards individuals at highest risk of reactivation, and decision rules and algorithms have been developed to identify who should undergo testing and treatment [81]. It is further acknowledged that no individuals should undergo testing for LTBI without the intention and resources available to treat if they are found to have latent infection [60]. However, concerns about treatment adherence, costs for different regimens,

and possible drug-related side effects have generated debate among clinicians and policy-makers about which regimens to recommend, and to whom they should be recommended.

2.1.4.2 LTBI Diagnosis: methods

Diagnosis of LTBI can be challenging due to limitations of current testing methods. LTBI is diagnosed most commonly using the tuberculin skin test (TST) [60]. With a TST, a small amount of purified protein derived from *M. tuberculosis* is injected intradermally. In previously infected individuals, a cell-mediated hypersensitivity reaction will occur within 48 to 72 hours, causing a small raised induration to develop at the injection site; in newly infected individuals, this cell-mediated reaction will develop 3-8 weeks after the infection is acquired[60]. Based on the size of the induration and patient risk group, an individual may or may not be recommended initiate LTBI treatment [60] (see Appendix 1 for summary of LTBI treatment recommendations for different TST induration sizes and patient risk groups). The major strength of the TST is that interpretation is based on multiple large scale epidemiologic studies that have defined risk of disease for various populations, associated clinical conditions, and sizes of TST reactions. From this information algorithms have been developed for diagnostic test interpretation [81]. However, false positive test results can result from previous vaccination with Bacille Calmette-Guerin (BCG), or cross-reaction due to exposure to non-tuberculosis mycobacteria (NTM) [82]. False negative TST results can also occur, primarily as a consequence of immune-suppression, or anergy [60, 83].

Newer tests, interferon-gamma release assays (IGRAs) (commercially available tests include QuantiFERON-TB® and T-Spot.TB®) offer promise as an alternative to the TST. Interferon-gamma release assays are in vitro, T-cell based, assays that measure interferon-gamma production from circulating lymphocytes in peripheral blood when stimulated by antigens that are quite specific to *M. tuberculosis* [60]. The major advantages of these newer tests is their improved specificity in detecting LTBI in BCG-vaccinated populations. They require only a single visit by the patient and pose no risk of serious allergic or skin reactions[60]. Discordant reactions over time in patients and with TST results, however, present challenges for test interpretation[60]. Further, neither TSTs nor interferon-gamma release assays are recommended for use in diagnosis of active TB, as they cannot distinguish between LTBI and active TB [60].

2.4.1.3 LTBI Treatment: recommended regimens

Once LTBI is diagnosed, the physician and patient must decide whether to start treatment. The current standard recommended treatment for LTBI in the US and Canada is 9 months of INH, taken daily (9INH) [84]. In Canada a 6-month regimen of INH (6INH) is considered an acceptable alternative regimen when treatment adherence to the longer 9-month regimen is a concern [60]. The 6-month regimen of INH continues to be the standard recommended LTBI regimen in some countries, such as the UK [85]. The recommended length of treatment with INH has changed over time in Canada and the US- initially 12 months were recommended [86], changing to the current 9 months based on extrapolation of clinical trial evidence [87].

Shorter-course regimens have also been recommended in the US (American Thoracic Society [7]) and Canada (Canadian Thoracic Society[2]), although currently only as an alternative to 9 months of daily INH [6, 8, 9]. RMP+pyrazinamide for 2 months was considered a strong alternative short-course regimen, particularly for individuals with HIV [88]. Early clinical trial results looked very promising [88]. However, larger-scale population-based studies in 'real-world' settings demonstrated that this regimen had a much higher rate of hepatotoxic adverse events than seen in clinical trials, leading to several fatalities [6]. Because of concerns about the safety of the RMP+pyrazinamide regimen, it is no longer recommended in Canada for LTBI treatment. Three other short-course regimens are currently recommended in Canada as alternatives to 9 months of daily INH: 3 months of daily INH+RMP, 3 months of once-weekly INH+rifapentine, and 4 months of daily RMP (4RMP). Recently recommended as an alternate regimen in Canada, 3 months of INH+RMP is considered a standard therapy in some other countries, notably in the UK [85].The regimen of 3 months once-weekly INH+rifapentine has undergone 3 clinical trials to assess long-term efficacy. However, high rates of hypersensitivity reactions have been observed with this regimen and it is not readily available in Canada [6]. The 4 month regimen of RMP was recommended as an alternative to 9INH by the American Thoracic Society, in LTBI treatment guidelines published in 2000[84]. The 4RMP regimen is currently undergoing a large clinical trial to assess efficacy. In the only published clinical trial of RMP efficacy for LTBI treatment, a trial of 679 patients with silicosis in Hong Kong, efficacy of 3 months of RMP was approximately 63% effective in reducing the 5-year incidence of active TB compared with untreated patients [10]. Lastly, LTBI treatment for suspected drug-resistant strains of TB may involve a first-line TB

drug along and/or second-line TB drugs (fluoroquinolones). This recommendation is based entirely on consensus rather than clinical data.

2.1.4.4 Barriers to LTBI treatment: poor adherence

One of the major criticisms of the current recommended standard of 9 months of INH is that poor treatment adherence rates are often seen with this lengthy regimen [51], which reduces the effectiveness of INH treatment . In a systematic review of US and Canadian studies, for example, LTBI treatment adherence was found to be less than 50% in many high-risk populations [3, 89]. Reported factors associated with poor treatment adherence in Canadian and US studies were numerous, and included age, sex, ethnicity, immigrant status, education level, presence of substance abuse, timing of exposure to TB, homelessness, marital status, health insurance, unemployment, social support, prior BCG vaccination, recent hospitalization, concomitant medication use, and patient's beliefs (e.g. about the importance of treatment completion, intention to adhere, perceived risk of active TB, concerns about drug-related side effects, and fear of venepuncture for TST) [3].

Due in part to concerns about poor treatment adherence, shorter-course regimens such as RMP have been increasingly recommended for LTBI treatment [6, 51]. Few studies, however, have compared treatment adherence rates between INH and RMP regimens (see Appendix 1 for a summary table). In one randomized controlled trial based in three countries (including Canada), treatment completion for 4 months of RMP was significantly higher (81%) compared with 9 months of INH (64%)[8]. Rates of treatment completion in this clinical trial were similar to reports from several US clinic-based studies, ranging from approximately 72%-91% treatment completion for RMP and 53-76% for INH [90-93]. Completion rates at the higher end of these ranges tend to be reported from clinical trials and from specialized TB referral clinics, making their applicability to the general population and to other practice settings uncertain.

2.1.4.5 Barriers to LTBI treatment: drug-related side effects

Hepatotoxicity is a concern for LTBI patients treated with INH. Reports of severe hepatotoxicity ranging from <1% to 2% have been described in large observational studies in the US, among populations of LTBI patients undergoing INH treatment [5, 92]. However, few population-based

studies of INH-related adverse events have been conducted among Canadian LTBI patients. In a recent population-based study in Quebec, 1.3% of patients experienced a severe adverse event (0.5% a severe hepatic adverse event) requiring hospitalization during LTBI treatment, with highest rates (6.0% for any severe adverse event, 2.6% for a severe hepatic adverse event) among patients aged over 65[94].

One controversy in the literature has been when to screen and treat LTBI in lower-risk patients, and whether there should be age thresholds in LTBI treatment guidelines for such patients [11, 95, 96]. Most advocate for treating patients with reactivation risk factors, regardless of age [11, 95, 97]. However, due in large part to evidence of the increased risk of INH-induced hepatotoxicity, the American Thoracic Society first restricted the use of INH prophylaxis for tuberculin reactors without other risk factors for reactivation to those younger than 35 years of age. They subsequently revised these guidelines to recommended that clinicians prescribe LTBI treatment to older age groups, with careful evaluation and monitoring of liver function [11]. Notably, a recent meta-analysis found no evidence for a significant increased risk of hepatotoxicity associated with INH in patients older than age 35 years, but acknowledged that there are gaps in the current literature, with few studies assessing risk in patients older than 55 years[4]. Some authors emphasize the need to exercise specific care in weighing the risks and benefits before starting older patients on LTBI treatment [94, 98].

In addition to better treatment adherence, another possible benefit of a RMP-based regimen is the better safety profile of RMP in selected patients compared with INH [51, 91]. Few studies, however, have compared rates of adverse events between RMP and INH regimens (see Appendix 1 for a summary table). Clinical trial results show lower rates of any adverse events with 4 months of RMP compared with 9 months of INH (3.8% versus 5.7%), and lower rates of serious adverse events (1.7% versus 4.0%), particularly lower rates of severe hepatotoxicity (0.7% versus 3.8%) [9]. Retrospective chart reviews from single-site clinics also show lower rates of adverse events with RMP versus INH regimens, particularly for hepatotoxicity, with rates of any hepatotoxicity ranging from 0-0.7% for RMP and up to 5% for INH [90-93].

2.2 ECONOMIC EVALUATION OF LTBI TREATMENT PROGRAMS

Some have proposed that the elimination of TB could be a feasible goal, through increased efforts to screen and treat individuals for both active TB and LTBI[99]. However, if this recommendation is to be translated into policy, either new resources would be needed, or TB treatment and prevention programs would need to be more efficient [99]. Economic evaluation can help TB control programs decide on the most efficient methods for allocating resources [99, 100, 102]

2.2.1 Prior economic evaluations of LTBI treatment programs

Prior decision and economic analyses have been influential in developing LTBI treatment recommendations [84, 101]. A number of decision and cost-effectiveness analyses of LTBI treatment have been completed in the past 3 decades [11], with the majority comparing INH treatment to no treatment in different population types (low-risk LTBI patients, those with severe co-morbidities [102] or HIV infection, contacts [103, 104], patients with prior active TB, recent immigrants [105, 106], travellers [107], and drug users [108]). Many analyses relate to LTBI screening as well as treatment, ie. the cost versus yield of identifying as well as treating persons with LTBI under different circumstances. Most, though not all, have recommended INH treatment compared to no treatment [11]. A recent systematic review of LTBI treatment programs also concluded that 9 months of INH was cost-effective in high-income countries when compared with no treatment [11].

Interestingly, few cost-effectiveness evaluations have considered the impact of older age and co-morbidities on cost-effectiveness of LTBI treatment. One of the few studies to evaluate the impact of both older age and co-morbidities was by Sarasin et al[102]. These authors used a Markov decision analysis model to estimate the risk-benefit of a 6- to 12-month INH regimen in cohorts of patients aged 50, 60, 70, and 80 years old, in three sub-groups: those with no co-morbidities, patients with congestive heart failure, and patients with severe chronic obstructive pulmonary disease (COPD). This study found that the risk of TB-related hepatotoxicity outweighed the benefit of the number of TB cases prevented in patients older than 50 years among those with heart failure, and older than 60 years among those with COPD. The authors found that the increase in life expectancy provided by INH was limited in patients with heart failure (3 days gain) and COPD (6 days gain). Furthermore, among patients without coexisting illness, the estimated gain in life expectancy declined to only 7 days in patients aged 80 years. A

recent study by Linas *at al* also found limited gains in quality-adjusted survival among screened and treated LTBI patients with chronic medical co-morbidities [109].

Additionally, few studies have compared INH to shorter-course regimens recommended by the American Thoracic Society [84]. Six studies have evaluated the potential cost-effectiveness of RMP versus INH for LTBI treatment. Pina *et al* found that 4RMP was more cost-effective than 9INH in contacts of TB patients (mean patient age was 32 years and 31 years, respectively) when efficacy of 4RMP was at least 75%[110]. Esfahani *et al* found that 4RMP was more cost-effective than 9INH in adults who were HIV-negative and TST-positive, and who were either recent contacts or patients with longstanding infections[111]. Their estimates were sensitive to the efficacy of RMP; INH was more cost-effective when RMP efficacy was below 69%. Using cost and adherence data primarily from a randomized clinical trial, Aspler *et al* found that 4RMP was more cost-effective than 9INH in recent close contacts (aged 18 years and older), but found similarly that estimates were sensitive to the costs and efficacy of RMP[112]. Holland *et al* found that RMP was most cost-effective for individuals recently exposed to TB (age 39 years) compared with other regimens or no treatment, and that RMP in place of INH would be cost-saving for most US and Canadian programs [103] Using estimates from a randomized controlled trial and two observational studies, Ziakis *et al* had similar conclusions for a general population of LTBI infected individuals [113]. Khan et al found that RMP was more cost-effective than INH among recent immigrants to the US coming from areas with high rates of INH resistance; however, the authors did not recommend RMP generally due to the higher drug cost, except in cases of INH resistance [114]

Thus, cost-effectiveness of LTBI treatment is heavily influenced by the overall effectiveness of a given regimen in the prevention of active TB [51], as well as by the costs of treating LTBI and costs of active TB disease. Recently published results from the randomized clinical trial comparing INH and RMP treatment for LTBI, for example, found that the average per patient cost of 9INH (C$970) was higher than with 4RMP (C$854), with the difference in cost primarily driven by the greater number of scheduled clinical visits for 9INH and unscheduled visits for the management of toxicity[112]. The authors concluded the RMP regimen to be cost-saving based on these cost data if the efficacy of the regimen in preventing TB reactivation was 75% or greater (compared to 90% efficacy for the INH regimen)[112]. If a shorter course four month regimen of RMP prevents many more cases of active TB (due to higher completion rates) compared to a

nine month regimen of INH, it could be more cost-effective or even cost-saving in the long run despite higher short-term treatment costs. Although such benefits may be challenging to estimate at the present time given uncertainties about RMP efficacy[51], understanding rates of LTBI treatment completion, as well as active TB and LTBI costs, are important components for cost-effectiveness analyses.

2.2.2 Health service utilization and costs of active TB

Understanding the health service utilization and costs incurred after patients develop active TB is a key component for economic modeling as it represents the impact on health systems and patients when the disease is not prevented. Most TB cost-of-illness studies in low TB incidence countries have been completed either as unique studies or as part of cost-effectiveness evaluations (see Appendix 1 for a summary of studies). The majority of studies estimating the costs of active TB have been conducted in the US [68, 115-119], and several have been published in Europe [120, 121]. Few studies have been published in Canada [105, 122]. Countries differ in respect to the range of treatments and health care facilities available to their populations; availability of health care resources and variations in clinical practice can impact disease costs and resulting cost-effectiveness of health care programs[100].

Most previous studies of active TB costs have focused on estimating direct healthcare costs, while a few have estimated indirect patient costs[121], including such costs as time lost from work, travel time, and caregiver time. Some have estimated inpatient costs only[68, 118, 123]. Others have estimated costs including more general TB costs needed for public health administration (such as contact tracing) and TB-related research[122]. Some studies have been completed using data from single clinics or hospital networks[105], while other studies have been completed using aggregated data from a variety of sources[116, 121, 122]. Total costs of active TB patients have varied between studies, primarily due to differences in the cost components included and length of follow-up.

Among studies estimating total direct costs, inpatient hospitalizations are generally found to be the largest cost item of TB treatment (accounting for more than 50% of TB costs in many studies) [68, 116, 119, 120, 122-124]. In the one Canada-wide cost-of-illness study, using aggregated data and surveys of provincial TB control programs, it was estimated to cost government roughly $50,000 (2004 Canadian dollars) to treat a patient with active TB[122]. Hospitalizations were

estimated to account for 50% of the total component costs for TB treatment [122]. In a national study by the Canadian Institute of Health Information using data from the Canadian Discharge Abstract Database, the estimated average 2005-2006 cost of an acute care hospitalization for TB patients in Canada (excluding Quebec) was $16,131 (standard deviation of $23,916) [63].

Health service utilization and costs can be influenced by a number of factors, ranging from the patient-level, to physician-level and even regional availability of health resources [125]. Among studies that have investigated determinants of health service utilization in TB patients, patient-level factors associated with higher service use and costs have included: older age[118, 121], male gender, ethnicity, TB disease type and severity[116, 120], co-morbidities such as HIV[68, 117-119, 121], factors associated with social marginalization (e.g. homelessness, substance abuse)[118], low socioeconomic status[126], living in a rural area[126], and poor access to healthcare[127]. Specifically looking at hospitalizations, factors predictive of higher hospitalization rates in TB patients have included being homeless, low income, black or Hispanic ethnicity, HIV-infected, and alcohol abusers, having public health insurance or no insurance, as well as having smear-positive TB, MDR-TB, and older age [68, 115, 118, 123, 128, 129]. Regional protocols can also predict hospitalizations, since in some jurisdictions hospitalizations may be required in order to isolate active TB cases. Factors associated with longer length of stay in hospital have included being a correctional facility resident or long-term care resident, having more severe disease, MDR-TB, a TB drug-related adverse event, alcohol abuse, being homeless and on Medicaid or without health insurance[68, 123, 128, 130 131]. Notably, most studies about hospitalization of TB patients have been from the US, and predictors of hospitalization from US studies may not be applicable to the Canadian setting.

2.2.2 Health administrative databases to estimate TB-related health service use and costs

Health administrative databases offer one source of data for measuring real-world use of health services and costs but have rarely been used to evaluate health service use, costs, and outcomes of TB patients. Only a handful of previous studies have used health administrative databases to estimate average rates of hospitalization in the population of TB patients[115, 116, 122], and few have used individual-level data available in health administrative databases to estimate rates of other health service use and actual health system costs for TB patients. Health administrative databases record contact with the healthcare system, primarily as billing data - such databases typically

consist of individual-level records for insurance plan members, including medical billing records and diagnoses for ambulatory care visits, hospital discharge abstracts, and drug prescriptions data [15, 132]. In Canada, provincial-based health administrative databases are generally available for each province, and given universal healthcare, are generally complete for the population [15].

Strengths and limitations of health administrative databases in general are well-known, but have not been well-described for TB research. Strengths include the relative ease and low-cost of obtaining large amounts of data compared to primary data collection, so that large studies can be conducted with increased statistical power to detect rare events [15]. There is generally complete capture of contact with the health care system and population-based coverage [12-15]. Such databases can allow investigation of the some measures of treatment effectiveness in the context of everyday practice (ie. 'real-world' setting),[133], and assessment of temporal patterns of health service use. Health administrative-based studies are also less prone to selection bias due to non-response as patient consent is not required, and less prone to recall bias compared to studies based on self-reporting of outcomes[15]. Limitations include the fact that disease identification relies on the patient's use of health services within a given period of time, so co-morbidities in relatively healthy persons with few medical encounters may not be detected[135]. There is also potential for bias due to missing data on variables (e.g. clinical characteristics, habits such as smoking or alcohol consumption, living conditions, etc) [13, 15, 136, 137]. Data may not be available for over-the-counter drugs, for drugs provided in-hospital or paid for outside of insurance plans, or for salaried or allied healthcare providers [15]. Further, data are also not collected for research purposes, so there is a potential for missing data or poor accuracy of some data fields, including misclassification of important variables such as diagnoses [12-14, 136, 138].

2.4 THESIS RATIONALE AND OUTLINE

This review has identified a number of gaps in the literature important for assessing the cost-effectiveness of LTBI treatment in Quebec. First, few studies have described the 'real-world' patterns of health service utilization and direct costs associated with treating active TB and LTBI, particularly in a Canadian setting. Second, few studies have compared treatment completion rates of INH and RMP regimens in the general population, including the wide range of patients who may be treated for LTBI (eg. older and co-morbid patients), and the multiple providers who prescribe treatment. Health administrative databases offer one potential data

source for evaluating 'real-world' health service use, costs, and LTBI treatment completion, but the accuracy of identifying TB patients in such databases is not clear.

My manuscript-based thesis includes four studies that will address the identified gaps in knowledge. Here I summarize the rationale, objectives, and the potential contributions that each study will make to the field, for each of the studies.

Study 1: Validated Methods for Identifying Tuberculosis Patients in Health Administrative Databases: A Systematic Literature Review

Rationale: An increasing number of studies are using health administrative databases for TB research, but few studies have evaluated the accuracy of methods to identify TB patients in such databases.

Objective: My primary objective was to conduct a systematic literature review of studies which have previously validated TB case definitions in health administrative databases.

Potential contribution: This will be the first study to critically review methods for identifying TB patients in health administrative databases.

Study 2: Patterns and Costs of Health Service Utilization by Active Tuberculosis Patients in Quebec: A Population-Based Study

Rationale: Few previous studies have described 'real-world' patterns and direct costs of health service utilization by active TB patients, particularly in Canadian populations

Objectives: My primary objectives were to describe the health service use patterns (including types and timing of service use) and associated direct costs, of active TB patients in the Quebec general population using data from the provincial health administrative database, and to estimate the total direct costs attributable to active TB disease

Potential contribution: This will be one of the first studies to describe population-based patterns of health service use and direct costs by active TB patients in a Canadian setting

Study 3: Predictors of Hospitalization during Diagnosis and Treatment of Active Tuberculosis in Montreal, Quebec: A Retrospective Cohort Study

Rationale: Hospitalization is typically the most costly component of TB care. However, few studies have evaluated predictors of hospitalization of patients during diagnosis and treatment of active TB, particularly in Canadian populations

Objective: My primary objective was to identify predictors of hospitalization and hospital length of stay of patients diagnosed with active TB in Montreal over a 10-year period, using data from a comprehensive clinical database.

Potential contribution: This study will provide data on predictors of hospitalization and hospital length of stay during diagnosis and treatment of active TB in a Canadian setting

Study 4: Completion, Adverse Events, and Direct Costs of Isoniazid and Rifampin Treatment for Latent Tuberculosis Infection: A Population-Based Study

Rationale: Poor treatment adherence and risk of drug-related side effects of the standard LTBI regimen of 9 months of INH are barriers to effective implementation of LTBI treatment programs. Shorter-course regimens such as 4 months of RMP may have better adherence and a reduced risk of adverse events, as suggested by randomized clinical trial results and single-clinic observational studies. However, few population-based studies, using data from multiple patients and providers in real-world settings, have compared rates of completion, side effects and costs of INH and RMP regimens.

Objectives: My primary objectives were to compare completion rates, drug-related adverse event rates, and direct costs of INH and RMP regimens in the Quebec general population

Potential contribution: This study will provide real-world rates of treatment completion, adverse events, and direct costs of INH and RMP regimens in a Canadian setting

CHAPTER 3: VALIDATED METHODS FOR IDENTIFYING TUBERCULOSIS CASES IN HEALTH ADMINISTRATIVE DATABASES: A SYSTEMATIC REVIEW (MANUSCRIPT #1)

3.1 Introduction

Health administrative databases are increasingly being used for disease surveillance, and in the investigation of the epidemiology, outcomes, health service use and costs of many diseases [13, 15, 132]. These databases are generated through the routine administration of health care programs and record patients' contact with the healthcare system. They typically include individual-level records for insurance plan members, including medical billing records and diagnoses for ambulatory care visits, hospital discharge abstracts, and drug prescriptions data [15, 132]. They may also include laboratory tests or other medical procedures, continuing care records, or a range of other clinical encounters or services provided, depending on the health information system and health plan coverage[139]. In the US, available databases include those of many health maintenance organizations (HMOs) and government-based insurance plans, such as Medicare, Medicaid, and the Veteran's Affairs Database [15, 132, 140]. In Canada, health administrative databases are generally available for each province, and given universal healthcare, are nearly complete for the general population[15].

Health administrative databases offer many advantages over primary data collection. The relative ease and low-cost of obtaining large amounts of data compared to many primary data collection studies means that large studies can be conducted, with increased statistical power to detect rare events [15]. There is generally complete capture of patient contact with the health care system and there is information on the entire population covered [12-15]. Health administrative-based studies are also less prone to selection bias due to non-response, as patient consent is not required to conduct such studies, and less prone to recall bias compared to primary data collection studies based on self-reporting of outcomes [15]. Their main limitation is that data are generally not collected for research purposes, with the potential for missing data or poor accuracy of some data fields [12-14, 136].

For tuberculosis (TB) research, the challenges to using health administrative databases have not been well documented. Recent studies have used health administrative databases to estimate

rates of TB in hospitalized patients[140], in patients started on TNF-alpha inhibitor treatments[141], and in the study of TB disease burden, health services use, and costs[115-117, 122]. Accurate identification of active TB is needed for valid studies, but few studies have reported efforts to validate methods for identifying TB cases in such databases. Therefore, the objective of the following study was to conduct a systematic review of studies which have validated TB case definitions in health administrative databases.

3.2 Methods

Search strategy and selection of studies for review:

A systematic literature search was conducted in two databases: Ovid Medline and Embase (see Table 1 for search terms). Secondary references were also manually retrieved from primary search articles plus a manual search was conducted in prominent journals which focus on TB or which frequently publish validated algorithms for health administrative databases (International Journal of Tuberculosis and Lung Disease, and Journal of Clinical Epidemiology). The search strategy was developed in consultation with a professional medical research librarian who has experience in conducting systematic reviews.

Studies were included for full-text review if they: 1) had a diagnostic accuracy or validation study design, including an identified reference standard dataset, and a test dataset derived from health administrative data (including hospital discharge records, drug prescriptions data, laboratory data, and/or physician billing records); 2) used mandatory reported TB surveillance data, medical chart review, or physician-reported diagnosis as the reference standard; 3) reported measures of diagnostic accuracy (sensitivity and/or positive predictive value (PPV)) of one or more algorithms to identify active TB cases or LTBI cases in the test dataset; 4) were published in English or French; 5) were conducted in low TB-incidence countries (TB incidence of <10/100,000 population[142]); and 6) were published between January 1980 and July 2013. A health administrative database was defined as a secondary database that captures patient contact with the health care system, in the form of billing claims or clinical encounters[139]. Electronic health records were included in this definition[143]. The reference dataset was defined as the dataset where TB cases were confirmed (our 'gold-standard') and the test dataset as the dataset on which algorithms were applied. Capture-recapture studies were excluded when they were designed to estimate rates of TB under-reporting and did not include an identified reference

standard (as above). From the search of the two electronic databases, a single data set of titles and abstracts was created, from which duplicate results were eliminated. The titles and abstracts were reviewed for initial selection by a single investigator (LR). Of these initially selected references, full texts were reviewed and selected independently by two investigators (LR, DL).

Data extraction:

From the final studies selected for the review, data were abstracted independently by two investigators (LR, DL) for the evidence table using a standardized form (Appendix 4). For each eligible study, the following information was summarized: citation (including first author, publication year and country), test dataset (including sample size, population characteristics, and data type), reference dataset type, reported diagnostic accuracy measurements, reasons for false positives, and authors' conclusions. From individual studies, data were extracted for all algorithms which included an International Classification of Diseases (ICD) code, a drug prescription, a procedure code using Current Procedural Terminology (CPT) codes or ICD codes, or laboratory testing data. Where studies examined additional algorithms for non-tuberculosis mycobacteria (NTM), diagnostic accuracy measurements were extracted for these algorithms. Algorithms were excluded when they used diagnostic or procedure codes unique to specific database systems (eg. COSTAR codes for ambulatory care records). Due to heterogeneity between datasets, test and reference populations, and algorithms, diagnostic accuracy estimates were not pooled with a formal meta-analysis.

3.3 Results

The initial search identified 926 unique citations; 23 were selected for a full-text review after review of titles and abstracts (Figure 1). Of these, 15 were excluded - most often because of inadequate information about the reference dataset, and 8 were selected as eligible for this review (Figure 1). All studies reported on algorithms to identify active TB; no studies reported on algorithms to identify LTBI. Information about the study populations and settings, test and reference standard datasets, and false positives are summarized in Table 2. Algorithms to identify active TB cases are summarized in Table 3. Table 4 summarizes algorithms tested to identify NTM. A detailed descriptive summary of each of the papers included in this review is provided in Appendix 4.

Of the 8 studies included in this study, all were from the US with the exception of one study from Italy[144]. Seven studies used chart review as the sole reference standard, two studies used a mandatory reporting TB registry, and one study used physician recall. Populations studied included HMO, Veteran's Affairs, and Medicaid registrants, rheumatoid arthritis patients, hospitalized patients, and patients dispensed TB drugs through the Italian national health system[144]. Algorithms and diagnostic accuracy outcomes varied widely across studies (PPV ranged from 1.3% to 100% and sensitivity ranged from 20% to 100%). Most studies tested algorithms including ICD-9 diagnostic codes only, pharmacy records only, or combinations of these. One study also reported laboratory test results[145] and one incorporated an order for a laboratory test (acid-fast bacilli smear)[146]. Sole use of ICD-9 codes in outpatient records provided the lowest PPV and highest sensitivity in all studies when compared against other algorithms within the same study[145, 147, 148]. Sole use of ICD-9 codes in hospital records [140] provided higher PPV compared to studies using outpatient or combined inpatient/outpatient records. Dispensing of TB drugs provided higher PPV than ICD-9 codes when algorithms were compared within studies[145, 147, 148]. Increasing the number of TB drugs increased PPV with a small decrease in sensitivity[148]. Use of combination algorithms with ICD-9 codes and TB drugs dispensed generally increased PPV compared to sole use of ICD-9 codes or drug dispensation records[145, 147, 148]. Most false positives were reported as being due to LTBI, NTM, or suspected active TB later which was ruled out.

3.4 Discussion

This review found eight studies reporting diagnostic accuracy of algorithms to identify TB in health administrative databases. Notably, diagnostic accuracy estimates varied widely across studies. Among included studies, the lowest PPV values were generally found in algorithms relying solely on ICD-9 diagnostic codes in outpatient records. Higher PPVs were found in studies limited to ICD-9 diagnoses in inpatient records. In studies using TB drug prescriptions data, PPV tended to increase when the number of TB drugs increased within a given algorithm, or when ICD-9 codes were combined with prescriptions for specific TB drugs.

These findings reflect a limitation to using ICD codes to identify active TB cases. In many jurisdictions , accurate ICD codes are not needed by physicians for reimbursement [15], and validation studies suggest that accuracy of ICD codes can vary between different databases, time

periods, and population subgroups [136, 149, 150]. Accuracy of hospital-based diagnostic codes are generally considered to be more accurate than physician-based codes, in part due to the fact that hospitals use trained medical archivists to identify the most relevant diagnostic codes within hospital charts [151]. This was reflected in the review, where studies using ICD codes in inpatient records tended to find better accuracy than studies using ICD codes in physician claims records. However, there are also issues with diagnostic codes that are specific to TB. Since there are no separate ICD codes for LTBI, patients with LTBI only or who are administered a tuberculin skin test, may be recorded with a TB diagnostic code. Miscoding of LTBI as active TB was reported in a number of studies in our review [146, 148]. Furthermore, there are no ICD codes to identify suspected active TB, thus cases suspected to be active TB but later established to be something else (eg. NTM) may be initially labeled with an active TB diagnostic code. The use of TB diagnostic codes for suspected TB and NTM was reported in several studies[148, 152]. The number of suspected TB cases may be quite substantial[153]. For example, a large US study of TB-related health department costs in several US jurisdictions found almost twice as many patients with suspected active TB as documented active TB[153]. There are also no diagnostic codes to identify suspected LTBI. Therefore, studies relying solely on ICD codes to identify active TB, particularly when using physician billing records, are likely to overestimate the number of cases.

This review suggested that there is a need for further validation work to develop TB case definitions in health administrative databases. The most frequent reasons for false positive identification of active TB were NTM, suspected (but not confirmed) TB, and LTBI. We found two studies that reported algorithms to identify NTM[140, 145]; both found that sole use of ICD codes for NTM had relatively high PPV, and addition of a macrolide prescription to the algorithm increased PPV. However, neither tested NTM algorithms as a method to improve accuracy to detect patients with active TB. Yokoe et al suggested using a macrolide drug as a marker to identify NTM cases but they did not test this algorithm[148]. Similarly, pyrazinamide may be used as a marker to exclude NTM (since NTM are universally resistant to the drug, which should not be prescribed for NTM). Pyrazinamide is also no longer recommended for treatment of LTBI, and not used for other indications (eg. rifampin has some non-mycobacterial use). Several algorithms included a prescription for pyrazinamide but none of the studies explicitly stated their reasoning for including it [145-147]. Furthermore, no studies reported on the accuracy of algorithms to differentiate between active TB and LTBI cases specifically.

In addition, several studies recommended including a minimum treatment duration in algorithms to differentiate active TB from suspected TB[144, 148].This seems reasonable given that treatment for tuberculosis is mandatory in most jurisdictions and with completion rates higher than 90% reported in many studies (eg. [154]). Using a crude measure of treatment duration (number of TB drug prescriptions over the treatment period), Maggini *et al* noted that patients with confirmed TB had, on average, a higher number of prescriptions than patients whose TB was not recalled by their doctor. They suggested that their crude measure of treatment duration could be used to differentiate confirmed TB cases from patients with initially suspected TB but whose treatment was discontinued when the diagnosis was later proved false [144]. Yokoe et al suggested using a cut-off of 4 months for treatment duration to separate suspected from active TB cases, but did not test this algorithm[148]. Fiske et al reported finding no false positives for active TB when a limit of at least 3 months of TB treatment was applied[147]. None of the reviewed studies, however, reported on diagnostic accuracy of active TB case definitions when a treatment duration rule was included.

There are limitations to this review. First, this review reported overall sensitivity and PPV for the populations under study. However, underlying disease prevalence and spectrum is known to influence measures of diagnostic accuracy[155]. Compared to studies in populations with low TB prevalence, studies based in populations with higher TB rates may have better accuracy, given a higher baseline suspicion of TB among clinicians and patients. This is somewhat supported by Winthrop *et al*: higher accuracy measures were found in RA patients on anti-TNFα inhibitors (a known risk group for reactivation of LTBI), compared to the population of veterans[145]. Additionally, it was assumed that reference datasets in the included studies were complete. However, in studies relying on notifications to TB registry systems, TB reporting systems may not capture all cases, particularly with under-reporting of extra-pulmonary TB, and of clinical cases without microbiologic confirmation (notably in children)[156, 157]. Therefore, some of the included studies may have underestimated the true PPV of diagnostic algorithms. As well, capture-recapture studies without defined reference populations were excluded, some of which have made linkages to health administrative databases as part of their studies (eg. hospital discharge records and TB drug prescription records). These studies may provide additional estimates of diagnostic accuracy that were not included in this review.

Regarding generalizability, most studies in this review were from the US. No studies have evaluated diagnostic algorithms for identifying TB in Canadian health administrative databases, and it is possible that results from US studies may not be generalizable to the Canadian setting. For example, missing drug prescriptions data during inpatient hospital stays has been reported as a source of potential bias in Canadian health administrative databases[158], but no studies have investigated the impact of this gap on case validation rules. Furthermore, the studies in our review validated algorithms in different types of health administrative databases, including billing files, hospital abstracts, and electronic health records. Individual databases may have different characteristics – for example, some databases recorded drugs dispensed[144, 145, 148] while others recorded drugs prescribed[146]. This review also did not include algorithms which used laboratory results, or procedure codes unique to particular ambulatory care or claims-based databases. It is possible that use of these codes could improve diagnostic accuracy, but would require validation studies within these specific databases, which would not be applicable to other settings. Lastly, all studies reporting accuracy of ICD codes used the ICD-9 system. However, there are few changes from the ICD-9 to the newer ICD-10 system with regard to TB coding, thus it is unlikely that observed accuracy rates would change much with the newer ICD-10 coding system. Future revisions of the ICD coding system, however, should consider including categories for LTBI and for suspected TB, in order to improve the accuracy of TB diagnoses for research and surveillance purposes.

In conclusion, this study reviewed validated methods to identify active TB and LTBI cases in health administrative databases. Based on this review, algorithms based on TB drug prescriptions may provide better diagnostic accuracy than algorithms based solely on ICD codes, particularly when including non-hospitalized populations. Drug prescription-based algorithms specifying initial use of multiple TB drugs, with a minimum treatment duration, and markers to identify and exclude NTM cases may provide the highest PPV for capturing active TB cases.

Table 1: Systematic review search strategy

(Administrative data*.mp OR health maintenance organization.mp OR electronic health record.mp OR Electronic medical record.mp OR Secondary data*.mp OR Medicare.mp OR Medicaid.mp OR Veterans affairs.mp* OR Surveillance.mp OR International classification of disease*.mp OR Drug prescription*.mp) AND (Accuracy.mp OR algorithm.mp OR Sensitivity.mp OR Specificity.mp OR Predictive value.mp OR validation.mp OR completeness.mp) AND Tuberculosis.mp

Figure 1: Summary of study selection for systematic review

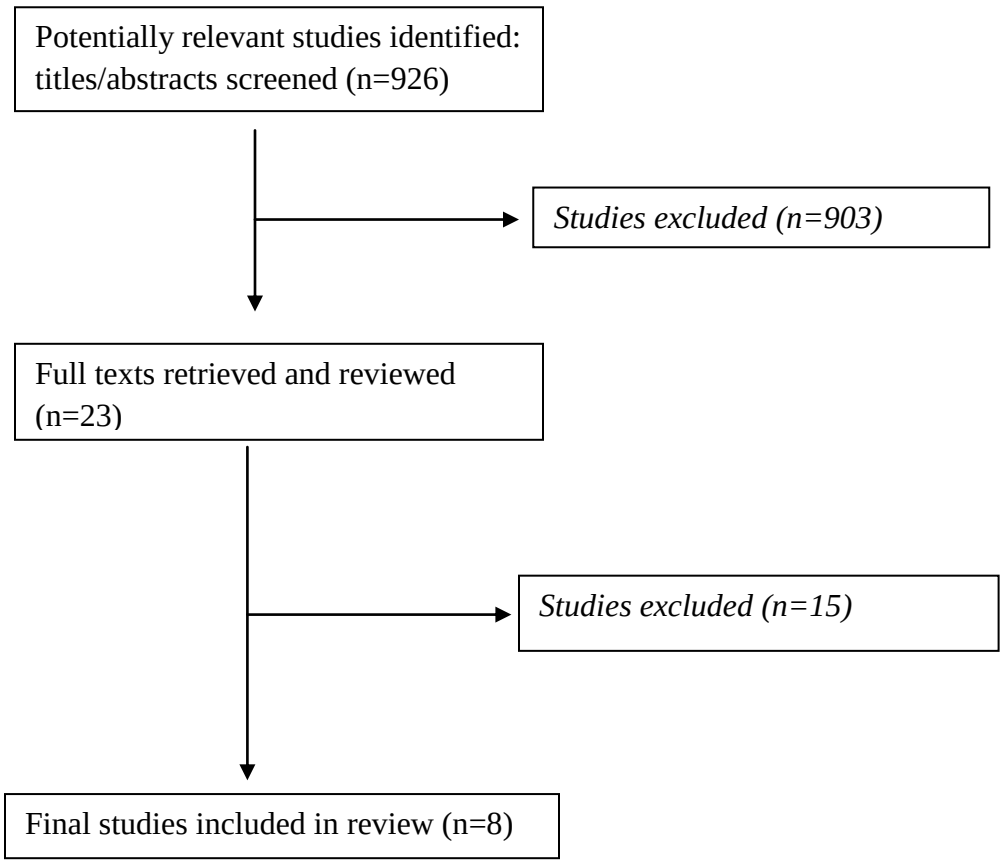


Table 2: Summary of validation studies to identify tuberculosis in health administrative databases

First author, year, Country Reference	Test population		Reference standard		Notes about false positives (FP)
	Study population and setting	Data source where TB algorithms applied	Source	Description	
Fiske, 2012 (US)[147]	Retrospective cohort of rheumatoid arthritis (RA) patients registered in Medicaid during years 2000-2005: aged ≥18 years and either 1) ICD9 RA-coded healthcare encounter and DMARD prescription filled or 2) RA-coded healthcare encounters ≥30 days apart + oral glucocorticoid prescription filled	Physician billing and pharmacy claims from Tennessee Medicaid database	TB Registry	Confirmed TB cases as defined by US CDC: 1) MTB isolated; 2) AFB positive; 3) clinical diagnosis; or 4) provider diagnosis.	High FP rates when drugs or ICD codes used alone or in combination. No FP's received ≥3 months of TB drugs; 3/6 had alternative diagnoses after initial TB diagnosis (2 NTM, 1 blastomycosis)
Winthrop, 2011 (US)[145]	Cohort #1: All patients in the Portland Veterans' Affairs Medical Centre database, between 2000-2008	Inpatient/ outpatient clinical, microbiologic, and pharmacy records in EHRs from VA database	State TB registry/ chart review	Cross-matched suspect case list to state TB registry to verify that cases met CDC TB case definition. Used ATS/IDSA criteria to confirm NTM.	Not specified
	Cohort #2: Rheumatoid arthritis patients on anti-TNFα inhibitors in the Kaiser Permanente Northern California HMO between 2000- 2008	Inpatient/ outpatient clinical, microbiologic, and pharmacy	Chart review	Review of full electronic chart, using CDC TB disease criteria to define confirmed TB. Used ATS/IDSA criteria to confirm NTM.	Of 12 cases misclassified as active TB, 6 had LTBI, 1 had community-acquired pneumonia, 1 had *M. gordonae*, and 4 had unknown

		records in EHRs from HMO database			reasons
Calderwood, 2010 (US)[146]	All patients in an ambulatory group practice (Atrius Health), including 27 health care settings in Massachusetts, between 1990-2006	Outpatient EHRs and written prescriptions / test orders	Chart review	CDC case definitions applied by nurses to determine if physician-suspected active TB during evaluation, and if case ultimately was active TB, latent TB, or no TB.	All false positives were LTBI
Sickbert-Bennett, 2010 (US)[159]	Retrospective cohort study: 6 non-federal acute health facilities in North Carolina: Patients with a TB diagnosis (ICD9-CM) in year 2003 (20% random sample)	Inpatient/ outpatient records from 6 non-federal acute care health systems	Chart review	CDC case definitions applied by trained epidemiologists to identify true reportable case (confirmed, suspected, or probable)	Not available
Schneeweiss, 2007 (US)[140]	Cross-sectional validation study: All hospitalized patients in the Veteran Affairs electronic database for the New England region, with hospital stays >3 days and who were discharged between 2001-2004.	Inpatient EHR records from VA Database	Chart review	Diagnostic decision rules based on clinical status, microbiology, and in-hospital therapy that would be applied by an infectious disease physician	Not available
Yokoe, 2004 (US)[152]	Patients with pharmacy coverage by one of three health plans in Michigan (1993-1999), Missouri (1996-1998), and Tennessee (1998).	Pharmacy dispensing records	Linkage to TB registry or chart review	Linkage to TB registries or chart review for cases not reported using CDC definition to identify, confirmed or clinical active	Suspected active TB with full course of treatment given, or with treatment stopped early; LTBI; other NTM; and other/unknown reason

				TB cases.	
Yokoe, 1999 (US)[148]	Patients with EHR who received care at Harvard Pilgrim Health Care centres or patients without EHR who had pharmacy coverage by an HMO in Massachusetts, 1992-1996	Inpatient/ outpatient claims and pharmacy dispensing records from HMO database	Chart review	For patients with EHR, full chart review was done. For patients without EHR, a standardized form was sent to primary care physicians asking if patient had suspected or confirmed active TB. If yes, full-text chart review was done using CDC criteria. In addition, 2 cases were identified through the state registry.	Reasons for FPs among patients with IC(codes included indication for prenatal TB screening test, previous history of TB, suspected active TB, and unknown reason. Reasons for FPs among those identified with 2+ TB drugs included TB diagnosed outside study period, NTM infection, LTBI treatment, non-TB conditions, and suspected active TB
Maggini, 1991 (Italy)[144]	Sample of residents in Italy registered in the National Health System, identified as having been dispensed combinations of INH, EMB, RMP, or streptomycin in 1986	Prescriptions dispensed from the National Health System	Physician recall	Interviewed 171 physicians in 1989, asked them to recall if their patient(s) had a diagnosis of TB in 1986, had undergone LTBI treatment, or had another respiratory disease. Interviewed physicians did not know data source of the TB diagnosis.	Not available

EHR=electronic health records; FP=false positives; HMO=health maintenance organization; INH=isoniazid; RMP=rifampin; EMB=ethambutol; NTM=non-tuberculosis mycobacteria; CDC=Centers for Disease Control; ICD=International Classification of Diseases

Table 3: Diagnostic accuracy measurements (sensitivity and positive predictive value) from validation studies to identify tuberculosis in health administrative databases

Reference	Algorithm applied to test population	# TB cases		Type of records used	Diagnostic accuracy	
		In reference dataset	Identified with algorithm		Sensitivity, % (95% CI)	PPV, % (95% CI)
Fiske, 2012 (US)[147]	ICD-9 code for TB (010-018, V12.01, V01.1, 647.3)	10	449	I	60 (26-88)	1 (1-3)
	Pharmacy claims for ≥2 1st or 2nd line TB drugs on same day	10	49	P	20 (3-56)	4 (1-14)
	Isoniazid+rifampin on same day, or rifamate (isoniazid/rifampin combination) ever, or pyrazinamide ever	10	12	P	20 (3-56)	17 (2-48)
	ICD-9 code for TB AND (≥2 TB drugs on same day, 30 days before/after ICD-9 code)	10	8	M	20 (3-56)	25 (3-65)
	ICD-9 code for TB AND (isoniazid+rifampin on same day, or rifamate ever, or pyrazinamide ever)	10	6	M	20 (3-56)	33 (4-78)
Winthrop, 2011 (US)[145] Cohort #1:Veterans	Any inpatient/outpatient TB ICD-9 code (011-018)	22	197	I	77 (55-92)	9 (5-14)
	≥2 ICD-9 codes 011-018	22	68	I	64 (41-83)	21 (12-32)
	Isoniazid+rifampin dispensed on same day	22	43	P	55 (32-76)	28 (15-44)
	Pyrazinamide at least once during study period	22	38	P	50 (28-72)	29 (15-46)
	Isoniazid+rifampin on same day and ICD-9 code 011-018	22	26	M	55 (32-76)	46 (27-67)
	Pyrazinamide at least once and ICD-9 code 011-018	22	24	M	50 (28-72)	46 (26-67)
	(Pyrazinamide, or isoniazid/rifampin) AND ICD-9 code 011-018	22	27	M	55 (32-76)	44 (26-65)
	(Pyrazinamide ,or isoniazid/rifampin) AND ≥2 ICD-9 codes 011-018	22	17	M	55 (32-76)	71 (44-90)
	Culture positive for *M. tuberculosis*	22	12	L	55 (32-76)	100 (74-100)
	Culture for *M. tuberculosis* OR (pyrazinamide or isoniazid/rifampin and ≥ 2	22	22	M	77 (55-92)	77 (55-92)

	ICD-9 codes 011-018)					
Winthrop, 2011 (US)[145] Cohort #2: Rheumatoid arthritis patients	Any TB ICD-9 codes (011-018)	14	26	I	100 (77-100)	54 (33-73)
	≥2 ICD-9 codes 011-018	14	14	I	71 (42-92)	71 (42-92)
	Isoniazid+rifampin on same day	14	17	P	79 (49-95)	64 (38-86)
	Pyrazinamide at least once during study period	14	12	P	85 (57-98)	100 (74-100)
	Isoniazid+rifampin on same day and ICD-9 code 011-018	14	13	M	79 (49-95)	85 (65-98)
	Pyrazinamide at least once and ICD-9 code 011-018	14	12	M	85 (57-98)	100 (74-100)
	(Pyrazinamide, or isoniazid/rifampin) AND ICD-9 code 011-018	14	15	M	93 (66-100)	87 (60-98)
	Culture positive for *M. tuberculosis*	14	10	L	79 (42-92)	100 (69-100)
Calderwood, 2010 (US)[146]	(Prescription written for pyrazinamide) OR (ICD-9 code for TB and order for AFB in past 60 days or post 14 days) OR (ICD-9 code for TB and order for ≥2 TB drugs within 60 days)	n/a	218	M	n/a	47 (40-54)
Sickbert-Bennett, 2010 (US)[159]	Any ICD-9 code for TB in outpatient or inpatient records	n/a	73	I	n/a	23 (12-40)
Schneeweiss, 2007 (US)[140]	ICD-9 code (primary) for TB (010-018) in inpatient records	n/a	22	I	n/a	77 (59-95)
	ICD-9 code (primary) for pulmonary TB (011)	n/a	20	I	n/a	85 (69-100)
Yokoe, 2004 (US)[152]	Dispensing of ≥2 TB drugs (1st- or 2nd-line)	207	244	P	36 (27-46)	33 (20-30)
Yokoe, 1999 (US)[148]	Any ICD9 code for TB (010-018, excluding 010.9) †	4	251	I	100 (40-100)	2 (0-40)
	Dispensing of ≥2 TB drugs	45	133	P	89 (76-96)	30 (22-39)
	Dispensing of ≥2 TB drugs on same date	45	108	P	87 (73-95)	36 (27-50)
	Dispensing ≥3 TB drugs	45	76	P	84 (71-94)	50 (38-62)
	Dispensing of any TB drug AND any ICD-9 code for TB‡	41	14	M	17 (7-32)	50 (23-77)
Maggini,	Isoniazid+rifampin+ethambutol	n/a	91	P	n/a	77 (68-86) ┼

1991 (Italy)[144]	Isoniazid	n/a	86	P	n/a	50 (39-61) ┼
	Isoniazid+rifampin	n/a	67	P	n/a	69 (58-80)┼
	Isoniazid+ethambutol	n/a	49	P	n/a	65 (55-74)┼
	Ethambutol	n/a	17	P	n/a	71 (49-93)┼
	7 regimens, including 6 with streptomycin	n/a	36	P	n/a	75 (51-100)┼

Abbreviations: ICD-9=International Classification of Disease, version 9; PPV=positive predictive value; Type of records: I=ICD-9 codes, P=TB drug prescriptions, L= laboratory records ; M=Mixed algorithms; EHR=electronic health records

†Including only the subset of patients without automated EHRs

‡Including only the subset of patients with automated EHRs

Diagnostic accuracy measurement for any TB-related indication (ie. including both active TB and LTBI treatment)

Table 4: Diagnostic accuracy measurements (sensitivity and positive predictive value) from validation studies to identify non-tuberculosis mycobacteria in health administrative databases

Reference	Algorithm applied to test population	# NTM cases		Type of records used	Diagnostic accuracy	
		In reference dataset	Identified with algorithm		Sensitivity, % (95% CI)	PPV, % (95% CI)
Winthrop, 2011 (US)[145] Cohort #1: Veterans	Any ICD code for NTM (031)	71	62	I	65 (53-76)	74 (62-85)
	Any ICD code for NTM (031) AND azithromycin or clarithromycin ≥30 days	71	24	M	34 (23-46)	100 (86-100)
	NTM isolated in culture	74	132	L	76 (65-85)	41 (32-50)
	NTM isolated in culture AND any ICD-9 code for NTM (031)	71	39	M	42 (31-55)	77 (61-89)
	NTM isolated in culture OR any ICD-9 code for NTM (031)	71	171	M	99 (92-100)	41 (34-49)
Winthrop, 2011 (US)[145] Cohort #2:Rheumatoid arthritis patients	Any ICD code for NTM (031)	18	9	I	50 (26-74)	82 (48-98)
	NTM isolated in culture	18	23	L	100 (81-100)	78 (56-93)
	NTM isolated in culture AND any ICD-9 code for NTM (031)	18	10	M	50 (26-74)	90 (56-100)
Schneeweiss, 2007 (US)[140]	ICD-9 code (primary diagnosis) for atypical *M. avium* complex (031.x)	n/a	10	I	n/a	70 (42-98)

Abbreviations: ICD=International Classification of Disease; NTM=non-tuberculosis mycobacteria; PPV=positive predictive value; Type: I=ICD-9 codes; P=TB drug prescriptions; L= laboratory records; M=Mixed algorithms

PREFACE TO CHAPTER 4 (MANUSCRIPT #2)

My previous manuscript summarized published validation studies of decision rules to identify TB patients in health administrative databases. This review suggested that decision rules based on TB drug prescriptions should provide better accuracy for capturing TB patients in health administrative databases compared to decision rules based solely on diagnostic (ICD) codes, particularly when including non-hospitalized patients. Rules including multiple TB drugs, a minimum treatment duration, and an exclusion marker for NTM should help to differentiate active TB patients from treated LTBI patients and non-tuberculosis mycobacteria patients.

In my next manuscript (Chapter 4), I apply lessons learned from the first manuscript by applying a series of TB drug prescription record-based decision rules to identify a cohort of active TB patients in the Quebec provincial RAMQ database. I detail the methods I used to identify the active TB cohort, including a description of the health administrative database, definitions of the study follow-up and TB drug treatment periods, and application of decision rules to differentiate active TB from patients treated for LTBI, NTM, or other rifampin indications. I conclude with a description of the patterns and direct costs of health service use by active TB patients in the Quebec general population over a ten-year period.

CHAPTER 4: PATTERNS AND DIRECT COSTS OF HEALTH SERVICE UTILIZATION BY ACTIVE TUBERCULOSIS PATIENTS IN QUEBEC, CANADA: A POPULATION-BASED STUDY (MANUSCRIPT #2)

4.1 Introduction

High rates of health service use and associated costs for diagnosing and treating active tuberculosis (TB) are a burden to many healthcare systems [116, 122, 123]. Understanding the 'real-world' rates and costs of health service use by TB patients is thus important for policy makers to predict resource needs of TB patients, and to evaluate the cost-effectiveness of TB prevention and control programs[160]. Despite this, few studies have investigated patterns and costs of health service use among TB patients, particularly in a Canadian setting. Furthermore, most studies to-date have used data from single-clinic sources[11-13], which can limit generalization of results to the wider population[125].

Health administrative databases have been used to estimate health service use and costs for many diseases[132, 161], but have rarely been used in TB studies. Advantages of health administrative data include near-complete capture of contact with the healthcare system for a given population, and individual-level data to capture the type and timing of use of specific services[132]. Therefore, the primary study objective was to describe the patterns and direct costs of health service utilization by patients with active TB over a 10-year period in the province of Quebec, using data from the provincial health administrative database, and to estimate TB-attributable direct costs. This study is part of a larger research project to estimate the cost-effectiveness of LTBI treatment for TB prevention in Quebec.

4.2 Methods

Data source

The primary data source was the Régie de l'assurance maladie du Québec (RAMQ) database**.** The RAMQ database contains the health administrative records of all publicly funded health care services in Quebec. An estimated 99% of Quebec permanent residents are registered in the

RAMQ, thus population coverage for health service use is nearly complete. In contrast to general RAMQ beneficiary coverage, coverage by the drug plans of the RAMQ is more limited. The RAMQ drug plans specifically cover all individuals who are either: not eligible for a private drug plan, 65 years and older, on social assistance, and/or are dependants of individuals who are on the RAMQ drug plan. RAMQ coverage (including RAMQ drug plans) is extended to the majority of Northern Cree and Inuit populations through the James Bay and Northern Quebec Agreement[164, 165].

Notably, since January 1, 1997, all drugs used to treat active TB and LTBI have been fully covered by the RAMQ for all RAMQ beneficiaries, regardless of whether an individual is eligible for the RAMQ drug plan. Given this coverage, private insurers will not reimburse since that date – hence virtually all persons in Quebec who are eligible for RAMQ coverage will receive their TB drugs through RAMQ, and thus information on dispensing TB drugs to Quebec residents should be near-complete from the RAMQ databases. The major exception is drugs administered to individuals in-hospital, which are covered by government hospital insurance and are not included in the RAMQ drug plan database.

Data were extracted from multiple files available through RAMQ (see Appendix 3), all of which are linked together through unique identifiers which are scrambled to protect confidentiality. The Beneficiary file includes demographic and vital statistics data of registrants. The Physician Registration file contains data on physicians registered in Quebec, including unique physician identifier and characteristics. The Physician Billing file includes details for each inpatient and outpatient visit, including patient and physician identifiers, primary diagnosis (International Classification of Diseases (ICD), Ninth Revision), procedure or type of visit, fees reimbursed, and type of facility where the visit occurred. Of note is that the RAMQ physician billing file does not include costs incurred by salaried physicians or allied healthcare workers such as public health nurses. The Drug Plan file contains records for all drugs dispensed through community pharmacies in Quebec and reimbursed in part or wholly by one of the RAMQ drug insurance plans. Data included for each prescription are drug identification codes, date filled, number of days and number of doses prescribed, dose, and costs borne by RAMQ and/or the patient. The Med-ECHO file includes records for all acute care admissions and day surgeries at hospitals in Quebec. It includes dates of admission and discharge; primary diagnosis (accounting for the

highest resource use during the hospital stay) and up to 15 secondary diagnoses (contributing to hospital resource use), up to 8 procedure codes, and an indicator of whether the patient died in-hospital death. Diagnoses prior to April 1, 2006 are coded using the ICD9 coding system; after April 1, 2006, diagnoses are coded with ICD10-CA. Hospital discharge diagnoses are typically coded by trained archivists [166].

Study design and populations

A matched cohort design was used to compare health service use and direct costs of active TB patients against those of patients not treated for TB. The active TB cohort included all active TB patients identified in the RAMQ database as starting treatment between January 1, 1998 and December 31, 2007. Decision rules based on TB drug dispensation records were used to identify study cohorts, given limitations to using ICD diagnostic codes to identify TB (Chapter 3). Data were first extracted from the RAMQ database for all individuals who were dispensed at least 30 days of a first-line anti-TB drug (isoniazid, rifampin, pyrazinamide, and/or ethambutol) from any community pharmacy in Quebec between 1998 and 2007. With few exceptions, these drugs are indicated and prescribed exclusively for TB and thus prescriptions for any one or more of these drugs were considered highly indicative of treatment for active TB or LTBI. TB drugs were identified in the RAMQ database using Health Canada Drug Identification Numbers and American Hospital Formulary Service codes (see Appendix 2 for summary). A 30-day dispensation rule was used because TB drugs in Quebec are typically dispensed for 30-day durations[167], and in order to exclude possible other indications of rifampin which can be given for shorter time intervals.

The start date of the first TB drug dispensation record between January 1, 1998 and December 31, 2007 was defined as the 'index date' for each individual. In order to identify incident treatment cohorts, the dataset was limited to patients who had not had a TB drug dispensation record in the past three years. This time period was selected based on a prior study of TB drug prescribing, which found that some patients had TB drugs prescribed over a three-year calendar period[144]. Up to 6 years of data were extracted for each patient, starting from three years before their index date and ending three years after their index date. At the time of the data extraction (October 2009), RAMQ hospital records were not available before January 1st, 1995, physician

billing records were not available before January 1st, 1996, and drug records were not available before January 1st, 1997. Additionally, hospital records were not available after March, 2008, and physician billing records and drug dispensation records were not available after October, 2009 (see Appendix 4 for a schematic).

An incident cohort of active TB patients was then identified using a series of decision rules (summarized in Table 5). The active TB cohort was comprised of patients who were dispensed at least 30 days of three or more first-line TB drugs, **or** two first-line TB drugs and one second-line drug, **or** who had a recent hospitalization of 60 days or longer plus two first- or second-line TB drugs. First-line TB drugs were identified as isoniazid, rifampin, pyrazinamide, ethambutol, rifabutin, rifapentine, and fixed dose combination tablets of first line TB drugs; second-line TB drugs were identified as fluroquinolones, aminoglycosides, para-amino salicylic acid, cycloserine, and ethionamide. Patients were identified as probable suspected active TB patients only, and subsequently excluded from this active TB cohort, if they were dispensed 90 days or less of multi-TB drug treatment and who did not die during the TB treatment period.

In order to compare health service use and costs of active TB patients against a population of individuals without treatment for active TB, a cohort of control subjects was also extracted from the RAMQ database (matched control cohort). Matching was done on five-year age group, sex, and postal code area (first three digits of postal code) of the home address at a ratio of 2:1 to each active TB patient, on the index date of the respective active TB patient. Controls were individuals who were registered in the RAMQ at the time of the index date, and who had no TB drugs dispensed for 30 or more days within the three years prior to or three years following the index date.

Ethical approval for this study was obtained through the Institutional Research Board of the McGill University Faculty of Medicine (IRB Study #A06-M88-09A).

Identifying TB treatment and follow-up periods

A patient's TB drug treatment period was identified as starting on their index date and ending thirty days after the last date that a first-line TB drug was dispensed (see Appendix 4 for a schematic). The end of the TB treatment period was extended by thirty days in order to account for the possible underestimation of the treatment period length due to overlapping drug dispensation records. In a few patients who were still on therapy at the end of three years of follow-up or at the end date of RAMQ data availability, it was assumed the TB treatment period was right-censored due to end of study if the last TB drug was dispensed within 15 days before this date (ie. three years after the index date, or October 2009, whichever was earliest). Days with TB drugs dispensed were identified based on the start date and duration of each RAMQ drug dispensation record. For the purposes of tracking patients longitudinally, each date that a TB drug was dispensed was calibrated against the patient's index date. Creation of this time axis allowed us to easily match the timing of health service records against patients' TB drug records, and to follow patients longitudinally with a common starting time point (index date=1) (see Appendix 4 for examples). The TB treatment period for each control was set to be the same length as their matched active TB patient.

Next, for the purposes of calculating health service use rates over time, the start date of a patient's follow-up period was identified as 3 years before their index date (see Appendix 4 for a schematic). Exceptions to this three year period were when data were not yet available from the RAMQ. The end date of a patient's follow-up period was identified as three years after their index date. Exceptions to this three-year period were when patients died before they reached three years of follow-up or when data were no longer available from the RAMQ.

Definitions of outcome variables

The primary outcomes were health service use events, including emergency department (ED) visits, inpatient hospitalizations, day procedures in an acute care hospital setting, physician visits, and first-line TB drug and other drug prescriptions dispensed. Health service use events were identified using the following definitions. An ED visit was identified from the physician billing records (where an ED location was specified). If ED-based claims were made on consecutive days for the same patient, they were counted as part of the same ED visit. This algorithm was previously validated in the RAMQ database, in a population of older patients who had ED visits

for any diagnosis and not ending in a hospital admission[168]. An acute care hospitalization was identified using Med-ECHO records with a Type of Care code specifying hospitalization. If two records were separated by one day (ie. the end date of one hospitalization record and the start date of a second hospitalization record were on consecutive days), this was coded as a transfer and counted as part of the same hospitalization event. Length of hospital stay was calculated as the number of days in-hospital, including the dates of admission and discharge. Lastly, hospital admissions from the ED were identified when an ED visit occurred on the same day or one day prior to a hospital admission date. When a hospital admission was from the ED, these events were counted separately (ie. one ED visit and one hospitalization, with hospital length-of-stay calculated based on the start date of the hospitalization). An in-hospital day procedure was identified using Med-ECHO records with a Type of Care code specifying hospital day procedure. Physician visits and procedures were identified in physician billing records. For counting the number of contacts with physicians, multiple physician billing records for the same individual, by the same physician, on the same date were counted as one physician billing event. First-line TB drug prescriptions dispensed were identified in records of drugs dispensed from community pharmacies, using DIN or AHFS codes. For counting the number of drug dispensations (ie. visits to pharmacists), multiple drugs dispensed on the same date by the same pharmacist were counted as one dispensation event.

Additional outcomes were the estimated direct health system costs of health resource use. Direct costs for each health service outcome above were estimated using costs paid by RAMQ as reported in the RAMQ database, or where not available (ie. for hospital stays, ED visits, and hospital day procedures), average costs and fee schedules were used. All costs were reported in 2011 Canadian dollars, with adjustment for inflation using the consumer price index (CPI)[169]. Health system costs for hospitalizations were estimated based on the number of days of each stay multiplied by the average per diem cost for Quebec residents in Montreal McGill University Health Centre (MUHC) hospitals[170]. Costs for ED visits and hospital day procedures were estimated based on the RAMQ billing costs for uninsured patients[171]. Costs for physician visits and procedures were calculated using the actual physician billed amounts paid by RAMQ. Costs for physician billing events were calculated as the sum of all costs for a patient as billed by the same physician on the same date. Costs for drug dispensations were calculated including all drug and pharmacist dispensing costs that were paid by RAMQ.

Definitions of patient demographic and co-morbidity variables

Variables were extracted from the RAMQ database at each patient's index date including year of index date, age group (0-19, 20-34, 35-49, 50-64, 65-79, and ≥80 years), sex, health region of residence, and pre-treatment co-morbidities. As a proxy measure of socioeconomic status (SES), we identified individuals who were registered in the year before the index date to receive RAMQ drug plan coverage due to unemployment or welfare status, refugee status, or maximum coverage through the guaranteed income supplement (GIS) for individuals aged 65 years and older. Both social assistance drug plan coverage and GIS supplements have been used in prior Canadian research to indicate SES [172, 173]. We grouped health regions of residence into two categories (central/peripheral and intermediate/remote), based on the Quebec Ministry of Health method of stratifying health regions according to distance to university network hospitals[174]. TB-specific co-morbidities were identified that are well-known to be associated with TB re-activation (cancer, diabetes, HIV/AIDS, end-stage renal disease, substance abuse, solid organ transplantation, silicosis, malnutrition, and use of TNF-alpha inhibitors[35]). Individuals were identified as having one of these specific co-morbidities at the time of the index date if an ICD-9/10 code for the co-morbid condition was present in one hospital record or in two or more physician billing records within the year before the index date. This algorithm has been shown previously to identify co-morbidities in health administrative databases[175]. We used a one-year time window in order to identify co-morbidities that were more likely active at the time of TB diagnosis, however, it is possible that this could have underestimated co-morbidity prevalence. An individual was also identified as being HIV-infected if one or more anti-retroviral drugs had been prescribed during this period for more than 1 month (with one month selected as the cut-off to exclude individuals taking HIV prophylaxis treatment). Individuals were identified as using TNF-alpha inhibitors if they had one or more prescription of any duration dispensed from a community pharmacy in the year prior.

Statistical analysis

We calculated descriptive statistics (counts and frequencies, medians and interquartile ranges) of characteristics of active TB patients and matched controls, identified at the index date for each

patient. We compared frequencies of characteristics between active TB patients and matched controls, using chi-square tests for categorical variables. We compared mean treatment period duration between active TB patients and controls using t-tests. In order to compare health service use costs in the months prior to and after the index date, total direct health system costs were summed for each 30-day period (roughly a 1 month period) over the study follow-up period. Total direct costs included the sum of costs for hospitalizations, ED visits, hospital day procedures, physician billing for visits and procedures, TB drugs dispensed, and other drugs dispensed. Monthly mean costs were plotted across the study period (36 months before and after the index date) as the mean total direct costs/30 days, both for active TB patients and controls. We first evaluated the timing of changes in mean monthly health service use costs for active TB patients over the follow-up period through visual inspection of the plot. We also used univariable gamma regression to model mean monthly costs for active TB patients, using a generalized linear model with a gamma distribution, log link, and autoregressive correlation structure. We used this model to identify the month where the cost ratio significantly diverged from one.

Patterns of health service use for active TB cases and matched controls were further compared for the combined time period leading up to the index date (within 6 months before the index date) and during the TB treatment period, stratified by case type and health service type. The starting time for this analysis was taken to be 6 months prior to the index date in order to incorporate the health service use and costs associated with the full episode of diagnostic delay and making the TB diagnosis. We used this time window based on the monthly mean data plot and gamma regression model identifying a statistically significant increase in health service use 6 months before the index date. Previous studies have also identified a significant rise in health service use in the 6 months before start of TB diagnosis[176]. Descriptive statistics included the proportion of patients with one or more events during this TB diagnostic and treatment episode, and of patients with any events, the mean (sd) and median (IQR) number of events per patient, stratified by event type. For hospitalizations, the mean and median hospital lengths of stay and proportion of hospitalizations with admissions from the ED were calculated. The proportions of hospitalizations, ED visits, hospital procedures, and physician billing records with an ICD TB diagnostic code were also calculated.

Total TB-attributable costs for active TB patients were estimated as the difference in means between sets of active TB patients and their matched controls. For sets with 2 matched controls, the mean was first calculated for each pair, then the difference taken between the active TB case and this control mean. P-values and 95% confidence intervals of the mean cost difference between matched sets were calculated using paired t-tests. Sensitivity analyses included limiting the calculation of TB-attributable costs from one month before the index date to the end of the treatment period, limiting the calculation of TB-attributable costs to those events with a TB diagnostic code or TB drug code only, and limiting the calculation of costs from patients with no TB-related co-morbidities.

4.3 Results

We initially extracted a dataset from the RAMQ database consisting of 23,220 individuals with one or more first-line TB drugs dispensed for the first time between January 1998 and December 2007. The application of decision rules to identify active TB patients is summarized in Figure 2. Supplemental tables about setting up the study cohort of active TB patients are included in Appendix 5.

A total of 1776 active TB patients and 3467 controls were included in the matched cohort study (Table 6). Active TB treatment was initiated by a total of 737 physicians within 18 health regions, with an average of 18.1 patients (range 1-284) per treating physician (data not shown). Slightly more than half of all active TB patients were male, and one-sixth resided in intermediate/remote health regions (Table 6). Co-morbidity levels were higher in active TB patients compared to controls (with a higher proportion of cases having any TB-related risk factors), and a higher proportion of active TB patients had a low socioeconomic status (Table 6). Absolute numbers of active TB patients decreased over the study period (Table 6). Of the 1776 active TB patients identified, 1750 patients were matched to one or more controls; unmatched active TB patients (n=26) were more likely to be older, female, and living in a remote health region than active TB patients who were successfully matched to one or more controls (n=1750) (data not shown).

The highest mean RAMQ-paid costs of health service use by all active TB patients occurred in the month before the index date, with monthly mean costs 26.6 times higher (95%CI: 18.0-39.3) than they had been twelve months before the index date (see Figure 3 for a summary). Costs began to rise significantly up to eight months before the index date in active TB patients, with mean monthly costs 3.55 times higher (95%CI=1.83-6.89) at six months before the index date compared to 12 months before the index date, and consistently increased until the first month after the index date (see Figure 3 for a summary). Costs of active TB patients remained significantly elevated up to 20 months after the index date (cost ratio=2.57, 95%CI: 1.46-4.53) compared to 12 months before the index date (see Figure 3).

Hospitalizations accounted for the majority of mean per-patient direct costs for both active TB patients (accounting for roughly 80% of costs) and matched controls (62% of costs), followed by physician billing and other drug dispensations (Table 7). More than half of all active TB patients had at least one hospitalization (61.2%) and ED visit (67.4%) within the six months prior to and during TB treatment; by contrast only 9.6% of controls had a hospitalization and 24.0% an ED visit (Table 7). A primary or secondary TB diagnostic code was reported for 40% of all hospitalizations of active TB patients, while no hospitalizations of controls had a TB diagnostic code (Table 7). Approximately half of all hospitalizations of both active TB patients and controls resulted from an admission through the ED (data not shown). Among patients with any ED visits, 68.8% had more than one visit during this period, and 7.8% had more than five ED visits (data not shown). Roughly two-thirds (68.8%) of hospitalizations and ED visits (63.5%) of active TB patients over this period occurred within the month before the index date (data not shown).

Total mean direct costs for active TB patients and matched control patients (including during the TB treatment period and in the six months before the index date) were estimated to be $31323.1 (standard deviation=46033.5) and $3181.2 (12679.7), respectively (Table 7). After subtracting costs of matched controls from active TB patients within matched sets only (Table 8), the total mean estimated RAMQ-paid cost for an active TB patient was $28048.6 (95% CI: $25896.0, 30201.2). Limiting the analysis to patients with no TB-related co-morbidities in the past year gave a total mean cost difference of $18323.1(95%CI: 16343.1, 20303.2). Limiting the analysis to events with a TB diagnostic code or TB drug code only gave a total mean cost difference of $14599.3 (13266.1, 15932.5). Limiting the analysis to the period from one month before the

index date to the end of the treatment period gave a total mean cost difference of $16083.5 ($14711.0, 17456.1) between active TB patients and controls (Table 8).

4.4 Discussion

This study found high rates and direct costs of health service use among active TB patients compared to matched controls. Total direct costs for health service use during the period of active TB diagnosis and treatment were estimated to be approximately $28,000 (in 2011 CDN dollars), with inpatient hospitalizations accounting for the majority of costs. Mean direct health service use costs of active TB cases were approximately twenty-seven times higher in the month before treatment started than they had been twelve months prior.

The finding of a marked increase in health service use in the months leading up to the start of treatment of active TB is consistent with other studies. Several studies, particularly, have documented increasing ED use in the months leading up to TB treatment. In the UK, almost one-third of TB patients attended the ED in the 6 months before their TB diagnosis [33]. In the one Canadian study to investigate ED use by active TB patients prior to diagnosis, 47% of TB patients attended the ED at least once in the 6 months before diagnosis, with ED use increasing the closer the patient was to the time of diagnosis (with the majority of visits occurring in the month immediately before diagnosis)[176]. Similarly in our study, more than half of TB patients visited the ED in the month before the index date, and some patients had multiple ED visits. As well, half of all patients are admitted to the hospital via the ED. The finding of frequent ED use pre-TB treatment has implications both for earlier diagnosis and for resource use, ie. if patients had active TB when they visited the ED but the diagnosis was missed and subsequently delayed. This has been shown previously in a Canadian study, where time spent in EDs prior to diagnosis accounted for almost all risk of nosocomial transmission and the majority of healthcare related costs pre-diagnosis[176].

Additionally, our estimate that more than half of all TB patients are hospitalized at least once prior to and during the TB treatment period is comparable to results reported in other studies[122, 160]. As well, the finding that hospitalizations accounted for the largest portion of direct healthcare costs parallels previously published TB cost-of-illness studies [116, 122]. Hospitalization may be

required in order to isolate some patients while they are infectious[177], however, acute inpatient care is costly and some hospitalizations for active TB may be unnecessary[124, 177]. In some cases, hospitalization may be the result of patients presenting late with more advanced disease[160]. We did not have clinical variables in our health administrative database, so we were unable to examine disease severity at the time of presentation to hospital or other factors associated with decision to hospitalize, and subsequent duration of hospital stay. Studies incorporating clinical and health service use data are needed for better understanding of factors associated with hospitalization, re-hospitalization, and extended hospital stays of TB patients.

The use of population-level data from the provincial health administrative database was a strength of this study. Given that most Quebec residents are covered by the RAMQ and that all TB drugs are paid for by RAMQ, this database thus provided a large sample size with near complete capture of health service use for treated active TB patients in the entire province. The use of longitudinal datasets further allowed for trends in health service use to be evaluated over time, both for changes over calendar time and for changes in the rates of health service use before and after the start of TB treatment.

There are also limitations of this study. First, it is possible that some active TB cases were misclassified, or were missed altogether. Since patients treated exclusively in-hospital would likely have been more severe cases, rates of health service use by active TB patients thus may have been underestimated since these patients were not in our cohort. This study would also have underestimated mortality rates if these patients died while undergoing treatment solely in-hospital. As well, we would not have captured cases who were not registered in the RAMQ medical services plan (eg. refugees covered by the federal insurance program, or patients who held visitor or working visa status with private health insurance). Second, while use of health administrative databases provided detailed information about major components of health service use paid for by the RAMQ, it did not capture all health service use. For example, visits to salaried physicians, psychologists, nurses, and other allied health workers, as well as work by public health personnel (eg. contact tracing activities) are not included in the RAMQ databases. We would thus have underestimated these costs. However, in Quebec, the majority of physicians with direct patient care roles work under a fee-for-service model, thus we would not have expected this to underestimate costs markedly. Further, we did not account for more resource-

intensive stays in-hospital (eg. stays in an ICU), extended ED stays, or more resource intensive hospital day surgeries (ie. requiring the services of an anaesthesiologist and nursing care). It is thus possible that some costs were underestimated.

Third, we attributed all excess health service use and costs among active TB patients to TB itself. While it is likely that TB is the major contributing factor to health service use, particularly around the time of diagnosis and initial treatment, it is possible that other co-morbidities may account for some of the observed excess service use. We also reported all health service use costs in the 6 months leading up to the index date, but this may have overestimated the length of the diagnostic delay period (ie. 'worst-case scenario'). As sensitivity analyses, we limited our calculation of health service use costs to those events with a TB diagnostic code or TB drug, which reduced our calculation of mean costs quite markedly. However, TB diagnostic codes are shown to have poor accuracy to identify TB, particularly among ambulatory populations (Chapter 3), thus limiting costs to TB diagnostic codes only would be expected to underestimate costs (ie. 'best-case scenario'). Lastly, we did not account for censoring of active TB costs. Studies have found that ignoring censoring in calculation of mean cost estimates can lead to an underestimate of mean total costs, since any costs incurred beyond the point of censoring are ignored[178]. However, we had a long follow-up period (up to 3 years), and there were few patients who were right-censored at the end of follow-up. Thus, it is unlikely that censoring would have led to significant underestimation of mean diagnosis and treatment costs.

In conclusion, this study found high rates and costs of health service use among active TB patients in the months leading up to treatment initiation and during TB treatment. The majority of direct healthcare costs were associated with hospitalizations. More research work is needed to understand which patients are hospitalized, and how different co-morbidities impact the costs of treating active TB patients. Future studies should investigate more detailed predictors and timing of health service use among active TB patients to better understand patient trajectories through the healthcare system. Future costing studies should investigate the impacts of longer-term active TB-related disability on disease costs, and provide more comprehensive direct and indirect cost estimates.

Table 5: Decision rules applied to RAMQ dataset to identify active TB and LTBI cohorts

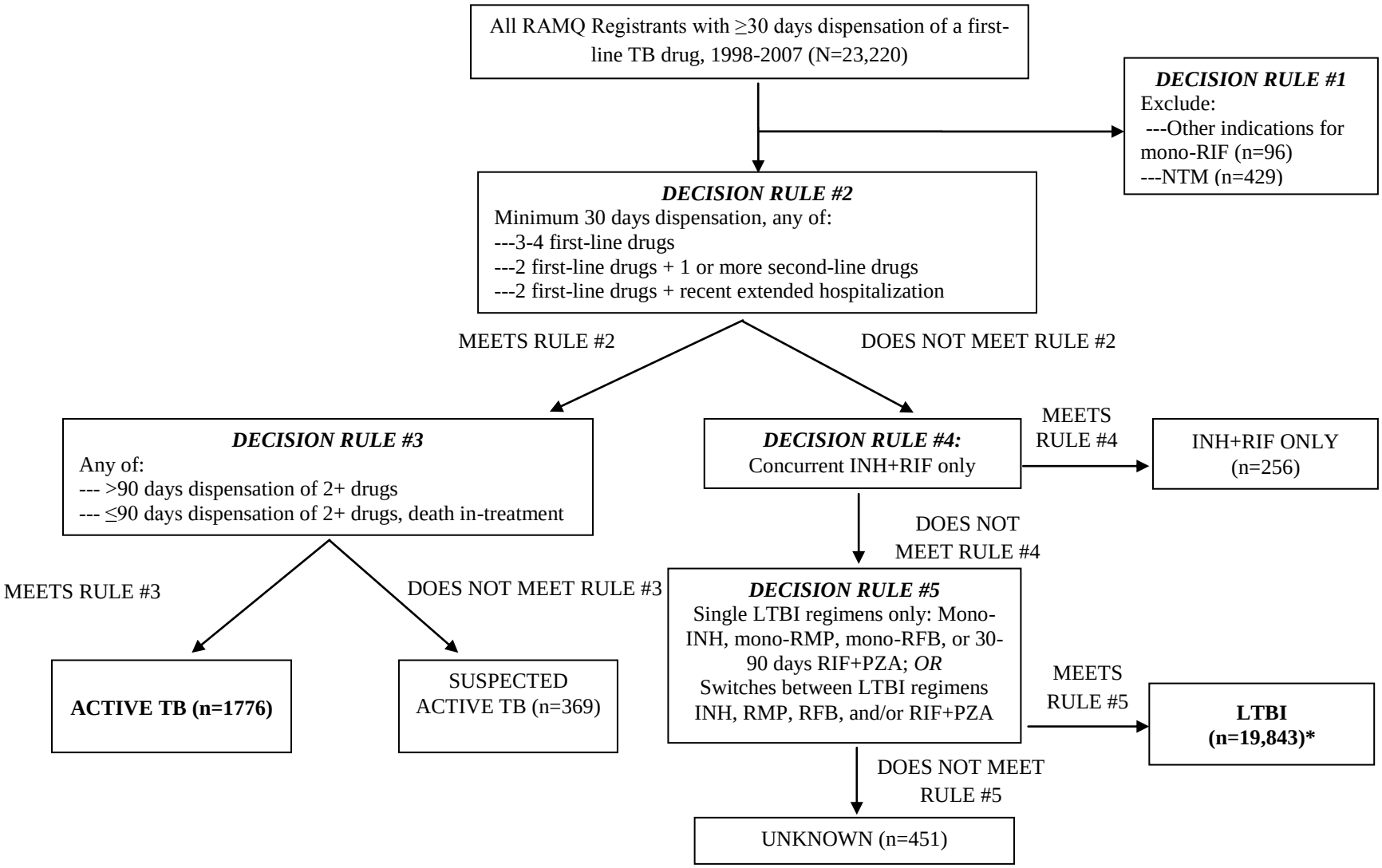
Rule #	Objective	Algorithm	
1	Exclude cases of NTM and other indications for mono-RIF	**NTM**: Dispensed at least 30 days of concurrent RIF and/or EMB with a macrolide.	
		Other RIF indications: Mono-RIF only AND ≥1 hospital discharge diagnoses or ≥2 physician billing record diagnoses indicative of other RIF indications* within 15 days before or 15 days after index date	
2	Identify probable active TB based on pattern of drugs dispensed	Dispensed at least 30 days of concurrent: ≥3 first-line TB drugs; OR 2 first-line TB drugs + 1 or more second-line TB drugs; OR 2 first-line TB drugs + hospitalization ending ≤15 days before index and for a stay of ≥ 60 days AND	
3	Differentiate active TB from suspected active TB based on treatment duration	**Active TB:**	Dispensed >90 days of multi-TB drug treatment, OR ≤90 days + death during treatment
		Suspected Active TB†:	Dispensed ≤90 days of multi-TB drug treatment (no death and no hospitalization ending ≤15 days before index and for a stay of ≥ 60 days)
4	Identify patients with concurrent INH+RIF	**INH+RIF only:** Dispensed at least 30 days of concurrent INH+RIF AND <30 days of mono-drug treatment (INH or RIF)	
5	Identify LTBI patients	**LTBI:** Dispensed at least 30 days of mono-treatment (INH or RIF), OR 30-90 days concurrent RIF+PZA; OR switch between LTBI regimens (ie. start second regimen ≥7 days after first regimen, with permanent discontinuation of first regimen)	
6	Classify other drug patterns as unknown	**Unknown:** All other regimens	

Abbreviations: RIF=Rifampin/ rifabutin; NTM=non-tuberculosis mycobacteria; LTBI=latent tuberculosis infection; INH=isoniazid

*Other RIF indications included osteomyelitis, multidrug resistant Staphylococcus aureus (MRSA), leprosy, brucellosis (see Appendix 3 for list of ICD9/10 codes)

†Suspected active TB=considered to probably have active TB and treatment initiated, which is later ruled out

Figure 2: Application of decision rules to identify active TB and LTBI cohorts in the RAMQ extraction dataset



Abbreviations: RIF=rifampin/rifabutin; RMP=rifampin; RFB=rifabutin; INH=isoniazid; PZA=pyrazinamide; LTBI=latent TB infection

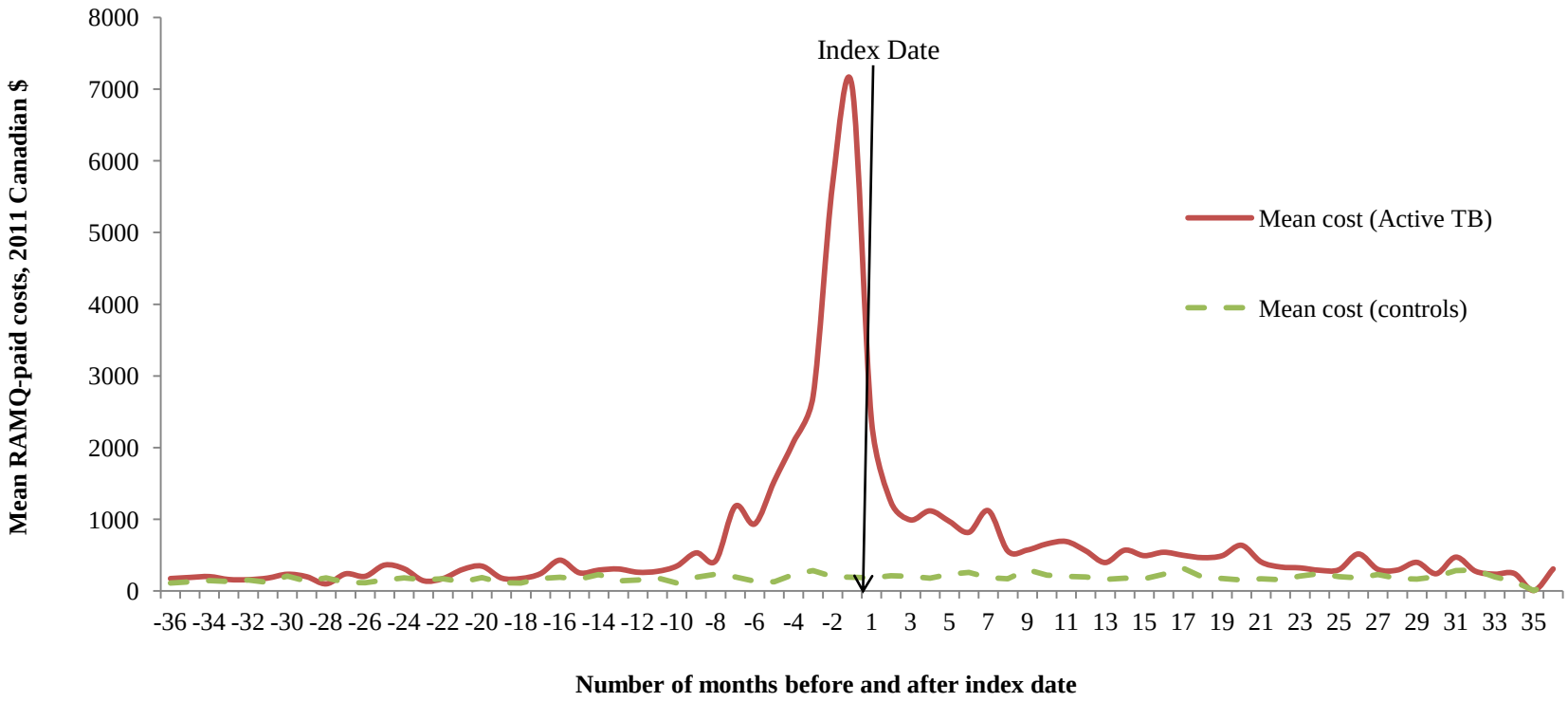
** Includes 18354 patients initially dispensed INH, 1419 RMP, 59 RIF+PZA, and 11 RFB*

Table 6: Patient characteristics at the index date and length of TB treatment period, active TB patients and matched control patients*, Quebec RAMQ provincial health administrative database, 1998-2007

	Active TB N=1776	Controls, N=3467	p-value
Patient characteristics at index date†			
Sex, male, n (%)	950 (53.5)	1854 (53.5)	0.99
Age group in years, n (%)			
0-19	75 (4.2)	147 (4.2)	1.00
20-34	329 (18.5)	653 (18.8)	
35-49	432 (24.3)	847 (24.4)	
50-64	337 (19.0)	662 (19.1)	
65-79	411 (23.2)	789 (22.8)	
80+	192 (10.8)	369 (10.6)	
Health region of residence, n (%)			
Intermediate/Remote	252 (14.3)	469 (13.5)	0.46
Low individual SES, n (%)			
Yes	508 (28.6)	524 (15.1)	<0.0001
TB-related co-morbidities, n (%)			
Cancer	334 (18.8)	148 (4.3)	
Diabetes	172 (9.7)	206 (5.9)	
HIV/AIDS	61 (3.4)	4 (0.1)	
Renal failure	75 (4.2)	34 (1.0)	
Substance abuse	96 (5.4)	46 (1.3)	
Solid organ transplant	20 (1.1)	6 (0.2)	
Silicosis	15 (0.8)	1 (<0.1)	
Malnutrition	45 (2.5)	5 (0.1)	
TNF-alpha inhibitors	3 (0.2)	0 (0)	
Any TB-related co-morbidities, n (%)	618 (34.8)	394 (11.4)	<0.0001
Year of treatment start, n (%)			
2007	142 (8.0)	279 (8.1)	1.00
2006	139 (7.8)	267 (7.7)	
2005	156 (8.9)	302 (8.7)	
2004	142 (8.0)	277 (8.0)	
2003	147 (8.3)	286 (8.3)	
2002	190 (10.7)	376 (10.9)	
2001	202 (11.4)	394 (11.7)	
2000	207 (11.4)	394 (11.4)	
1999	229 (12.9)	447 (12.9)	
1998	222 (12.5)	434 (12.5)	
Length of TB treatment period, in days‡			
Mean (sd)	304.7 (155.6)	303.7 (155.4)	0.84
Median (IQR)	250 (211-351.5)	248 (211-349)	
# (%) dying in TB treatment period	67 (3.8)	0	

Abbreviations: sd=standard deviation; IQR=interquartile range. Missing data: health region (n=59).
*Controls were patients with no first-line TB drugs and matched to active TB patients at a ratio of 2:1 by 5-year age group, sex, postal code area (first 3 digits of postal code), at the index date of the active TB patient
† Index date=first date with a TB drug dispensed from a community pharmacy
‡Length of treatment period = time period between index date to 30 days after last date with a TB drug dispensed. Time period was extended by 30 days to account for possible overlapping of dispensation records.

Figure 3: Estimated total mean health resource costs paid by RAMQ for active TB patients* and control patients†, stratified by number of months before and after index date, Quebec‡§



*Patients starting active TB treatment between 1998-2007
† Controls were patients with no first-line TB drugs and matched to active TB patients at a ratio of 2:1 by 5-year age group, sex, and postal code area (first 3 digits of postal code), at the index date of the active TB patient
‡Index date=start date of first drug dispensation record in the RAMQ database for a first-line TB drug
§Costs reported in 2011 Canadian dollars (rounded to the nearest dollar). Estimated total RAMQ-paid costs= sum of hospitalizations+ emergency department (ED) visits+ hospital day procedures+ physician billing + drugs dispensed. Unit costs assigned to hospitalizations ($1308/day), ED visits ($183.08/visit) and hospital day procedure ($183.08). Actual billed costs used for physician billing and drugs dispensed, adjusted to 2011 dollars using the Consumer Price Index. Drug costs include all amounts paid by RAMQ for drug dispensation, including sum of drug cost and pharmacist dispensing fee, minus deductable and co-pay by patient

Table 7: Patterns of health service use by active TB patients and matched control* patients in Quebec, from 6 months before index date to end of TB treatment period, RAMQ provincial health administrative database, 1998-2007

Health service utilization and estimated RAMQ paid costs, per component†§	Active TB patients (N=1776)	Controls (N=3467)
Hospitalizations		
Mean cost, per patient starting treatment (sd)	$24854.9 (41754.9)	$1949.7 (11533.7)
Total number of hospitalizations	1819	429
Patients with any event, n (%)	1088 (61.2%)	334 (9.6%)
Mean # of hospitalizations/patient (sd) ‡	1.7 (1.2)	1.3 (0.7)
Median (IQR), max ‡	1 (1-2), 11	1 (1-1), 6
# days in-hospital, per stay ‡		
Mean (sd)	17.5 (21.9)	11.4 (18.6)
Median (IQR), max	11 (5-21), 182	5 (2-12), 151
Hospitalizations with a TB code, n (%)	755 (41.5%)	0
Emergency department visits (ED)		
Mean cost, per patient starting treatment (sd)	$302.9 (41754.9)	$77.5 (183.4)
Total number of ED visits	2942	1471
Patients with any ED visit, n (%)	1198 (67.4%)	831 (24.0%)
Mean # of ED visits /patient (sd) ‡	2.5 (2.3)	1.8 (1.4)
Median (IQR) , max ‡	2 (1-3), 38	1 (1-2), 12
ED visits with a TB code, n (%)	302 (10.3%)	0
Hospital day procedures		
Mean cost, per patient starting treatment (sd)	$40.1 (101.5)	$10.2 (50.1)
Total number of procedures	389	194
Patients with any event, n (%)	293 (16.5%)	164 (4.7%)
Mean # of events/patient (sd) ‡	1.3 (0.6)	1.2 (0.5)
Median (IQR), max ‡	1 (1-2), 5	1 (1-1), 4
Procedures with a TB code, n (%)	83 (21.3%)	0
Physician billing		
Mean cost, per patient starting treatment (sd)	$2983.4 (3186.9)	$529.4 (1007.2)
Total number of physician contacts events	103387	34343
Patients with any event, n (%)	1773 (99.8%)	2765 (79.8%)
Mean # of events/patient (sd) ‡	58.3 (62.7)	12.4 (17.1)
Median (IQR), max ‡	39 (22-70), 794	8 (3-15), 212
Billing events with a TB code, n (%)	4847 (4.7%)	1 (<0.1%)
First-line TB drug dispensations		
Mean cost, per patient starting treatment (sd)	$982.7 (644.3)	0
Total number of TB drug dispensations	19910	0
Patients with any event, n (%)	1776 (100.0%)	0
Mean # of events/patient (sd) ‡	11.2 (13.9)	-
Median (IQR), max ‡	8 (6-12), 436	-
Other drugs dispensations		
Mean cost, per patient starting treatment (sd)	$2159.0 (5813.1)	$614.4 (1686.1)
Total number of other drug dispensations	37165	30754
Patients with any event, n (%)	1677 (94.4%)	1614 (46.6%)
Mean # of events/patient (sd) ‡	22.2 (27.3)	19.1 (21.6)
Median (IQR), max ‡	14 (7-28), 550	14 (5-26), 324
Total RAMQ-paid costs, mean (sd)	$31323.1 (46033.5)	$3181.2 (12679.7)
Total RAMQ-paid costs, median (IQR)	$13660.8 (2959.9, 40685.3)	$391.6 (60.1, 1544.6)

Abbreviations: sd=standard deviation; IQR=interquartile range

*Controls were patients with no first-line TB drugs and matched to active TB patients at a ratio of 2:1 at the index date, by age group, sex, postal code area (first 3 digits of postal code)

†TB treatment period=from the index date (start date of first prescription drug dispensation record in the RAMQ database for a first-line TB drug) to 30 days after the last TB drug was dispensed

‡Among patients with one or more events
§Costs reported in 2011 Canadian dollars
‖ Number of days at-risk during study follow-up period: 967,318 (active TB cases); 1,856,571 (controls)

Table 8: Sensitivity analyses of mean total cost estimates, RAMQ-paid health service use for active TB patients and matched controls*, Quebec 1998-2007, limited to matched sets†

	Active TB patients, mean total costs (sd)	Matched controls, mean total costs (sd)	Mean difference in costs (95%CI), active TB - controls
All patients (n=1750 matched sets) ‡	$31,198.3 (45981.0)	$3,174.8 (9031.9)	$28,023.6 (25807.9, 30176.2)
Patients with no co-morbidities (n=1123 matched sets) ‡§	$20,108.7 (33650.6)	$1,785.5 (6437.2)	$18,323.1 (16343.1, 20303.2)
TB diagnostic codes or TB drugs only (n=1750 matched sets) ‡	$14,599.4 (28436.5)	$0.06 (2.49)	$14,599.3 (13266.1, 15932.5)
Limiting to 1 month pre-index date to end of TB treatment period (n=1750 matched sets)	$18,298.8 (28995.0)	$2,215.2 (7475.1)	$16,083.5 (14711.0, 17456.1)

*Matched on 5-year age group, sex, and postal area, at the index date of active TB case.

†Analyses limited to sets of active TB cases with one or more matched controls. Costs reported in 2011 Canadian dollars.

‡Within 6 months before index date to 30 days after last TB drug dispensed

§Co-morbidities defined as any of cancer, diabetes, HIV, renal, substance abuse, solid organ transplant, silicosis, malnutrition, or dispensation of TNF-alpha inhibitors

PREFACE TO CHAPTER 5 (MANUSCRIPT #3)

In the previous chapter, I applied a series of drug dispensation-based decision rules to the Quebec provincial RAMQ health administrative database in order to identify a cohort of active TB patients. I then described the patterns and direct costs of health service use by these active TB patients, and estimated TB-related costs. Results suggested that hospitalizations accounted for the majority of costs for diagnosing and treating active TB disease, corroborating findings from other jurisdictions and countries. However, evaluation of predictors of hospitalization was limited in the RAMQ database due to limited availability of clinical and demographic covariates.

To better understand factors predictive of hospitalizations during TB diagnosis and treatment in this population, in my next manuscript (Chapter 5), I evaluate more detailed clinical, social, and demographic predictors of hospitalization and hospital length of stay of patients with active TB. This study involves analysis of data from a comprehensive clinical database of patients with confirmed active TB over a ten-year period, in the largest Quebec health region (Montreal Island), accounting for two-thirds of all active TB patients in the province. This study provides additional insight into this key resource use of active TB patients.

CHAPTER 5: PREDICTORS OF HOSPITALIZATION DURING DIAGNOSIS AND TREATMENT OF ACTIVE TUBERCULOSIS PATIENTS IN MONTREAL, QUEBEC: A RETROSPECTIVE COHORT STUDY (MANUSCRIPT #3)

5.1 Introduction

The debate about hospitalization versus outpatient treatment for tuberculosis (TB) patients is not new[179]. Since the advent of antibiotics to treat TB and directly observed therapy for treatment delivery, TB is today generally considered an ambulatory disease[177]. However, inpatient hospitalization continues to be a treatment standard in many cases[124, 180]. Benefits of hospitalization include the ability to isolate patients while they are infectious, with the consequent reduction of transmission within the community. As well, patients with higher risk for complications and death may require hospitalization for medical stabilization before treatment as outpatients[177]. For some patients with challenges to outpatient treatment, such as being homeless or living in group settings, having psychiatric or substance abuse issues, or having difficulties with activities of daily living, extended inpatient treatment may be warranted to ensure completion of treatment[181, 182]. Some regions may also hospitalize patients because they do not have adequate resources to treat people in the community, ie. they have not made the necessary investments to set up systems required for outpatient directly observed therapy (DOT).

However, hospitalization increases the risk of nosocomial transmission to health care workers and vulnerable patients[183]. Many patients are diagnosed with TB after they are admitted to hospital, and delays in TB diagnosis among inpatients can further increase the risk of transmission in this vulnerable population[53, 55]. Hospitalizations for TB can also lead to psychological issues for patients associated with isolation and detention[177]. Lastly, there are also major cost implications for the decision to hospitalize[123, 124, 184]. Hospitalizations are generally found to be the largest direct cost component of TB case management, often accounting for more than 50% of treatment costs [116, 118-120, 122].

Increasing spending on TB prevention rather than care provision [122], including the targeting of prevention efforts towards those active TB patients most likely to be hospitalized [123], re-hospitalized[130], and with extended lengths of hospital stay[68, 130], and shifting the balance of

treatment from inpatient to outpatient care[124], have all been advocated as important ways to improve TB control program efficiency. Few studies, however, have examined factors associated with hospitalizations of TB patients, or factors associated with length of stay in-hospital once admitted. Better understanding of which patients are hospitalized during diagnosis and treatment of active TB will help health Canadian policy-makers and clinicians to more efficiently target prevention programs and plan resource utilization needs. Therefore, the objectives of the following study were to identify factors associated with hospitalization and length of hospital stay during diagnosis and treatment of active TB patients in the largest health region in Quebec (Montreal), using patient-level clinical and demographic data from a clinical research database. This study was part of a larger research project aimed at evaluating the cost-effectiveness of TB prevention programs.

5.2 Methods

Data source and study population

A retrospective cohort was identified of all individuals in the Montreal Health region with confirmed active TB, as notified to Montreal Public Health between January 1996 and May 2007. Data were extracted from the Montreal TB Cohort database, which was compiled retrospectively as part of a larger study to investigate treatment patterns and resource use of active TB patients in Montreal. To build the Montreal TB Cohort database, data were first extracted from the Montreal Public Health database (MADO or Maladies à déclaration obligatoire), to identify all confirmed cases of active TB. In Quebec, it is mandatory for all physicians and laboratories to report confirmed cases of active TB to the relevant public health authority within 48 hours of diagnosis[186]. Confirmed cases can include both laboratory-confirmed cases, as well as clinical cases diagnosed pre- or post-mortem, where there is evidence of active TB and treatment initiated but no culture results are available[186]. Reporting is required for all cases diagnosed in Canada, among Canadian citizens, permanent residents, or refugees; for temporary residents of Canada, reporting is only required if treatment is started in Canada[186].

Supplemental information on patients' clinical status, including drug resistance and contact investigations, was then extracted from the public health charts. Detailed information on co-

morbidities, hospitalization, and treatment was also extracted from medical charts at treating hospitals and clinics for each case. Data extraction from the public health and hospital charts was performed by trained research assistants using standardized data extraction forms. Given the mandatory requirement to report all TB cases in the province of Quebec, this is considered to be a virtually complete capture of all confirmed TB cases on the Island of Montreal (covering a catchment population of approximately two million people). Further, approximately two-thirds of TB cases in Quebec are reported on Montreal Island [186], thus the database includes the majority of active TB cases in the province for this time period.

Ethical approval for this study was obtained through the McGill University Health Centre Research Ethics Board (#BMB-06-023t).

Identifying outcome and predictor variables

The main outcomes were whether or not the individual had a TB-related hospitalization and the length (LOS) of hospitalizations. Hospitalizations were defined as admissions to an acute care hospital for one or more nights, and excluded emergency department visits for less than 24 hours, hospital day clinics, and day surgeries. Hospital transfers were identified when a hospital discharge and a new hospital admission date were on the same day or on the next day. When a hospital transfer was identified, these were not counted as separate hospitalization events, rather they were counted as one continuous hospitalization event. LOS was calculated for each continuous hospitalization as the difference between discharge and admission dates. We excluded hospitalizations missing admission or discharge dates (n=19).

The TB diagnosis date was identified as the start date of TB treatment, or when not available, the date of mandatory notification to the Montreal public health department. Hospitalizations were stratified into two types based on their timing: 1) an initial TB-related hospitalization was identified as any hospitalization starting within one month before or up to one month after the date of TB diagnosis, or a hospitalization where TB was diagnosed in-hospital; and 2) a hospitalization later during the treatment period was identified when a hospital admission occurred more than one month after the TB diagnosis date and while the patient was still undergoing TB treatment. It was hypothesized that factors associated with hospitalizations at the

diagnosis and initial treatment phase would differ from those of hospitalizations occurring later during treatment. A similar definition based on timing of hospitalizations was used in a previous study [118]. It was not possible to identify in these data whether TB was the primary cause or a contributing factor for the hospitalizations. However, it was assumed that if active TB was diagnosed, any hospitalization occurring in close proximity to the date of diagnosis would be associated with active TB (either to the disease itself, or to adverse TB drug-related toxicity or intolerance).

Demographic patient-level variables extracted from the database were age in years and sex. Also, RAMQ provincial health insurance registration, Aboriginal status, immigration details, and homeless status were extracted when noted in either public health records or clinical records (note: the validity of these data were not evaluated and are dependent on whether or not case workers noted these data within the patient's records). We stratified age into five groups (0-19, 20-34, 35-49, 50-64, ≥65). We stratified patients by place of birth into Canadian-born and foreign-born (in Canada 0-2 years, 3-14 years, and 15 or more years), based on previous literature indicating that rates of TB are highest within the first 2 years of arrival to Canada, followed by a decreasing trend with increasing time spent in Canada [187]. We further identified if a patient had immigrated from a high TB incidence country or a low-moderate TB incidence country[142].

Additional extracted factors included smoking history, drug and alcohol abuse history, if the patient was HIV co-infected, and TB clinical characteristics (smear and culture results, disease site, TB drug resistance patterns, if the patient had cavitary or miliary TB, and whether the patient had pulmonary and/or systemic symptoms at the time of diagnosis). Patient co-morbidities were extracted from notations in hospital and public health charts, and included whether the patient had diabetes, cancer, renal disease, HIV, substance abuse, liver disease or other conditions. When patients were hospitalized, we identified if the patient was reported as dying in-hospital, and if the hospital was a teaching hospital or non-teaching hospital. Teaching hospital status has been associated with extended LOS in previous studies.

Statistical analyses

We first calculated descriptive statistics of patient demographics, clinical characteristics, and prescribed treatment regimens of all active TB patients in our cohort, including frequencies, mean (standard deviation, sd) and median (interquartile range, IQR) duration of treatment (in days). We calculated the proportion of patients with TB-related hospitalizations, in total and stratified by timing of hospitalization, as well as the mean (sd) and median (IQR) LOS (in days). We further estimated the proportion of patients starting treatment in-hospital, and for these patients, we estimated the length of in-hospital diagnostic delay as the median (IQR) number of days after hospital admission when TB treatment was started.

We identified factors associated with an occurrence of a hospitalization by calculating univariable and multivariable odds ratios using logistic regression (SAS version 9.2, SAS Institute Inc, Cary, USA). We stratified models on the timing of hospitalizations based on the hypothesis that predictors would differ depending on proximity to TB diagnosis. We considered variables for inclusion in adjusted models using a backward selection procedure. We included variables in multivariable modeling if they reached a statistical significance level of $p<0.20$ and we selected our final models based on minimizing the AIC statistic. We assessed global model fit using the Hosmer-Lemeshow goodness-of-fit test.

We identified factors predictive of hospital LOS using univariable and multivariable Cox proportional hazards regression. Survival analysis allows for the analysis of skewed data with repeated events and time-varying covariates while accounting for censoring, and has been recommended for analysis of LOS data[188]. In this context, survival time is the duration of time spent in-hospital and the event is discharge from hospital. Patients were censored when they died in-hospital. Given that some patients were transferred between hospitals as part of the same continuous hospitalization, we included hospital type in the model as a time-dependent covariate (see Appendix 5 for a summary of the data set-up). Since some patients had multiple separate hospitalizations (ie. repeated events), we used a conditional counting process model whereby each hospitalization was assigned to a separate stratum and the time scale was time since study entry[189] (ie. stratified according to whether the hospitalization was the first or second hospitalization, and including up to 2 separate hospitalizations per patient). This allowed the baseline hazard to differ depending on whether it was the patient's first or second hospitalization[189]. We used a robust sandwich variance estimator for estimating standard errors.

We tested the proportional hazards assumption that the hazard ratio was constant over time using log-rank tests to compare survival curves for each variable included in the modeling, and by visually inspecting log-negative-log plots of survival. When there was strong evidence that proportional hazards assumptions did not hold (particularly when lines crossed in the log-log plot), we included an interaction term in the model of the variable multiplied by time. We considered variables for inclusion in adjusted models using a backward selection procedure. We included variables in multivariable modeling if they reached a statistical significance level of $p<0.20$ and we selected our final models based on minimizing the AIC statistic.

5.3 Results

Characteristics of active TB patients

As summarized in Table 9, there were 1852 patients with confirmed active TB reported to Montreal Public Health between January 1996 and May 2007. Slightly more than half of the patients were male, with a median age of 44.0 (20.8) years (range from 0 to 95 years). Most patients were reported to be registered in the provincial health insurance RAMQ plan, and were foreign-born (80.5%, with slightly more than one-quarter having arrived to Canada within 2 years before the TB notification date). Few patients were homeless, roughly one-quarter were current or past smokers, and almost one-sixth of patients reported past or current substance abuse (Table 9). Concomitant HIV infection was reported in 7.9% of patients. Approximately half of patients had one or more co-morbidities (Table 9).

Most patients had pulmonary TB disease, of which one-third were smear-positive (Table 10). Most patients presented with some pulmonary TB-related symptoms, while close to half presented with systemic-related symptoms. Few cases were TB drug resistant:6.6% were mono-resistant and 1.8% were multi- or poly-drug resistant (note: multi-resistant TB defined as resistance to both INH and RMP, and poly-drug resistant TB defined as resistance to two or more TB drugs, other than the specific combination of INH and RMP). Most patients were cured (82%), while 6.9% died and the remainder moved, defaulted, or failed their TB treatment (Table 10). The average treatment duration for all cases was 250.1 days (std=146.0), with a median of 208 days (IQR=183-295). Treatment duration was longest for multi- and poly-drug resistant

cases (mean 479.4 days, median 517 days), followed by mono-drug resistant cases (mean 309.9 days, median 344 days). (Table 10).

Further stratification of covariates by years since immigration suggested that recent immigrants (within the past 2 years) were on average younger and had less co-morbidity than Canadian-born active TB patients and foreign-born patients in Canada for 15 or more years, were more likely to have pulmonary TB that was smear-negative and less likely to be symptomatic at the time of presentation (Table 11).

Predictors of hospitalizations and hospital LOS

A total of 1001 patients (54.1%) had one or more hospitalizations initially or during treatment, with a mean LOS of 27.2 days (standard deviation=38.6) and a median LOS of 16.5 (8-29) days (Table 12). Most patients (approximately 88%) had only one hospitalization, while 12% had multiple hospitalizations. Roughly half of all patients had a hospitalization initially, while approximately one in ten had a hospitalization later during the treatment period (Table 12). Of the 167 people hospitalized more than one month after treatment start, 105 (62.9%) of these patients were re-hospitalized after an initial hospitalization. The median LOS of initial hospitalizations was 17.5 days (IQR=9-31) and of hospitalizations later during treatment was 13 days (IQR=6-22). Of patients starting treatment in-hospital (38.5%), the median time to starting treatment after being admitted was 4 days (IQR 2-8). A total of 40 patients were reported as dying in-hospital. The proportion of patients hospitalized, and the median length of stay for initial hospitalizations, did not change significantly over the study period (Figure 4).

Factors predictive of hospitalization are summarized in Table 13. In adjusted models, patients were more likely to be hospitalized initially if they were children (adjOR=2.52, 95%CI: 1.63-3.92), had HIV co-infection (adjOR=1.46, 95%CI=0.90-2.36), renal disease (adjOR=1.99, 95%CI=1.10-3.59), multiple co-morbidities (adjOR=3.56, 95%CI:2.50-5.07) or one co-morbidity (adjOR=1.43, 95%CI:1.08-1.89), had smear-positive pulmonary TB (adjOR=1.48, 95%CI:1.04-2.09), if they presented with cavitary TB (1.75, 95%CI: 1.28-2.40), military TB (3.53, 1.26-9.88), any pulmonary (adjOR=2.12, 95%CI: 1.44-3.11) or systemic (adjOR=3.55, 95%CI:2.82-4.46) TB-related symptoms, and if they had multi- or poly-TB drug resistance

(adjOR=6.98, 95%CI:2.65-18.30). Many of the factors associated with having a higher risk of hospitalization later during treatment were similar to those predictive of initial hospitalizations (ie. younger age, HIV, co-morbidities, miliary TB, systemic TB-related symptoms, and multi- or poly-drug resistant TB), while the effect estimates of pulmonary TB diagnosis and pulmonary symptoms were attenuated (Table 13).

The longest median lengths of initial hospital stays (Table 14) were observed in patients who were Aboriginal (36.5 days, IQR: 29-43), had renal disease (28 days, 11-60), were HIV-infected (27 days, 16-43), or had multi-or poly-drug resistance (23 days, 12-67). Patients who were aboriginal or homeless had the longest median LOS when hospitalized later during treatment (Table 14). Major factors predictive of longer initial LOS in adjusted models included having HIV, renal disease, pulmonary smear-positive TB, having pulmonary symptoms, multi- or poly-TB drug resistance, and being in a teaching hospital (Table 15). Increasing age had a varying effect on length of stay, ie. was associated with a reduced length of hospital stay in the early part of hospitalization, and with a longer length of hospital stay as the duration of hospital stay increased (Table 15). Factors predictive of increased length of stay when hospitalized later during treatment were similar (ie having HIV, renal disease, symptomatic disease, and multi- or poly-drug resistance); in contrast, having extra-pulmonary TB was associated with a longer LOS, and the changing effect of age was attenuated (Table 15).

5.4 Discussion

This study found that a high proportion of active TB patients in Montreal were hospitalized during diagnosis and treatment over this 10-year study period. Roughly half of all TB patients were hospitalized initially, while one in ten patients subsequently required admission more than one month after starting treatment. Canadian-born patients tended to be older and have more co-morbidity, with more severe TB disease at the time of diagnosis and with subsequent poorer treatment outcomes, compared to recent immigrants.

Treatment guidelines regarding admission criteria to hospital for active TB can vary between different jurisdictions. Despite this, the crude hospitalization rates and LOS in this study are comparable to reported rates in other US and Canadian studies. Hospitalization rates in US

studies have ranged from approximately 50% to 80% of all TB cases [68, 116, 118]. In one US study to differentiate initial and during-treatment hospitalizations, Taylor found that 49% of TB patients had a hospitalization for TB (45% initially and 8% during treatment), with a median LOS of 11 days[118]. A Canada-wide study using hospital discharge data estimated that 50.2% of patients were hospitalized with a TB diagnosis, with an average LOS of 20.6 days[122]. A recent study of culture-positive pulmonary TB patients in Montreal found that 44.6% of patients were hospitalized, with a median LOS of 17 days (IQR: 10-28)[190].

This study identified several population sub-groups with a higher probability of hospitalization and longer length of stay. First, the finding that being of younger age and older age, and having more co-morbidities, was associated with an increased hospitalization rate and longer LOS is similar to other studies of respiratory infectious diseases, and reflects those patients at highest risk of poor health outcomes[38, 39]. Second, it was noteworthy that having drug resistance was associated with a higher risk of hospitalization and longer LOS. This is similar to the US study by Taylor, which found that MDR-TB cases were almost 6 times more likely to be hospitalized during treatment than non-MDR patients, after adjustment for age, co-morbidities, and social marginalization-related factors[118]. In a small US study of hospitalized patients with MDR-TB, LOS ranged from 5 to 90 days, and hospitalization costs were about $90,000 higher than costs for other hospitalized TB patients[68]. This finding has potential implications for resource planning, given increasing rates of drug-resistant TB globally.

Third, we found some evidence that hospitalization rates among immigrants increased with longer time since immigration, with the lowest rates among recent immigrants (arrival to Canada within 2 years of diagnosis), and approaching rates of Canadian-born patients by 15 years post-arrival. Studies comparing active TB among recent immigrants to native-born patients in the US have similarly found that recent immigrants are more frequently asymptomatic[191] and less likely to be hospitalized. These findings may partly reflect a "healthy immigrant effect", whereby immigrants' health at the time of arrival is better than the Canadian-born population, an effect that tends to diminish as time spent in Canada increases[192]. Recent immigrant patients may also be less likely symptomatic due to diagnosis through active screening activities that target new immigrants (e.g. post-landing surveillance programs), compared to passive diagnosis through presentation of symptoms. This was suggested by our study, whereby TB patients who were

recent immigrants tended to be younger than Canadian-born TB patients, and were less likely to be smear-positive pulmonary TB, have co-morbidities, smoke, have a history of substance abuse, or die during treatment.

Lastly, previous studies have reported that socially marginalized TB patients, particularly those with substance abuse issues and who are homeless, have higher hospitalization rates and longer LOS[118, 128]. Few of our active TB cases were listed as being homeless, which was somewhat surprising given the urban setting and the higher frequencies of homelessness reported in other studies of TB patients (eg. Taylor found that homeless persons comprised 9.9% of the US study population aged 15 and older, and 15.9% of all hospitalization episodes[118]). Despite the low numbers of reported homeless patients in our study, there was some evidence for an increased hospitalization rate and longer LOS in homeless patients. Marks *et al* have argued that providing better access to medical care for early detection and treatment of TB in homeless patients can reduce hospital utilization[128]. Further studies should investigate the impact of factors associated with social marginalization on health service use in TB patients.

This study adds to our knowledge by providing data about patterns of hospitalization during the diagnosis and treatment of active TB, among patients in a large urban Canadian population. These data can be used by health planners to better capture the resource implications of active TB in different patient populations, and to target prevention programs to those at highest likelihood of being hospitalized if they develop active TB. Some hospitalizations may be preventable, for example, with improved communication between providers, proper care management, adherence to guidelines, and other evidence-based strategies[193]. This has been argued previously in TB patients: in a US study, for example, close to 40% of hospitalizations of active TB patients in New York City were considered likely to have been avoidable[177]. The authors suggested that physicians may be reluctant to treat patients at home when there are language or cultural barriers, or that they may be reluctant to discharge patients with a positive smear if they are not aware of how to manage a potentially infectious patient in their home[177]. Future studies should evaluate the impact of cultural barriers between physicians and patients on rates and patterns of health service use.

Strengths of this study include the virtually complete capture of all confirmed active TB cases in a large Quebec health region. The population of Montreal represents approximately two-thirds of all active TB cases in Quebec[186], thus this study captures a large proportion of active TB cases in the province. The combination of a medical chart review with public health records allowed investigation into the clinical and social determinants of hospitalization in the general population of active TB patients which are not typically available in public health charts or administrative data alone.

There are also limitations. First, these data were collected retrospectively from public health and hospital charts. While reporting of TB cases is mandatory in Canada, it is possible that recording of some details, such as co-morbidity and demographic information, may not be complete, or that some predictors of hospitalization or hospital length of stay were not measured. Further, while co-morbidity data are recorded in public health charts, it is possible that co-morbidity data would be reported in more detail within hospital charts. This could lead to some bias in identifying predictors of hospitalization, since documentation of co-morbidities would be associated with hospitalization. Additionally, we only had access to hospital records for Montreal area hospitals. It is possible that some patients were hospitalized in hospitals outside of Montreal, and as such, would not have been recorded in the study database, thus underestimating rates of hospitalization. Less than half of recent immigrants were registered in the RAMQ and it is possible that some of these patients, such as foreign students or temporary workers, would have returned to their home countries. However, hospitalization costs for active TB are generally covered by public health authorities, for individuals without other health care coverage, thus it is not likely that we would have greatly underestimated the hospitalization rate. We also could not assess whether hospitalizations were appropriate and did not identify the primary cause of hospitalization. TB is often associated with additional co-morbidities and it is possible that some of these hospitalizations were due to co-morbidities, rather than presentation of active TB symptoms (thus overestimating the TB-related hospitalization rate). This study also represents a predominantly urban population in Canada, and it is possible that these results will not be generalizable to other jurisdictions. Hospitalization rates for TB, for example, have been shown to vary based on whether TB patients were living in urban or rural areas in Manitoba[126].

In conclusion, we found a high rate of hospitalizations, many of which were prolonged, during diagnosis and treatment of patients with active TB in Montreal. Diagnostic delay due to low index of suspicion may lead to some patients presenting with more severe disease at this time of diagnosis. Further studies should investigate the impact of social marginalization, co-morbidities, drug resistance, and delayed diagnosis by healthcare providers on health service use by active TB patients.

Table 9: Active TB patient characteristics, Montreal Resource Cohort, with notification to Montreal Public Health between January 1996-May 2007, N=1852

TB case characteristics*	Number (%) of active TB cases	
	N	%
Patient demographics		
Sex- male	992	53.6
Age, in years (mean, sd)	44.0 (20.8)	
Age group		
0-19 years	143	7.7
20-34 years	602	32.5
35-49 years	455	24.6
50-64 years	256	13.8
65+ years	390	21.1
RAMQ health insurance number	1499	80.9
Country of birth		
Canada	317	17.1
Foreign-born, low/moderate TB incidence country	1112	60.0
Foreign-born, high TB incidence country	380	20.5
Immigration, years since arrival		
Canadian-born, Aboriginal	6	0.3
Canadian-born, non-Aboriginal	311	18.0
≤ 2 years	485	26.2
3-14 years	541	29.2
15 or more years	338	18.3
Immigrant, unknown year of arrival	43	2.3
Homeless	9	0.5
Patient co-morbidities		
Cancer	41	2.2
Diabetes	132	7.1
HIV status- known HIV+	146	7.9
Renal failure	105	5.7
Liver disease		
Substance abuse history	249	13.4
Number of co-morbidities[†]		
2 or more	412	22.3
1	446	24.1
0	994	53.7
Ever smoker	489	26.4
Year of treatment start		
2007 (to May)	45	2.4
2006	137	7.4
2005	133	7.2
2004	133	7.2
2003	174	9.4
2002	172	9.3
2001	159	8.6
2000	195	10.5
1999	168	9.1
1998	157	8.5
1997	187	10.1
1996	175	9.6
1995	17	0.9

Abbreviations: sd=standard deviation

*Missing data: sex (n=19), age (n=6), year of arrival to Canada (n=128)

†Co-morbidities include renal disease, liver disease, lung disease, diabetes, cancer, substance abuse, HIV infection, or other (as reported in public health or hospital records)

Table 10: Active TB clinical characteristics, with notification to Montreal Public Health between January 1996-May 2007, N=1852

	Number of active TB cases	
	n	%
Mycobacteriology and disease site		
Pulmonary, S+C+	604	32.6
Pulmonary, S+C-	15	0.8
Pulmonary, S- C+	504	27.2
Pulmonary, S- C-	121	6.5
Extra-pulmonary, C+	511	27.6
Extra-pulmonary, C-	52	2.8
Clinical and radiographic features of TB disease		
Miliary TB	35	1.9
Cavitary TB	336	18.1
Any pulmonary TB-related symptoms†	1530	82.6
Cough	953	51.5
Hemoptysis	200	10.8
Abnormal chest x-ray	1490	80.5
Any systemic TB-related symptoms‡	853	46.1
Weight loss	635	34.3
Fever	650	35.1
Fatigue	344	18.6
Night sweats	331	17.9
	Mean, days (sd)	Median, days (IQR)
Treatment duration, all cases	250.1 (146.0)	208 (183-295)
Treatment duration, by therapy outcome		
Cured (n=1518)	267.7 (131.7)	224 (185-305)
Defaulted (n=32)	100.8 (68.9)	93 (44-139)
Died (n=127)	97.3 (219.0)	153 (14.5-110.5)
Failed (n=2)	179.0 (33.9)	179 (155-203)
Moved (n=69)	129.2 (126.9)	96.5 (47-181)
Missing outcome data (n=104)	218.6 (155.9)	189 (78-312)
Treatment duration, by drug resistance status		
Multi- and poly-TB drug resistant (n=33) §	479.4 (235.9)	517 (283-592)
Mono-TB drug resistant (n=122) ‖	309.9 (131.2)	344 (212-376.5)
Pan-sensitive (n=1664)	239.8 (139.3)	200 (182-280)
Missing drug resistance data (n=33)	257.0 (162.6)	197 (182-269)

Abbreviations: sd=standard deviation

* Missing data: mycobacteriology (n=45), drug resistance (n=33), treatment outcome (n=104)

† Pulmonary TB-related symptoms: cough, hemoptysis, and abnormal chest x-ray

‡Systemic TB-related symptoms: weight loss, fever, fatigue, night sweats

§Includes INH+RMP resistant (n=18), INH+EMB resistant (n=10), INH+PZA resistant (n=4), and RMP+PZA resistant (n=1)

‖Includes mono-INH resistant cases (n=105), mono-RMP resistant (n=3) and mono-PZA resistant (n=14)

Table 11: Characteristics and hospitalization-related outcomes of confirmed active TB cases, stratified by foreign-born status – Montreal Resource Cohort, January 1996-May 2007

Characteristics of Active TB Patients*	Foreign-born, years since arrival to Canada						Canada-born		p-value
	0-2 (N=485)		3-14 (N=541)		15+ (N=338)		(N=317)		
	n	%	N	%	N	%	n	%	
Sex, male	281	(58.3)	275	(51.7)	172	(51.3)	172	(54.8)	0.22
Age group, in years									<0.01
0-19	51	(15.9)	35	(6.5)	1	(0.3)	50	(15.9)	
20-34	257	(53.1)	233	(43.2)	40	(11.8)	37	(11.8)	
35-49	111	(22.9)	172	(31.9)	80	(23.7)	53	(16.7)	
50-64	36	(7.4)	50	(9.3)	89	(26.3)	52	(16.6)	
65+	29	(6.0)	50	(9.3)	128	(37.9)	122	(38.9)	
RAMQ health insurance #	213	(43.9)	499	(92.2)	328	(97.0)	308	(97.2)	
Homeless	1	(0.2)	0	(0)	1	(0.3)	7	(2.2)	<0.01
Smoker									<0.01
Current	59	(12.2)	69	(12.8)	50	(14.8)	96	(30.3)	
Past	63	(6.4)	30	(5.6)	48	(14.2)	63	(19.9)	
Substance abuse history	27	(5.6)	56	(10.4)	51	(15.1)	98	(30.9)	<0.01
HIV	35	(7.2)	51	(9.4)	21	(6.2)	28	(8.8)	0.38
Number of co-morbidities †									<0.01
2 or more	53	(10.9)	78	(14.4)	104	(30.8)	130	(41.0)	
1	93	(19.2)	116	(21.4)	102	(30.2)	92	(29.0)	
TB diagnosis									<0.01
Pulmonary, S+	126	(26.8)	188	(35.4)	123	(37.2)	144	(46.9)	
Pulmonary, other	257	(54.6)	124	(23.4)	77	(23.3)	108	(35.2)	
Extra-pulmonary	88	(18.7)	219	(41.2)	131	(39.6)	55	(17.9)	
Any pulmonary symptoms ‡	435	(89.7)	403	(74.5)	273	(80.8)	291	(91.8)	<0.01
Any systemic symptoms §	166	(34.2)	276	(51.0)	183	(54.1)	162	(51.1)	<0.01
Multi- or poly-drug resistant	13	(2.7)	12	(2.3)	2	(0.6)	4	(1.3)	0.20
Treatment outcome									<0.01
Died	3	(0.7)	16	(3.1)	41	(13.1)	45	(14.5)	
Cured	421	(90.5)	465	(91.0)	263	(84.0)	246	(81.2)	
Defaulted/failed	7	(1.5)	10	(2.0)	4	(1.3)	9	(3.0)	
Moved	34	(7.3)	20	(3.9)	5	(1.6)	3	(1.0)	

Abbreviations: RAMQ= the Régie de l'assurance maladie du Québec; S+=smear positive

* Missing data: immigration years since arrival (n=113), country of birth (n=43), sex (n=19), age (n=6) country of birth (n=43), TB diagnosis (n=60), drug resistance (n=33), treatment outcome (n=104)

† Co-morbidities include renal disease, liver disease, diabetes, cancer, substance abuse, HIV infection, or other (as reported in public health or hospital records)

‡ Pulmonary TB-related symptoms include cough, hemoptysis, and/or abnormal chest x-ray

§ Systemic TB-related symptoms include weight loss, fever, fatigue, and/or night sweats

Table 12: Number of hospitalizations and lengths of hospital stay of active TB cases, notified to Montreal Public Health between January 1996-May 2007, stratified by timing of hospitalization (N=1852)

	Timing of hospitalization		All hospitalizations
	Initial*	During†	
Patients with a hospitalization, n (%)	942 (50.9)	167 (9.0)	1001 (54.1)
Total number of hospitalizations	1006	206	1212
Mean length of hospital stay (LOS), in days (se)	28.2 (39.0)	21.6 (36.1)	27.2 (38.6)
Median length of hospital stay (LOS), in days (IQR)	17.5 (9-31)	13 (6-22)	16.5 (8-29)
Number of hospitalizations, per patient			
1	828 (87.9)	132 (79.0)	877 (87.6)
2	104 (11.0)	27(16.2)	112 (11.2)
3 or more	10 (1.1)	8 (4.8)	12 (1.2)
Number of hospitalizations with any transfers	53 (5.3)	3 (1.5)	56 (4.6)
Number of hospitalizations ending in death	31 (3.1)	9 (4.4)	40 (3.3)
Patients starting TB treatment in-hospital, n (%)	713 (38.5%)	-	713 (38.5%)
Median # days (IQR) from admission to treat start	4 (2-8)	-	4 (2-8)

Abbreviations: LOS=length of stay; se=standard error; IQR=interquartile range

* Initial= hospital admission within 1 month before start of TB treatment or up to one month after treatment start, or any admission where TB treatment started in-hospital

† During=hospital admission more than 1 month after start of TB treatment and during TB treatment period

Figure 4: Number of initial hospitalizations and median length of hospital stay, active TB cases, Montreal, stratified by year of notification (N=1852)

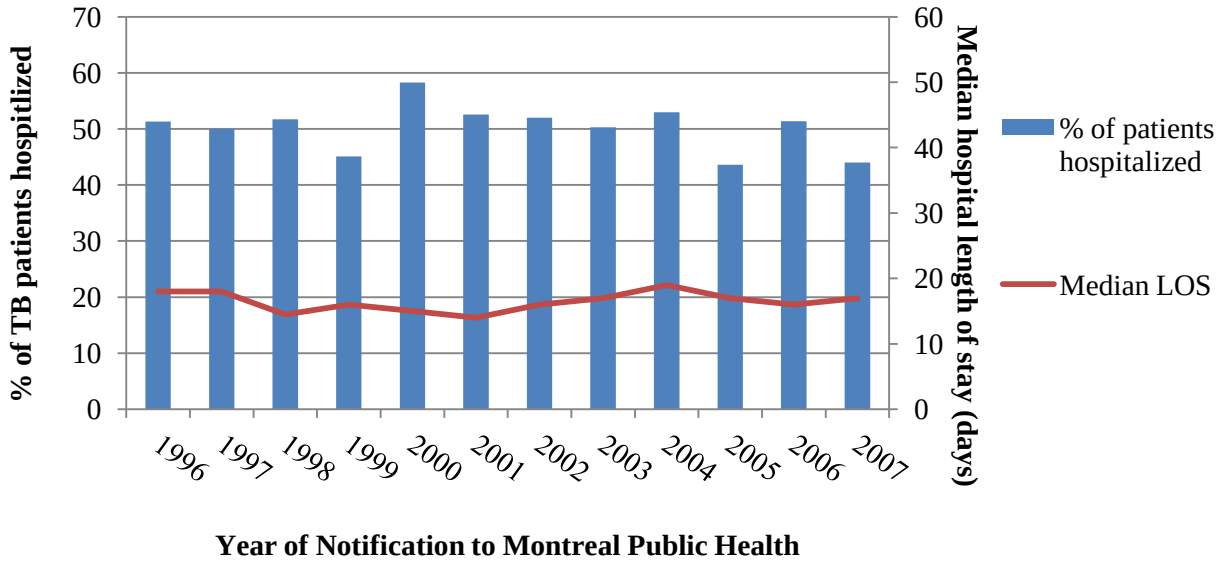


Table 13: Predictors of hospitalization during diagnosis and treatment of active TB cases, notified to Montreal Public Health between January 1996-May 2007, stratified by timing of hospitalization (N=1852)

Characteristics*	Any initial hospitalization (yes/no)†			Any hospitalization during treatment (yes/no)†		
	Number of patients (%)	Crude OR (95% CI)	Adjusted OR‡ (95% CI)	Number of patients (%)	Crude OR (95% CI)	Adjusted OR‡ (95% CI)
Male	536 (54.0)	1.30 (1.07-1.57)	-	92 (9.3)	1.00 (0.72-1.39)	-
Female	399 (47.4)	1.00		73 (8.7)	1.00	
Age group						
0-19 years	85 (59.4)	2.04 (1.38-3.00)	2.52 (1.63-3.92)	15 (10.5)	1.93 (0.98-3.79)	2.73 (1.34-5.56)
20-34 years	279 (46.4)	1.00	1.00	33 (5.5)	1.00	1.00
35-64 years	249 (54.7)	1.39 (1.11-1.73)	1.09 (0.83-1.43)	36 (7.9)	1.56 (0.95-2.57)	0.98 (0.57-1.68)
≥65 years	258 (66.2)	1.92 (1.47-2.51)	1.13 (0.80-1.59)	59 (15.1)	2.95 (1.86-4.69)	2.23 (1.27-3.93)
Reported a RAMQ health insurance #						
Yes	804 (53.6)	1.75 (1.37-2.24)	-	149 (9.9)	2.11 (1.24-3.59)	-
No	138 (39.1)	1.00		18 (5.1)	1.00	
Country of birth			-			-
Canada	196 (61.8)	2.02 (1.48-2.75)		52 (16.4)	2.63 (1.58-4.37)	
Foreign, low-moderate TB incidence	551 (49.6)	1.16 (0.92-1.47)		86 (7.7)	1.15 (0.72-1.83)	
Foreign, high TB incidence country	171 (45.8)	1.00		26 (6.8)	1.00	
Immigration, years since arrival						
Immigrant, unknown arrival	53 (41.4)	0.41 (0.27-0.63)	-	13 (10.2)	0.63 (0.33-1.22)	-
15 or more years	204 (60.4)	0.90 (0.65-1.25)		37 (11.0)	0.67 (0.42-1.06)	
3-14 years	269 (49.7)	0.58 (0.43-0.77)		39 (7.2)	0.39 (0.25-0.62)	
0-2 years	199 (41.0)	0.41 (0.30-0.54)		23 (4.7)	0.27 (0.16-0.45)	
Canadian-born	196 (61.8)	1.00		51 (16.1)	1.00	
Homeless			-			-
Yes	8 (88.9)	7.46 (0.93-59.66)		2 (22.2)	2.95 (0.61-14.33)	
No	1934 (50.7)	1.00		167 (9.1)	1.00	
Cancer			-			
Yes	30 (73.2)	2.23 (1.09-4.53)		13 (31.7)	5.96 (2.97-11.96)	3.28 (1.56-6.89)
No	912 (50.4)	1.00		156 (8.6)	1.00	1.00
Diabetes			-			-
Yes	98 (74.2)	2.83 (1.88-4.26)		22 (16.7)	1.91 (1.14-3.21)	
No	844 (49.1)	1.00		147 (8.6)	1.00	
HIV						
Positive	111 (76.0)	3.24 (2.17-4.85)	1.46 (0.90-2.36)	36 (24.7)	4.36 (2.85-6.65)	3.55 (2.04-6.18)

Negative or unknown	831 (48.7)	1.00	1.00	133 (7.8)	1.00	1.00
Renal disease						-
Yes	83 (79.1)	3.92 (2.38-6.47)	1.99 (1.10-3.59)	22 (21.0)	3.03 (1.81-5.06)	
No	859 (49.2)	1.00	1.00	147 (8.4)	1.00	
Liver disease						-
Yes	105 (68.6)	2.02 (1.40-2.92)	-	25 (16.3)	2.17 (1.34-3.51)	
No	837 (49.3)	1.00		144 (8.5)	1.00	
Substance abuse history						-
Yes	176 (70.7)	2.69 (1.99-3.63)	-	32 (12.9)	1.67 (1.09-2.53)	
No	766 (47.8)	1.00		137 (8.6)	1.00	
Number of co-morbidities§						
2 or more	316 (77.3)	5.31 (4.04-6.98)	3.56 (2.50-5.07)	77 (18.8)	5.18 (3.41-7.85)	2.80 (1.63-4.81)
1	242 (53.9)	1.84 (1.46-2.32)	1.43 (1.08-1.89)	51 (11.4)	3.04 (1.95-4.73)	2.08 (1.25-3.45)
0	384 (38.6)	1.00	1.00	41 (4.1)	1.00	1.00
Smoking history						-
Yes	306 (62.6)	1.92 (1.54-2.39)	-	62 (12.7)	1.70 (1.21-2.40)	
No	636 (46.7)	1.00		107 (7.9)	1.00	
TB diagnosis						-
Pulmonary, S+	447 (72.2)	3.87 (3.02-4.96)	1.48 (1.04-2.09)	72 (11.6)	1.47 (0.99-2.19)	
Pulmonary, S-	257 (41.2)	1.05 (0.83-1.32)	0.65 (0.46-0.90)	47 (7.5)	0.86 (0.56-1.34)	
Extra-pulmonary	228 (40.5)	1.00	1.00	46 (8.2)	1.00	
Cavitary TB						-
Yes	230 (68.5)	2.49 (1.92-3.23)	1.75 (1.28-2.40)	26 (7.7)	0.79 (0.50-1.25)	
No	712 (47.0)	1.00	1.00	1.00	1.00	
Miliary TB						
Yes	29 (82.9)	5.33 (2.05-13.87)	3.53 (1.26-9.88)	8 (22.9)	3.40 (1.51-7.67)	2.06 (0.87-4.87)
No	913 (50.3)	1.00	1.00	161 (8.9)	1.00	1.00
Any pulmonary TB-related symptoms[!]						
Yes	853 (55.8)	3.45 (2.63-4.53)	2.12 (1.44-3.11)	151 (9.9)	1.79 (1.06-3.00)	-
No	89 (27.6)	1.00	1.00	18 (5.6)	1.00	
Any systemic TB-related symptoms[#]						
Yes	697 (68.5)	5.18 (4.22-6.36)	3.54 (2.82-4.46)	123 (12.1)	2.31 (1.60-3.33)	1.63 (1.10-2.41)
No	245 (28.4)	1.00	1.00	46 (5.5)	1.00	1.00
Multidrug or poly-drug resistance						
Yes	26 (78.8)	3.95 (1.61-9.67)	6.98 (2.65-18.30)	8 (24.2)	3.08 (1.30-7.27)	5.43 (2.14-13.80)
No	914 (51.2)	1.00	1.00	159 (8.9)	1.00	1.00

Abbreviations: OR=odds ratio; CI=confidence interval; S+=smear positive; S-=smear negative

* Missing data: sex (n=19), age (n=6) country of birth (n=43), TB diagnosis (n=45), drug resistance (n=33)

† Initial=1 month before to up to 1 month after start of treatment, or any hospitalization where treatment started in-hospital. During=hospital admission more than 1 month after start of TB treatment and during TB treatment period.

‡ Models adjusted for all reported variables

§ Co-morbidities include renal disease, liver disease, diabetes, cancer, substance abuse, HIV infection, or other (as reported in public health or hospital records)
‖ Pulmonary TB-related symptoms include cough, hemoptysis, and/or abnormal chest x-ray
Systemic TB-related symptoms include weight loss, fever, fatigue, and/or night sweats

Table 14: Median lengths of hospital stay during diagnosis and treatment of active TB, stratified by timing of hospitalization, Montreal, January 1996-May 2007

	Initial hospitalizations * (n=1006)			Hospitalizations during treatment † (n=167)		
Characteristics	# hospital stays	Median LOS in days (IQR)	p-value‡	# hospital stays	Median LOS in days (IQR)	p-value‡
Sex			0.98			0.77
Male	570	17 (9-32)		105	13 (9-15)	
Female	428	18 (10-30)		96	13 (10-15)	
Age group, in years			<0.001			0.03
0-19	87	15 (10-23)		15	11 (6-13)	
20-34	271	17 (9-27)		36	11.5 (6-15)	
35-64	392	17 (8-30.5)		79	17 (10-21)	
≥65	254	22 (10-42)		73	13 (9-15)	
Reported a RAMQ health insurance #			0.46			0.78
Yes	860	17 (9-30.5)		184	12 (6-22)	
No	146	17 (10-28)		22	14 (7-26)	
Country of birth			0.002			0.63
Canada	206	21 (11-36)		63	13 (15-26)	
Foreign, low-moderate incidence	593	17 (9-31)		106	13 (9-15)	
Foreign, high incidence country	182	14 (6-27)		31	14 (8-18)	
Immigration, years since arrival			<0.001			0.61
Immigrant, unknown arrival	56	15.5 (8.5-26.5)		15	11 (4-56)	
15 or more years	229	20 (7-36)		49	14 (7-22)	
3-14 years	279	16 (9-28)		46	13 (7-23)	
0-2 years	211	16 (9-25)		27	9 (6-21)	
Canadian-born, aboriginal	6	36.5 (29-43)		5	23 (19-34)	
Canadian-born, non-aboriginal	200	20 (11-35.5)		58	11 (3-20)	
Homeless			0.74			0.10
Yes	8	21 (13.5-36)		2	83.5 (56-111)	
No	998	17 (9-31)		204	13 (10-14)	
Cancer			0.30			0.73
Yes	32	13.5 (6-53)		19	17 (9-18)	
No	974	18 (9-30)		187	13 (10-14)	
Diabetes			0.12			0.51
Yes	107	21 (10-39)		30	11 (7-18)	
No	899	17 (9-30)		176	13 (11-15)	
HIV			0.004			0.15
Positive	117	27 (16-43)		46	19 (10-22)	
Negative or unknown	889	16 (9-28)		160	12 (9-14)	
Renal disease			<0.001			0.02
Yes	91	28 (11-60)		33	18 (11-21)	
No	915	17 (9-29)		173	13 (9-14)	
Liver disease			0.10			0.09
Yes	118	21.5 (10-39)		31	9 (5-13)	
No	888	17 (9-30)		175	13 (11-15)	
Substance abuse history			0.20			0.30
Yes	188	19 (12.5-33)		42	19 (14-21)	
No	818	17 (9-30)		164	11 (9-13)	
Number of co-morbidities						0.37
2 or more	343	22 (12-42)	<0.001	102	14 (10-18)	
1	262	18 (8-30)		62	13 (8-15)	
0	401	15 (8-24)		42	12.5 (8-14)	
Smoker			0.23			0.79

Yes	325	18 (9-35)		74	14 (9-19)	
Never smoker	681	17 (9-28)		132	13 (9-14)	
TB diagnosis			<0.001			0.51
Pulmonary, S+	467	22 (13-36)		93	13 (9-14)	
Pulmonary, S-	280	14 (7-24)		53	14 (8-18)	
Extra-pulmonary	249	13 (6-26)		56	14 (11-18)	
Cavitary TB			0.45			0.02
Yes	240	18 (11.5-33)		31	7 (4-14)	
No	766	17 (8-30)		175	13 (11-15)	
Miliary TB			0.28			0.79
Yes	33	20 (12-46)		8	20.5 (6-31)	
No	973	17 (9-30)		198	13 (10-14)	
Any pulmonary TB-related symptoms			<0.001			0.38
Yes	906	18 (10-32)		184	13 (10-15)	
No	100	11 (5-23.5)		22	13 (7-21)	
Any systemic TB-related symptoms			0.006			0.55
Yes	744	19 (10-34)		155	13 (9-14)	
No	262	14 (8-23)		51	14 (8-17)	
Multidrug or poly-drug resistance			0.04			0.30
Yes	28	23 (12-67)		8	13 (8-86)	
No	976	16 (8-29)		196	13 (10-15)	
Teaching hospital§			0.06			0.43
Yes	675	18 (10-33)		131	13 (6-23)	
No	329	16 (8-28)		74	9.5 (6-20)	

Abbreviations: IQR=interquartile range; LOS=length of stay; HR=hazard ratio; CI=confidence interval; S+=smear positive; S-=smear negative

Missing: sex (n=8), age (n=2), TB diagnosis (n=10), country of birth (n=25), drug resistance (n=2), hospital (n=3)

*Initial=1 month before to up to 1 month after start of treatment, or any hospitalization where treatment started in-hospital

†During=hospital admission more than 1 month after start of TB treatment and during TB treatment period.

‡p-values calculated using log-rank tests

§ When calculating median LOS in the case of transfers, median LOS assigned to the last hospital ID in the patient's hospitalization episode

Table 15: Predictors of *time to discharge* from hospital during diagnosis and treatment of active TB, stratified by timing of hospitalization, Montreal, January 1996-May 2007

	Initial hospitalizations * (n=1006)		Hospitalizations during treatment† (n=167)	
Characteristics	Crude HR (95% CI)	Adjusted HR‡ (95% CI)	Crude HR (95% CI)	Adjusted HR‡ (95% CI)
Sex				
Male	1.02 (0.88-1.14)	-	1.19 (0.74-1.91)	-
Female	1.00		1.00	
Age in years§				0.99 (0.98-1.00)
log(LOS)≤2.5	1.02 (1.02-1.03)	1.02 (1.02-1.03)	-	-
log(LOS)>2.5	0.96 (0.96-0.96)	0.96 (0.96-0.96)	-	-
Reported a RAMQ health insurance #				
Yes	0.93 (0.78-1.11)	-	0.84 (0.47-1.49)	-
No	1.00		1.00	
Aboriginal				
Yes	0.61 (0.40-0.94)	-	0.49 (0.12-1.93)	-
No	1.00		1.00	
Country of birth				
Canada	0.68 (0.55-0.83)	-	0.85 (0.49-1.47)	-
Foreign, low-moderate incidence	0.88 (0.74-1.04)		0.60 (0.34-1.04)	
Foreign, high incidence country	1.00		1.00	
Immigration, years since arrival				
Immigrant, unknown arrival	1.44 (1.10-1.88)	-	0.51 (0.26-1.03)	-
15 or more years	1.10 (0.91-1.35)		0.58 (0.29-1.16)	
3-14 years	1.47 (1.23-1.76)		0.67 (0.41-1.07)	
0-2 years	1.42 (1.17-1.72)		1.10 (0.54-1.89)	
Canadian-born, aboriginal	0.91 (0.61-1.36)		0.33 (0.08-1.47)	
Canadian-born, non-aboriginal	1.00		1.00	
Homeless		-		-
Yes	0.89 (0.56-1.40)		0.26 (0.11-0.63)	
No	1.00		1.00	
Cancer		-		
Yes	0.81 (0.54-1.22)		1.36 (0.91-2.03)	-
No	1.00		1.00	
Diabetes		-		
Yes	0.94 (0.78-1.14)		1.01 (0.60-1.70)	-
No	1.00		1.00	
HIV				
Positive	0.73 (0.62-0.85)	0.73 (0.62-0.87)	0.97 (0.62-1.50)	0.61 (0.41-0.90)
Negative or unknown	1.00	1.00	1.00	1.00
Renal disease				
Yes	0.55 (0.43-0.70)	0.56 (0.42-0.73)	0.45 (0.21-0.95)	0.60 (0.33-1.08)
No	1.00	1.00	1.00	1.00
Liver disease				
Yes	0.79 (0.66-0.94)	-	1.49 (0.91-2.46)	-
No	1.00		1.00	
Substance abuse history				
Yes	0.89 (0.77-1.03)	-	0.98 (0.65-1.47)	-
No	1.00		1.00	
Number of co-morbidities				
2 or more	0.65 (0.56-0.75)	-	0.59 (0.37-0.94)	-
1	0.86 (0.73-1.00)		0.53 (0.28-0.98)	
0	1.00		1.00	
Smoker				

Yes	0.85 (0.75-0.97)	-	0.92 (0.60-1.42)	-
Never smoker	1.00		1.00	
TB diagnosis				
Pulmonary, S+	0.61 (0.52-0.73)	0.63 (0.53-0.76)	1.62 (0.92-2.84)	1.33 (0.87-2.04)
Pulmonary, S-	0.92 (0.75-1.13)	1.01 (0.82-1.26)	1.71 (0.91-3.22)	1.88 (1.14-3.10)
Extra-pulmonary	1.00	1.00	1.00	1.00
Cavitary TB				
Yes	0.91 (0.79-1.04)	-	2.02 (1.18-3.44)	-
No	1.00		1.00	
Miliary TB				
Yes	0.81 (0.61-1.07)	-	1.15 (0.71-1.88)	-
No	1.00		1.00	
Any pulmonary TB-related symptoms				
Yes	0.63 (0.51-0.78)	0.72 (0.55-0.95)	0.57 (0.39-0.85)	0.47 (0.28-0.80)
No	1.00	1.00	1.00	1.00
Any systemic TB-related symptoms				
Yes	0.84 (0.71-0.99)	-	1.28 (0.65-2.52)	-
No	1.00		1.00	
Multidrug or poly-drug resistance				
Yes	0.64 (0.48-0.83)	0.45 (0.35-0.59)	0.93 (0.37-2.34)	0.45 (0.20-1.03)
No	1.00	1.00	1.00	1.00
Teaching hospital				
Yes	0.87 (0.76-1.00)	0.84 (0.74-0.96)	1.01 (0.62-1.63)	-
No	1.00	1.00	1.00	

Abbreviations: IQR=interquartile range; LOS=length of stay; HR=hazard ratio; CI=confidence interval; S+=smear positive; S-=smear negative

Missing: sex (n=5), age (n=3), TB diagnosis (n=4), country of birth (n=6), drug resistance (n=2), hospital (n=1)

*Initial=1 month before to up to 1 month after start of treatment, or any hospitalization where treatment started in-hospital

†During=hospital admission more than 1 month after start of TB treatment and during TB treatment period.

‡Hazard ratios calculated by Cox proportional hazards regression, accounting for repeated hospitalizations among patients using a conditional counting process model (stratified by hospitalization number) and a robust sandwich variance estimator. Patients were censored on death in-hospital, and transfers between hospitals were counted as a time-dependent effect. The Cox Proportional Hazard model is modeling the time to discharge; a hazard ratio of less than one indicates a longer LOS (ie. A HR for multidrug or poly-drug resistance=0.45 can be interpreted as: the rate of discharge from hospital is 55% slower for patients with drug resistance compared to those without drug resistance. A HR for pulmonary S+ TB=1.33 can be interpreted as: the rate of discharge from hospital is 33% faster in patients with pulmonary S+ compared to patients with extra-pulmonary TB.).

§Given strong evidence that proportional hazards assumptions did not hold for age (lines crossed in the log-log plot), we included an interaction term in the model of age (continuous, in years) multiplied by the LOS. This interaction term indicates that the effect of age was not constant throughout the length of stay.

PREFACE TO CHAPTER 6 (MANUSCRIPT #4)

In Chapter 4, I applied a series of drug dispensation-based decision rules to the Quebec provincial RAMQ health administrative database in order to identify a cohort of active TB patients. I then estimated the costs of active TB disease to the healthcare system, ie. when TB disease is not prevented. In applying these decision rules, I also identified two populations of patients treated for LTBI in the RAMQ database, the first treated with INH and the second treated with RMP.

In the next manuscript (Chapter 6), I compare treatment completion rates, severe adverse event rates, and direct costs of health service use of patients treated with these two LTBI regimens, INH and RMP, in the general Quebec population. The Quebec provincial health administrative database provides near complete capture of all TB drugs dispensed in community pharmacies in the province, and thus provides a data source for evaluating LTBI treatment completion and costs in the general population.

CHAPTER 6: COMPLETION, ADVERSE EVENTS, AND DIRECT COSTS OF TREATMENT WITH ISONIAZID AND RIFAMPIN FOR LATENT TUBERCULOSIS INFECTION IN QUEBEC: A POPULATION-BASED STUDY (MANUSCRIPT #4)

6.1 Introduction

Treatment for latent tuberculosis infection (LTBI) is considered a key component of TB prevention programs, particularly in low-TB incidence countries[35]. The current recommended LTBI treatment regimen in Canada and the US is 9 months of daily isoniazid (INH)[84]. Six months of daily INH (6INH) is considered an acceptable alternative regimen when treatment adherence to the longer 9INH is a concern [60]; it also remains a standard recommended regimen in some countries, such as the UK[85]. The standard regimen (9INH) was derived from clinical trial evidence suggesting a 93% reduction in TB incidence rates, and has been recommended since the publication of new LTBI treatment guidelines in the year 2000[84]. However, there are challenges with this lengthy regimen. High rates of treatment non-adherence have been observed, with less than 50% completion reported in many populations[3]. Furthermore, rates of severe hepatotoxicity ranging from 0.1% to 2% have been previously reported in large observational studies in the US, among populations of LTBI patients receiving INH [5].

Concerns about INH hepatotoxicity and low adherence with this long regimen, as well as increasing rates of INH resistance, have prompted trials of shorter-course and less-toxic treatment regimens. Four months of Rifampin (RMP) is a promising alternative; a recent randomized controlled trial showed that adherence to RIF was higher and that patients had fewer adverse events compared to INH[8, 9]. However, there remain outstanding questions about adherence and adverse effects of the two regimens. Further, while RMP is a more costly drug than INH, costs of monthly monitoring and for unplanned visits to manage drug-related adverse events may be higher with the 9INH regimen[112]. Most studies to date of RMP have been clinical trials [8, 9] or single-clinic observational studies[91, 92]. These studies may overestimate adherence and underestimate rates of drug-related adverse events and costs occurring in 'real-world' settings with more diverse patient populations and provider types.

The main objective of the current study was to compare rates of treatment completion for two LTBI regimens, RMP and INH, in the general population, using data from the Quebec provincial health administrative database. Secondary objectives were to compare rates of adverse events and direct costs between these two regimens. This is a follow-up to a previously published study about rates of adverse drug events during LTBI treatment in the Quebec general population over a 5-year period (1998-2002) [94]. The hypotheses were that treatment completion rates would be higher for 4RMP compared to 9INH, that rates of severe hepatic adverse events would be higher with 9INH, and that direct costs of health service use would be higher with 9INH.

6.2 Methods

Data source and study population

A retrospective cohort was identified, composed of all individuals who started treatment for LTBI from 1998 through 2007 inclusively, in the province of Quebec. The cohort was extracted from the provincial Régie de l'assurance maladie du Québec (RAMQ) database. Approximately 99% of permanent residents in the province are beneficiaries of the RAMQ Medical Services Plan, covering inpatient and outpatient medical services. In contrast, fewer than half of Quebec residents are covered by the RAMQ Prescription Drug Plan, with the majority of patients covered through private drug plans (predominately through employers). However, since 1997, all TB drugs in Quebec have been universally paid for by the RAMQ Prescription Drug Plan through a special program (ie. the RAMQ TB drug program)[194]. Thus, the RAMQ database is considered nearly complete for capturing TB drugs dispensed in the province (with a few exceptions, such as drug treatment provided in-hospital).

For this study, an incident cohort was identified of patients who were dispensed for the first time at least 30 days of INH alone or RMP alone (these were considered LTBI treatment regimens), without a diagnosis code for other long-term RMP indications (ie. multi-drug resistant *Staphylococcus aureus*, osteomyelitis, brucellosis, leprosy), and who had not been dispensed any TB drugs in the previous three years. A detailed description of the RAMQ database and methods for selecting the LTBI cohort is provided in Chapter 4 and Appendix 4.

The first date that a patient was dispensed either INH or RMP in the RAMQ database was identified as their 'index date'. Pre-treatment covariates were defined on the basis of all RAMQ records within one year before the index date. The RAMQ records included physician billing records, hospitalizations, drug plan coverage type, and drugs dispensed. Treatment outcomes were defined on the basis of all RAMQ records up to three years after the index date, or earlier in the case of death or a switch in LTBI regimens. As well, for patients whose index date was after October 2006, this date was truncated in October 2009, which marked the end of available data at the time of the data extraction. Data were also extracted for up to three years before the index date, in order to examine health service use before treatment start. We defined the LTBI treatment period for each patient as starting on their index date and ending 30 days after the last TB drug was dispensed. We counted doses based on the duration of each RAMQ drug dispensing record and assumed daily treatment. Days with multiple doses dispensed (ie. drug records with overlapping days) were assumed to be early prescription refills. One exception to this rule was when patients had multiple records for the same drug with the same start date for the prescription; in these cases, we only included the first dispensing record when counting the number of doses dispensed.

Ethical approval for this study was obtained through the Institutional Research Board of the McGill University Faculty of Medicine (IRB Study #A06-M88-09A).

Definitions of outcome variables

Treatment completion

The primary outcome of interest was LTBI treatment completion. We identified LTBI 'treatment completers' as individuals who were dispensed a minimum of 120 RMP doses or 270 INH doses over the study follow-up period. Clinical trials have shown low efficacy with completion of less than 6 months of INH, and current guidelines recommend 9 months of INH as optimal[87]. Therefore we did not consider a measure of percent completion or completion of less than 6 months of INH as relevant primary outcomes for our study. As a secondary analysis, however, we calculated treatment completion of 180 INH doses (ie. equivalent to a 6 month INH regimen).

For our main analyses, we defined treatment completion as the minimum number of doses dispensed within recommended time limits (ie. 120 doses dispensed within 6 months for the 4RMP regimen, and 270 doses within 12 months for the 9INH regimen)[84]. For our secondary analysis, we defined treatment completion for a 6INH regimen as 180 doses within 9 months. This definition has been used as the measure of treatment completion in a number of previous studies [89, 91, 93] and corresponds to LTBI treatment recommendations[84]. Since different definitions of treatment completion have been used in the literature, we also ran several sensitivity analyses to test the robustness of our primary results to different definitions. First, we measured treatment completion if the minimum number of doses were dispensed within three years).We tested this definition of completion to assess whether patients were completing 100% of doses, but within an extended period of time (ie. to see whether the time limits applied in our primary analysis were too conservative). Second, we assumed that each day spent in hospital during the TB treatment period had a drug dose dispensed. We tested this definition to assess the impact that missing TB treatment data during inpatient stays could have on completion rates. Third, to further assess the potential bias of missing treatment data during hospitalizations, we limited our calculation of completion to the subset of patients who had no hospitalizations during the treatment period. Fourth, we re-ran our primary analysis excluding patients who switched LTBI regimens, in order to assess the impact of switching on completion rates. Lastly, we limited our calculation of completion to drug records with a TB drug program code in the RAMQ database. Since there are numerous coverage programs within the RAMQ Prescription Drug Plan, a TB drug program code is assigned to drug records to identify that the dispensation cost was attributed to the TB drug program. The purpose of the RAMQ TB drug program is to ensure that patients receive their TB drugs for free. This method of calculating treatment completion using solely RAMQ records with a TB drug program code was employed in a previous Quebec study[195].

Drug-related adverse events

As secondary outcomes, we identified if the patient experienced adverse outcomes during treatment (ie. a severe hepatic adverse event requiring hospitalization, a switch to a different LTBI regimen, or death). We identified a probable severe hepatic adverse event as any hospital admission occurring within 30 days after the last TB drug dose was dispensed, with a primary or

secondary ICD9/10 diagnostic code indicative of a potential TB drug-related hepatic adverse event followed by permanent discontinuation of the TB drug. We identified hepatic adverse events using ICD9/*ICD10* codes in hospital records: hepatic necrosis (570, *K71.1*), hepatic encephalopathy (572.2, *K72.0, K72.9*), toxic hepatitis (573.3, *K71.2, K71.6, K71.9*), and liver transplant (V427, *Z944*); also the combined algorithm of jaundice (782.4, *R17*) or abnormal elevation of liver function enzymes (790.4, 790.5, *R74, R94.5*), with a concomitant diagnosis code of poisoning by antimycobacterial or antibiotic drugs (961.8, 960.6, *E931.8, E930.6*). If patients had been hospitalized in the year before the index date for the same liver-related diagnosis, we assumed that the condition was pre-existing and we did not count this as a drug-related adverse event. In the present analysis, we did not validate our algorithm within the RAMQ database. However, we used a similar algorithm to previously reported [94, 196] and validated [197] algorithms to identify drug-induced hepatotoxic events in health administrative databases.

We identified switches in LTBI regimen when there was a change in LTBI regimen occurring 7 or more days after the initial regimen prescription date, with permanent discontinuation of the initial LTBI regimen. When patients switched from one LTBI regimen to another, we calculated the number of doses dispensed for the first LTBI regimen only. Lastly, we identified a death as occurring during treatment if a death was recorded in the hospital or vital statistics records within 30 days after the last TB drug dose was dispensed.

Direct costs of health service utilization

Health service use events included emergency department (ED) visits, inpatient hospitalizations, day procedures in an acute care hospital setting, physician visits, and first-line TB drug and other drug prescriptions dispensed. Detailed definitions and methods of costing health service use events were provided in Chapter 4. Health service use costs during the LTBI treatment period were accumulated up to 30 days after the last TB drug was dispensed or to the recommended time limit for each regimen (180 days for rifampin or 365 days for isoniazid), whichever was earliest.

Definitions of exposure variables and potential confounders

The main exposure variable of interest was the LTBI regimen the patient initially started (INH or RMP). Potential confounders were identified based on *a priori* hypotheses about factors associated with treatment completion[3] and availability in the RAMQ database. Potential confounders extracted from the RAMQ database at each patient's index date included year of treatment initiation, age group (0-19, 20-34, 35-49, 50-64, 65-74, and ≥80 years), sex, health region of residence, pre-treatment co-morbidities (in the year prior), socioeconomic status (SES), and TB-related experience and training of the treating physician.

Pre-treatment co-morbidities:

We hypothesized that age, as well as number and severity of co-morbidities, would be important predictors of which LTBI regimen a patient would be started on. We also hypothesized that age and co-morbidity level would be associated with treatment completion, as reported in US and Canadian studies[3]. Specifically, US observational studies have reported that patients starting on RMP are on average older than patients starting on INH[92]. Efficacy of RMP is also unknown in children and thus the RMP regimen may be less likely to be prescribed in young age groups. Furthermore, given the longer treatment duration and reported worse safety profile of INH, it is hypothesized that RMP will be prescribed more frequently to patients with underlying liver disease[92], and to patients with serious underlying co-morbidities that could affect their ability to complete a longer INH regimen. Also, RMP is contraindicated in patients taking certain anti-retroviral drugs for HIV infection, so we expected that RMP would be less likely to be prescribed in patients with HIV infection[92].

We therefore measured pre-treatment co-morbidities using several measures. First, we identified specific TB-related medical risk factors based on known risk factors for TB reactivation (diabetes, cancer, renal failure, HIV/AIDS, silicosis, TNF-alpha inhibitors, solid organ transplant, malnutrition, and substance abuse)[84]. We hypothesized that having TB-related medical risk factors would increase the likelihood of treatment completion, based on perceived risk of developing active TB[3]; this has been reported previously[198]. We identified an individual as having a TB-related medical risk factor when they had one or more relevant ICD9/10 diagnostic codes from hospital discharge abstracts, or two or more relevant codes from physician billing records, in the year prior to the index date (see Appendix 2 for a summary of ICD codes

used to identify TB risk factors). An individual was also identified as being HIV-infected if one or more anti-retroviral drugs had been prescribed during this period for more than 1 month (with one month selected as the cut-off to exclude individuals taking HIV prophylaxis treatment). Individuals were identified as using TNF-alpha inhibitors if they had one or more prescription of any duration dispensed from a community pharmacy in the year prior.

Second, we calculated a Charlson-Deyo co-morbidity score for each patient, as an indicator of general co-morbidity severity (see Appendix 2 for a summary of ICD codes included in the Charlson score). The Charlson Deyo score is a weighted risk score predicting short-term mortality based on hospital discharge abstracts in the previous year[199]; it has been validated in other US and Canadian health administrative databases[199-201]. This was re-coded into three levels (0, 1-2, 3 or more). Lastly, we identified two specific conditions (using the algorithm of any hospital ICD9/10 code or ≥2 physician billing ICD9/10 codes in the past year): 1) a psychiatric diagnosis; and 2) pre-existing liver disease. Having a psychiatric diagnosis has been associated with non-adherence with treatment of LTBI and other conditions[3, 202-204]. Having liver disease was expected to be associated with the choice of LTBI regimen and risk of developing a liver-related adverse event during treatment[4].

Third, we identified if a patient had been hospitalized at any time during the year before the index date, and calculated the total number of days spent in-hospital during the preceding year.

Socioeconomic status (SES) and health region:

As a proxy measure of SES, we identified individuals who were registered in the year before the index date to receive RAMQ drug plan coverage due to unemployment or welfare status, refugee status, or maximum coverage through the guaranteed income supplement (GIS) for individuals aged 65 years and older. Both social assistance drug plan coverage and GIS supplements have been used in prior Canadian research to indicate SES [172, 173]. Further, we grouped health regions of residence into two categories (central/peripheral, and intermediate/remote), based on the Quebec Ministry of Health method of stratifying health regions according to distance to university network hospitals (ie. the four central regions include 4 universities with faculties of medicine)[174]. Health care utilization has been shown to vary between these groups of health regions[174, 205].

TB-related experience and training of treating physician:

Additionally, we identified the physician who initiated the initial TB drug regimen by extracting the unique physician identifier assigned to the index prescription record. We included two factors associated with the treating physician: 1) if the physician was trained in a specialty compared with being a general practitioner, and 2) if the physician was experienced with treating active TB (defined as having treated an average of one or more active TB cases annually between 1998 and 2007). A detailed description of the method we used to identify active TB cases in the RAMQ database is summarized in Chapter 3. These variables were found to be predictive of TB-related survival and LTBI treatment completion in previous Canadian and US studies[54, 206].

Statistical analysis

We calculated descriptive statistics (counts and frequencies, medians and interquartile ranges) of pre-treatment characteristics of patients initiating LTBI regimens, stratified by starting regimen and index year period. We compared frequencies of characteristics between INH and RMP patients, using chi-square tests for categorical variables (and Fisher's exact tests for small cell counts) and Wilcoxon rank-sum tests to compare medians. We calculated the crude treatment completion rate as the number of patients completing treatment divided by the number of patients starting treatment, stratified by regimen and index year. We stratified completion rates into 5-year time periods (1998-2002 and 2003-2007) corresponding to periods before and after the adoption of new LTBI treatment guidelines.

We performed univariable and multivariable log-binomial regression to evaluate predictors for LTBI treatment completion in the index years after the LTBI treatment guidelines changed (2003-2007). The main outcome variable - whether or not an individual completed treatment - was binary and was not a rare event, therefore we used log-binomial regression to model risk ratios[207]. Log-binomial regression has been used previously to evaluate predictors of treatment completion of LTBI regimens[198]. We used generalized estimating equation (GEE) methods to adjust for the effect of clustering of patients within treating physicians, using PROC GENMOD in SAS version 9.2 (SAS Institute Inc, Cary, NC). We fit our models with a compound symmetric working correlation structure, and used a robust empirical "sandwich" covariance

estimator for calculation of standard errors[208]. We chose our correlation structure in order to minimize the QIC. Our main analysis was to compare 4RMP to 9INH. We assessed collinearity between categorical predictor variables by comparing distributions in cross-tables and through calculation of Pearson chi-square statistics. We collapsed categorical variables into fewer categories when cell sizes were small (eg. Charlson co-morbidity level was reduced from 3 categories to a binary indicator of any *vs* no co-morbidities). We also collapsed variables when there was homogeneity in effect estimates between categories (eg. age group). We used a backward selection procedure for model-building. We included variables in multivariable modeling if they reached a statistical significance level of $p<0.20$. We selected our final models based on minimizing the QIC statistic. Secondary subgroup analyses were explored using stratified models of 4RMP only and 9INH only, as well as testing for interactions between LTBI regimen with age group and with co-morbidity level within the full sample model.

We assessed adverse outcomes during treatment using two measures. First, we calculated the proportions of patients who started LTBI treatment and who had an adverse event during treatment (severe hepatic adverse event, switch, and death). We identified all events occurring up to 30 days after the last TB dose was dispensed, within the time limits for the respective regimens (180 days for RMP, 365 days for INH). We calculated crude risks and risk differences (with 95% confidence intervals) of adverse outcomes. Second, we calculated rates of adverse outcomes (severe hepatic adverse event, switch, and death) as the number of events/10,000 person-doses of exposure. Rate ratios (with 95% CIs) were estimated from Poisson regression models adjusted for individual risk factors (age, sex, and Charlson co-morbidity level). We used GEE methods to adjust for clustering of patients within treating physicians. Given negative intra-class correlation, we fit our models with an independent correlation structure[209]. We modelled rates using the natural log of the number of person-doses dispensed as an offset in the model and we included a parameter to adjust for underdispersion (dscale option in SAS PROC GENMOD). We calculated the total number of doses dispensed up to the day of the event or within the time limits for the respective regimens. As a sensitivity analysis, we limited our calculation of event risks and rates to the first 180 days of follow-up for INH-treated patients.

Lastly, we calculated descriptive statistics of health service use during the TB treatment period (mean, standard deviation, median and interquartile range of direct costs per patient starting

treatment, total number of events, percentage of patients with one or more event, and among patients with one or more event, the mean, standard deviation, median and interquartile range of number of events). Descriptive statistics were calculated separately for hospitalizations, ED visits, physician visits, hospital day procedures, TB drugs dispensed, and other drugs dispensed. We further calculated monthly (30-day) mean (sd) and median (IQR) total costs for each treatment regimen, in total and stratified by first-line TB drugs versus other health service use costs. We lastly performed univariable and multivariable gamma regression to compare direct costs of RMP and INH patients (excluding TB drugs) during the TB treatment period. The gamma distribution has been found to be appropriate for the analysis of skewed cost data, while the log-link guarantees non-negative outcomes and retains the original (arithmetic mean) scale of the data [210]. We added $1 to every patient's health service use costs in order to include patients in the gamma regression models who had no health service use costs during the treatment period. We used generalized estimating equation (GEE) methods to adjust for the effect of clustering of patients within treating physicians, fit our models with a compound symmetric working correlation structure, and used a robust empirical "sandwich" covariance estimator for calculation of standard errors[208]. We chose our correlation structure in order to minimize the QIC. As a sensitivity analysis, we limited our calculation of costs to the first 180 days of follow-up for INH-treated patients. Lastly, in order to evaluate costs of the two regimens prior to treatment start, total direct health system costs were calculated for each 30-day period up to 3 years before and after the index date.

6.3 Results

Characteristics of patients starting LTBI treatment with INH or RMP regimens

A total of 19,773 patients started INH alone or RMP alone in Quebec between 1998 and 2007 (Figure 5). Of these, the majority were started on INH (n=18354, 93%). There was an increasing trend in the number of new prescriptions for both INH and RMP between the years 1998 and 2007 (Figure 5). LTBI treatment was initiated by a total of 3234 physicians within 18 health regions (3003 physicians started one or more patients on INH, 457 started one or more patients on RMP), with an average cluster size of 6.1 patients (range 1-916) per treating physician (data not shown).

Comparing pre-treatment characteristics of LTBI patients who initiated treatment between 2003 and 2007 (Table 16), RMP patients were more likely than INH patients to be male, older, of higher SES, and to have more co-morbidities, including cancer, diabetes, have had a solid organ transplant, renal failure, substance abuse, malnutrition, to have a psychiatric diagnosis or liver disease. RMP patients were also more likely to have been treated by a TB specialist physician and by a physician with more experience with treating active TB (Table 16). RMP patients also were more likely to have had a hospitalization in the year prior and to have a hospitalization during treatment (Table 16). RMP patients also spent more days in hospital, on average, in the year prior and during treatment (Table 16). Similar trends were observed between RMP and INH patients who initiated treated between 1998 and 2002 (data not shown).

LTBI treatment completion rates

As summarized in Figure 6, dropout rates in the first month were higher for RMP (n=143, 20.0%) than INH (n=1199, 12.4%). Between 2003 and 2007, there was a fairly steady dropout rate after the first month in patients taking INH (approximately 7% of patients per 30 doses). Notably, between 1998 and 2002, the monthly dropout rate for INH patients increased markedly at 180 doses, suggesting that a number of these patients were prescribed 6 months of INH in the years before the LTBI treatment guidelines changed to recommend 9 months of INH (thus these patients would have been considered completers if they initially had been prescribed a 6-month regimen). Between 2003 and 2007, monthly drop-off rates for RMP were fairly steady after the first month, at an average of 12% per 30 days of doses dispensed (Figure 6).

Treatment completion rates increased after the year 2000 - when new LTBI treatment guidelines were published, and generally stabilized after 2002, for 4RMP and 9INH (Figure 7). Between 2003 and 2007, an estimated 53.5% (95% CI: 50.2-56.8) of patients completed the 4RMP regimen and 36.9% (35.9-37.8%) completed 9INH (Table 17). Further, on crude analysis, 59.5% (58.5-60.5%) of the INH patients completed 180 doses within 210 days, ie. equivalent to a 6INH regimen (data not shown). In multivariable models (Table 17), 4RMP completion was significantly higher than 9INH (adjRR=1.51, 95% CI: 1.31-1.75) after adjustment for confounders. Factors which were associated with higher rates of treatment completion in

multivariable analyses (Table 17) included being male (adjRR=1.09, 95%CI: 1.04-1.14), age 1-19 years (adjRR=1.20, 95%CI:1.08-1.34), 35-64 years (adjRR=1.17, 95%CI:1.07-1.27), or ≥65 years (adjRR=1.22, 95%CI:1.06-1.39), and having HIV/AIDS (adjRR=1.59, 95%CI:1.31-1.92). Co-morbidities generally were associated with reduced LTBI completion, particularly having any Charlson co-morbidities (adjRR=0.79, 95%CI:0.65-0.96) or a hospitalization in the year prior (adjRR=0.70, 95%CI:0.62-0.79). The estimated intraclass correlation coefficient (ICC) for our main analysis was 0.06.

Interaction effects between LTBI regimen and age group, and between LTBI regimen and co-morbidity level, were significant in the multivariate model ($p<0.001$ and $p<0.01$, respectively). Thus we further investigated possible effect modification through comparing stratified models of RMP and INH (Table 18). Among INH patients, treatment completion rates were lowest among patients aged 20-34 years old while the reverse pattern was observed in RMP patients, with completion rates highest in this age group and lowest among patients aged ≥65 years. The reduction in completion rates with co-morbidities (any Charlson co-morbidities and having a hospitalization in the year prior) was observed in both INH and RMP patients, but the effect was larger with RMP patients (Table 18). Our results suggested that RMP patients aged 65 years and older who did not complete treatment tended to be a highly co-morbid group of patients, with 82% having a hospitalization in the past year (compared to 33% of INH non-completers of the same age group), 65% having a hospitalization during the treatment period (vs 34% of INH non-completers), and 41% having a Charlson score of 1 or more (vs 25% of INH non-completers) (data not shown).

Sensitivity analyses run to test different assumptions about definitions of completion did change estimates of completion rates in some scenarios, but did not change the direction of effect estimates (Table 19). When completion rates were calculated without time limits applied (sensitivity analysis #1), rates increased negligibly, suggesting that most patients either completed within the recommended time limits, or failed to complete at all. When completion rates were calculated by including any days spent in hospital during the treatment window as being days with a TB drug dispensed (a ‘worst-case scenario” to assess the potential bias due to missing data), overall completion rates changed very little, suggesting that missing drug dispensing data during hospitalizations likely had a minimal impact on calculation of completion

rates in this population (sensitivity analysis #2). Furthermore, even with the extreme scenario of assuming that TB treatment was taken during all days spent in hospital in the previous year, the estimated completion rates did not change markedly (data not shown). When completion rates were calculated as on-time completion and excluding patients who had any hospitalizations during treatment, completion rates increased to 61.6% for RMP patients and 37.1% for INH patients (sensitivity analysis #3). When completion rates were calculated among patients who did not experience a switch in LTBI regimen, completion rates increased slightly to 54.6% for 4RMP and 38.5% for 9INH (sensitivity analysis #4). When completion rates were calculated limiting the analyses to TB drug prescription records with a RAMQ TB drug program code (sensitivity analysis #5), rates of completion for 4RMP increased to 65.0% and 9INH rates dropped to 29.2% (similar to rates reported in a previous Quebec study[195]).

Lastly, we assessed the impact of potential missing data during hospitalizations on completion rates by stratifying completion rates by LTBI regimen and hospitalization during treatment status, across study years. As shown in Table 20, RMP completion rates were greater than 65% for each study year (with an exception in 2003) among non-hospitalized patients, while completion rates were less than 25% among hospitalized RMP patients in the same study years. Hospitalized RMP patients who did not complete treatment had on average a higher Charlson co-morbidity score (26.2% had a score of 3 or higher, compared to 12.7% of hospitalized INH patients who did not complete and 4.3% of hospitalized RMP patients who did complete) than other patient types (data not shown).

Risk of severe hepatic adverse events, regimen switches, and death during treatment

A total of 1 RMP patient (0.1%) and 20 INH patients (0.2%) had an incident severe hepatic adverse event during LTBI treatment (Table 21). The median time to a severe hepatic adverse event was 31 days for the RMP patient and 151.5 days after the index date for INH patients (Table 21). Neither the risks nor rates of an incident severe hepatic adverse event during treatment were significantly higher for INH than RMP: crude risk difference, 4RMP vs 9INH=-0.1% (95% CI: -0.1, 0.3%); adjRR: 0.73 (0.10-5.43). Patients with a severe hepatic event during LTBI treatment were more likely to have pre-treatment liver disease and to be older (data not shown). The one RMP patient and the majority of INH patients (n=15) were hospitalized with a

diagnostic code for toxic hepatitis (data not shown). Lengths of hospital stay for a severe hepatotoxic adverse event were mean=13.9 days (sd=11.5), median=11 days (4-23.5), and max=37 days for the INH-treated patients (data not shown). The RMP patient had a hospital length of stay of 8 days (data not shown).

In total, 13 (1.5%) patients switched from RMP to another LTBI regimen during treatment, compared with 394 (4.1%) patients switching from INH to another LTBI regimen (Table 21). The median time to switch was 30 days for RMP patients and 58 days for INH patients. Risks and adjusted rates of a switch during treatment were higher for INH than RMP: 4RMP vs 9INH= -2.6% (95% CI: -3.5%,-1.7%), adj RR=0.72 (0.45-1.15).

In total, 4 (0.5%) RMP patients and 30 (0.3%) INH patients died during LTBI treatment (Table 21). The median time to death was 46.5 days (range 32-58 days) for patients starting RMP and 143.5 days for patients starting INH (range 42-227 days). Patients who died during LTBI treatment were older and more likely to have co-morbidities (data not shown). The age and sex-adjusted rate ratio (RR=1.43, 0.49-4.20) was significantly higher for RMP compared to INH patients. Further, the one-year death rates, regardless of whether patients were still being dispensed LTBI drugs, was higher for RMP (2.4%, n=21) compared to INH (0.6%, n=58) patients (data not shown).

Health service use patterns and direct costs

RMP-treated LTBI patients had higher health service utilization-related costs prior to treatment start compared to INH-treated patients, with a roughly three times higher monthly cost of health service use in the month before the index date compared to twelve months prior (Figure 8).

Stratified by month on treatment, mean monthly costs for all health service utilization, TB drugs only, and other health service use only, were higher for RMP-treated patients compared to INH-treated patients (Table 22). Total mean costs for RMP- and INH-treated LTBI patients during the LTBI treatment period were $3044.5 (standard deviation (sd)=10486.2) and $2685.5 ($13519.3), respectively (Table 23). For both RMP and INH patients, the majority of direct costs were for hospitalizations, followed by other drug dispensations and physician billing (Table 23).

Mean first-line TB drug dispensation costs were higher for RMP patients than INH patients (Table 23), with the majority of costs of both regimens due to pharmacist dispensing fees (data not shown). Costs for patients who completed the treatment regimen were higher for INH patients ($3015.8, sd=12240.1) compared to RMP patients ($1172.9, sd=3151.7), reflecting the longer duration of the INH regimen (Table 23).

In multivariable models (Table 24), 4RMP costs for other health service use (excluding TB drugs) were not significantly different than 9INH (adjRR=0.87, 95% CI: 0.59-1.27) after adjustment for confounders. Factors which were associated with higher mean costs of other health service use in multivariable analyses (Table 25) included being aged 35-64 years (adjRR=2.22, 95%CI:1.58-3.12) or aged ≥65 years (adjRR=6.25, 95%CI:3.89-10.03), having HIV/AIDS (adjRR=5.27, 95%CI:3.50-7.94), cancer (adjRR=4.27, 95%CI:2.61-6.99), renal failure (adjRR=4.06, 95%CI:3.01-5.47), any psychiatric diagnosis (adjRR=2.69, 95%CI=1.84-3.94), a hospitalization in the past year (adjRR=2.89, 5%CI: 2.23-3.73), treatment initiated by a specialist physician (adjRR=1.51, 1.06-2.13), and number of months on treatment (adjRR=1.09, 95%CI: 1.06-1.12). Being aged 1-19 (0.69, 0.41-1.15) and having treatment initiated by a physician with active TB experience (adjRR=0.56, 95%CI: 0.41-0.77) were associated with lower mean costs. There was a trend towards higher mean costs of other health service utilization in patients with co-morbidities compared to patients without co-morbidities within the same age group, as well as a corresponding decrease in treatment completion and TB drug costs (Table 25). However, an interaction term of age group and co-morbidity level was not significant in multivariable models of other health service use costs.

6.4 Discussion

This study found higher rates of treatment completion for 4RMP compared to 9INH (estimated completion rates of approximately 54% for 4RMP and 37% for 9INH). Rates of severe hepatic events during treatment did not differ significantly between the 9INH and 4RMP regimens, after adjusting for age group, sex, and co-morbidities. Direct costs of TB drugs were higher for the 4RMP regimen than the 9INH regimen, but direct costs for other health service use did not significantly differ after adjustment for age, co-morbidity level and other confounders.

Rates of treatment completion for both the 9INH and 4RMP regimens were lower in our study compared to other published studies [8, 89, 91-93, 198, 211, 212]. For example, among single-site observational studies conducted predominantly in the US, rates of completion have ranged from approximately 69% to 91% for 4 months of RMP, and 44% to 74% for 9 months of INH[8, 89, 91-93, 198, 211, 212]. Similarly, in the one randomized clinical trial to compare INH and RMP adherence, 81% completed 4 months of RMP and 64% completed 9 months of INH[212]. Some of the variability in rates may be explained by the different definitions of completion and different study populations included in these studies. For example, we used a time-limited measure of adherence that was similar to adherence definitions in several observational studies (ie. 12 months for completion of 100% of INH doses and 6 months for completion of 100% of RMP doses), but not all studies have used this definition [90, 195, 211]. While results from our study suggested that few patients continue treatment after these time limits, including time limits in completion measurements could lead to lower estimated completion rates. Indications for LTBI treatment and study populations may have differed between studies. Other studies have also defined adherence as taking ≥ 80% of prescribed doses[8, 92, 212]; in the clinical trial studies [8, 212], this was assessed by electronic pill monitoring devices which measured each time a pill bottle was opened. This measure of completion may not be directly comparable to our measure using pharmacy-dispensed doses. For example, patients may not have taken the doses, despite having filled the prescription. As well, rates of adherence in clinical trials can be higher than observational settings, due in part to the attention study patients receive as being part of a trial and to the selection of the patients (eg. volunteer bias)[204].

In a recent study using Quebec RAMQ data, reported rates of treatment completion were 64.9% for 4RIF and 31.3% for 9INH [195]. This previous study limited their analyses to drug records containing a RAMQ TB drug program code, while in our study we used all drug records, regardless of which RAMQ plan was associated with the record. We chose not to limit our study to records with RAMQ drug program codes based on our finding that TB drug program codes were not highly reliable; among patients aged 65 years and older, for example, fewer than half of all records for INH (a highly TB-specific drug) had a TB drug program code, and within individual patients, only roughly two-thirds of prescription records for INH were consistently coded with a TB drug program code (Appendix 5). Future studies should focus on validating TB drug program codes in the RAMQ database to help researchers better understand their validity.

Despite differences in estimated crude rates of completion, however, all studies to-date have found rates of 4RMP completion to be higher (nearly twice as high in many studies) than 9INH. This finding may be expected, given the monthly drop-out rates observed in our study. Previous studies have reported similarly that dropout rates are highest in the first month, whereby patients may fail to return after the first prescription is filled[89, 92, 198]. After the first month, with a fairly steady drop-off rate observed with each new prescription refill among INH patients (in our study, approximately 7% per 30 days dispensed), it would be expected that by 6 months approximately one-half of patients would remain, and by 9 months, only one-third of the study population would remain. The 6INH regimen is currently recommended as an alternative to 9INH in Canada, with clinical trials showing lower efficacy (69%) with this regimen compared to the standard 9INH (93%). Results from our study and others suggest that completion rates for two alternative regimens (6INH and 4RMP) would be comparable.

Similar to clinical trial results and other single-clinic sites, we found that drug costs for RMP were higher than for INH. However, in contrast to clinical trial results, crude costs in our study for other health service use were higher for RMP patients, both prior to and during the TB treatment period. Given that LTBI is asymptomatic, it is unlikely that the increase in costs observed prior to the index date were attributable to LTBI. Rather, it is more likely that patients were diagnosed with other co-morbidities which were also risk factors for TB reactivation (and LTBI treatment was subsequently initiated). Further, RMP patients were older and had more co-morbidities when starting treatment, which would have explained some of the differences in costs between RMP and INH patients. Costs during the LTBI treatment period did not differ significantly between the two regimens, however, after adjustment for age, co-morbidity level, and other confounders.

A strength of our study is that we were able to include a general population cohort, across multiple providers, without limiting patients based on age or co-morbidity levels. Further, the majority of previous studies have either been randomized controlled trials, or have been observational studies based in single medical clinics and/or specialized chest clinics, particularly within urban settings. Such studies may accurately capture completion rates within their specific clinics, but results may not generalize to the general population of patients treated for LTBI. In

jurisdictions such as the province of Quebec, where LTBI is not a notifiable infection, we were able to track LTBI treatment outcomes for the entire population using a health administrative database. Unlike some other provinces in Canada, there is also no central TB drug dispensary in Quebec; thus any physician can prescribe drugs to treat LTBI. Therefore, through our study design, we were able to observe LTBI treatment initiated by close to 20,000 patients, by more than 3000 different physicians over the study time period, in all 18 health regions within the province.

There are a number of limitations of this study that need to be considered. First, health administrative databases offer large amounts of data and population-level coverage, however, the quality of data may vary and there may be important gaps in data availability. Importantly, drug exposure data were missing during inpatient hospital stays. This misclassification bias of missing drug treatment data during hospitalizations has been described previously as 'immeasurable time bias' in studies using secondary administrative data[158]. Given that overall only 7% of patients were hospitalized during the treatment window, with a median of 9 days spent in hospital, we are not likely to have underestimated treatment adherence to a great extent. However in our study, this misclassification bias was not balanced in the two treatment groups, with higher rates of hospitalization and more days spent in hospital, on average, in RMP compared to INH patients (17% of RMP and 6% of INH patients were hospitalized, with a median of 19 and 7 days spent in-hospital, respectively). Given the direction of the imbalance between our two treatment groups, this could have led to an underestimation of effect estimates in our study. We assessed the potential impact of this bias in sensitivity analyses, by assuming that all days spent in hospital were days with a TB drug dispensed. These sensitivity analyses did not markedly change our effect estimates comparing these two regimens, suggesting that missing drug treatment data during hospitalizations did not lead to substantial bias in our results.

An additional limitation was that we only had data about drugs dispensed- thus we were not able to differentiate whether an individual was initially prescribed a 6 month or a 9 month regimen of INH, or to determine whether all dispensed doses were ingested. We limited our modelling of adherence rates to the years after the LTBI guidelines had changed, which should have increased the likelihood that intended regimens would have been for 9INH rather than 6INH. As well, we did not see a noticeable drop-off at the 180 dose level in the years after the LTBI treatment

guidelines had changed, which would suggest that we did not have many patients prescribed 6INH. Further, we saw a stabilization of treatment completion rates for 9INH after 2002. This suggests that most patients were prescribed a 9INH regimen during the time period we analyzed in multivariable models, but we cannot be certain.

A further limitation is that RMP may also be prescribed for a handful of other conditions. Most other indications for RMP are only for a few days, while a few are for longer periods; it would be rare, however, to see RMP prescribed for longer than one month for any indication other than for LTBI treatment. We attempted to exclude RMP prescriptions for other indications, by limiting the cohort to patients with at least one 30-day prescription for RMP and by excluding patients with mono-RMP prescriptions plus diagnoses for other RMP indications. But it is possible that we inadvertently included some cases of RMP prescribed for conditions other than LTBI, and this could have led to an underestimation of RMP completion rates by including these patients.

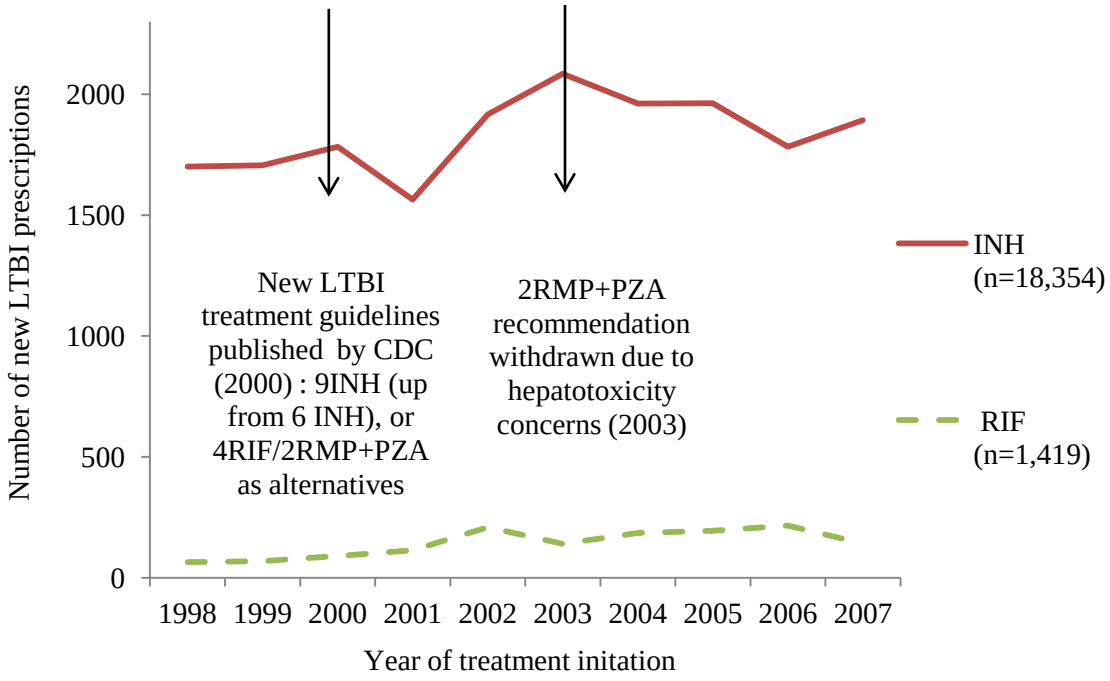
Confounding by indication was a further potential bias in our study. We found (similar to other observational studies[92]) that RMP patients were a more acutely ill population at the start of treatment compared to INH patients, with more co-morbidities and higher rates of hospitalization. We adjusted for pre-treatment co-morbidity risk through use of multiple co-morbidity measures; however, it is possible that we still had residual confounding in our measurements. For example, we used a binary indicator to adjust for TB-related medical risk factors, however, it is possible that this measure did not adequately capture the influence of these individual conditions. There may also have been misclassification of some comorbidities. For example, diagnostic coding of malnutrition in health administrative databases has been shown to underestimate prevalence of malnutrition. Further, we developed our measure using a patient's one-year history of diagnostic codes in physician billing and hospitalization records, which could have misclassified these conditions. As well, given that we did not have prescription drug data available for non-TB drugs for a large proportion of the population, we did not include a prescription drug-related measure of comorbidity adjustment (eg. the Chronic Disease Score), which could have provided better adjustment for comorbid conditions[200].

We also may have been missing some confounders which we could not measure in our health administrative database and which could have led to misspecification of our models. For

example, we did not have data available about whether a patient was recently infected or if they had chest radiographic abnormalities, both of which have been shown to impact adherence[3]. Other factors shown to influence LTBI completion include the patient's perception of their risk of developing active TB and/or developing drug-related side effects, immigration history, cultural beliefs and language barriers, comfort in communicating with their care provider, and social marginalization[3]. We attempted to capture individual-level socioeconomic status and included a measure of psychiatric diagnoses, but we were not able to capture such factors as homelessness.

In conclusion, this study found a higher treatment completion rate for 4RMP compared to 9INH in the Quebec general population, and comparable rates of severe hepatotoxic adverse events and direct costs for health service utilization (other than TB drugs), after adjustment for measured confounders. These results confirm previous reports of higher completion rates with the short-course RMP regimen. Future studies should be conducted in other Canadian populations; provinces which have LTBI registries, such as British Columbia, for example, could provide additional insight into the impact of potential unmeasured confounders which may not have been available in our health administrative database, as well as to better assess the potential impact of missing treatment data during hospitalizations. The finding of reduced completion rates, particularly for RMP-treated patients, when co-morbidities were present warrants further investigation. Further, future studies should investigate the cost-effectiveness of using different LTBI treatment regimens within different population types (including older patients and patients with co-morbidities).

Figure 5: Number of patients starting LTBI treatment regimens (INH and RMP) in Quebec, by index year, 1998-2007 (N=19,773)



Abbreviations: INH=isoniazid; RMP=rifampin

Table 16: Characteristics of patients treated for LTBI in Quebec, stratified by initial regimen (INH or RMP) and start year of treatment, 2003-2007 (N=10,559)

*Patient and physician characteristics at index date**	RMP (n=875), n (%)	INH (n=9684), n (%)	p-value
Sex- male	421 (48.1%)	4155 (42.9%)	<0.01
Age group (years)			
0-19	63 (7.2%)	2296 (23.7%)	<0.01
20-34	309 (35.3%)	3005 (31.0%)	
35-49	220 (25.1%)	2557 (26.4%)	
50-64	147 (16.8%)	1233 (12.7%)	
65-79	106 (12.1%)	531 (5.5%)	
80+	30 (3.4%)	62 (0.6%)	
Health region of residence			
Intermediate/Remote	91 (10.5%)	1008 (10.5%)	1.00
Low individual SES			
Yes	193 (22.0%)	2644 (27.3%)	<0.01
TB-related co-morbidities			
HIV/AIDS	5 (0.6%)	103 (1.1%)	0.17
Cancer	50 (5.7%)	301 (3.1%)	<0.01
Diabetes	73 (8.3%)	393 (4.0%)	<0.01
Renal failure	40 (4.6%)	240 (2.5%)	<0.01
Substance abuse	35 (4.0%)	132 (1.4%)	<0.01
Solid organ transplant	11 (1.3%)	30 (0.3%)	<0.01
Silicosis	2 (0.2%)	22 (0.2%)	1.0
Malnutrition	18 (2.1%)	37 (0.4%)	<0.01
TNF-alpha inhibitors	1 (0.1%)	31 (0.3%)	0.52
Any TB-related medical risk factors†	159 (18.2%)	984 (10.2%)	<0.01
Charlson-Deyo co-morbidity level			
High (score=3 or more)	41 (4.7)	172 (1.8)	<0.01
Moderate (score=1-2)	50 (5.7)	122 (1.3)	
Any psychiatric diagnosis			
Yes	789 (8.2%)	112 (12.8%)	<0.01
Any liver disease diagnosis			
Yes	46 (5.3%)	129 (1.3%)	<0.01
Hospital admission in year before index			
N (%) of patients	222 (25.4%)	904 (9.3%)	<0.01
Median (IQR) total number of days spent in-hospital	20 (9-41)	5 (2-12)	<0.01
Treated started by specialist physician			
TB-related specialist‡	626 (72.3%)	6081 (63.2%)	<0.01
Other specialist	94 (10.9%)	1489 (15.5%)	
Treating physician experienced with active TB§			
Yes	442 (51.0%)	2789 (29.0%)	<0.01
Year of treatment start			
2007	141 (16.1%)	1893 (19.6%)	<0.01
2006	215 (24.6%)	1783 (18.4%)	
2005	194 (22.2%)	1963 (20.3%)	
2004	185 (21.1%)	1961 (20.3%)	
2003	140 (16.0%)	2084 (21.5%)	

Abbreviations: INH=isoniazid; RMP=rifampin; IQR=interquartile range

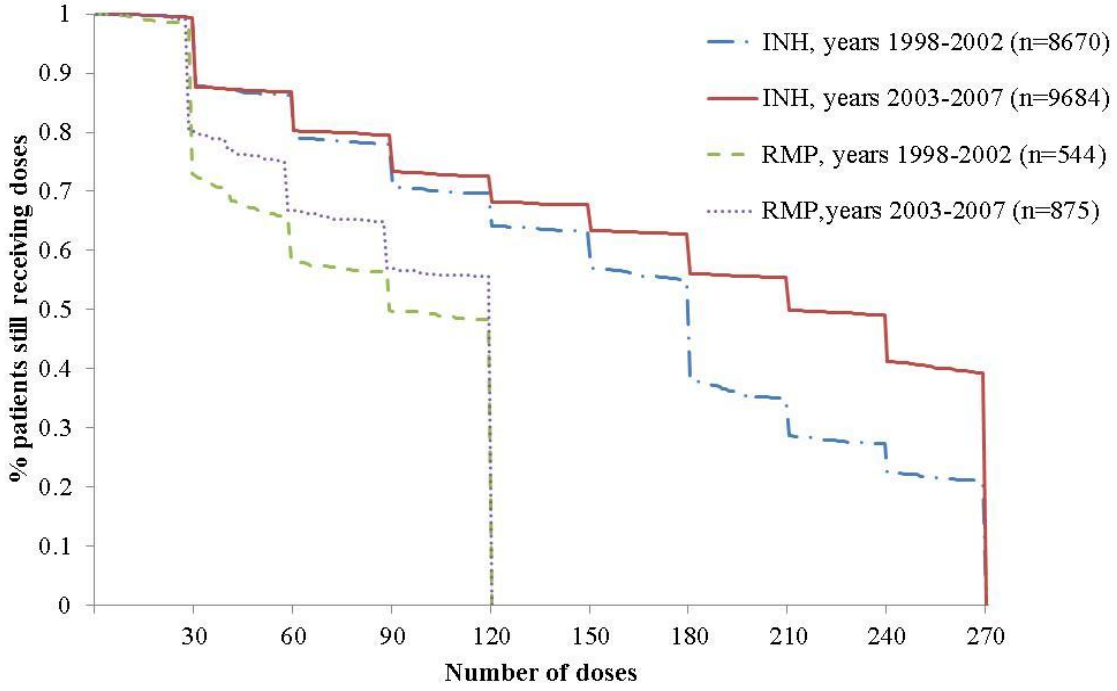
*Missing data: treating physician (n=141), health region (n=49). p-values calculated using chi-squared test for categorical variables and Wilcoxon rank sum test for continuous variables

† TB-related risk factors: cancer, diabetes, HIV/AIDS, renal failure, substance abuse, solid organ transplant, silicosis, malnutrition, and TNF-alpha inhibitors

‡TB-related specialist=trained in respiratory medicine or infectious diseases

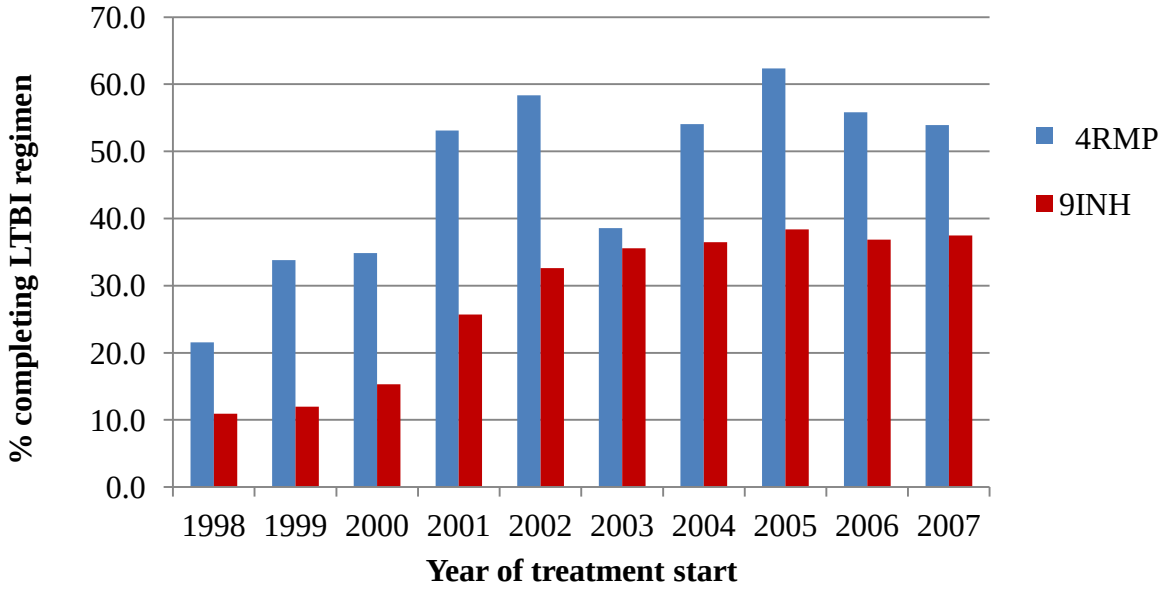
§Active TB experienced=physician treated more than 10 active TB cases over the 10-year study period

Figure 6: Number of LTBI doses dispensed in Quebec, stratified by starting regimen (INH *vs* RMP) and periods of treatment start years (N=19,773)



Abbreviations: INH=isoniazid; RMP=rifampin

Figure 7: Crude rates of treatment completion for 4RMP and 9INH, by year of treatment start (N=19,773)*



Abbreviations: INH=isoniazid; RMP=rifampin.

*Treatment completion=9INH: 270 doses dispensed in 365 days; 4RMP: 120 doses in 180 days

Table 17: Predictors of LTBI treatment completion (4RMP *vs* 9INH)*, Quebec, 2003-2007, univariable and multivariable log-binomial regression (n=10,559)

Patient and physician characteristics†‡	Number (%) completing treatment	Crude RR (95% CI)	Adjusted RR (95% CI)
Starting LTBI regimen			
RMP	468 (53.5)	1.41 (1.17-1.69)	1.51 (1.31-1.75)
INH	3570 (36.9)	1.00	1.00
Sex			
Male	1859 (40.6)	1.12 (1.06-1.18)	1.09 (1.04-1.14)
Female	2179 (36.4)	1.00	1.00
Age group (years)			
1-19	975 (41.3)	1.20 (1.07-1.34)	1.20 (1.08-1.34)
20-34	1162 (35.1)	1.00	1.00
35-64	1629 (39.2)	1.20 (1.09-1.31)	1.17 (1.07-1.27)
≥65	272 (37.3)	1.20 (1.06-1.36)	1.22 (1.06-1.39)
Low individual SES			
Yes	1087 (38.3)	1.00 (0.94-1.07)	-
No	2951 (38.2)	1.00	
HIV/AIDS			
Yes	55 (50.9)	1.47 (1.21-1.79)	1.59 (1.31-1.92)
No	3983 (38.1)	1.00	1.00
Cancer			
Yes	106 (30.2)	0.85 (0.71-1.00)	-
No	3932 (38.5)	1.00	
Diabetes			
Yes	172 (37.7)	1.04 (0.91-1.18)	-
No	3866 (38.3)	1.00	
Renal failure			
Yes	108 (38.6)	1.11 (0.93-1.35)	-
No	3930 (38.2)	1.00	
Substance abuse			
Yes	49 (29.3%)	0.81 (0.63-1.03)	-
No	3989 (38.4%)	1.00	
Any Charlson co-morbidities			
Yes	100 (26.0)	0.71 (0.60-0.85)	0.79 (0.65-0.96)
No	3938 (38.7)	1.00	1.00
Any psychiatric diagnosis			
Yes	305 (33.9)	0.92 (0.83-1.02)	-
No	3733 (38.7)	1.00	
Liver disease			
Yes	68 (38.9)	1.07 (0.87-1.30)	-
No	3970 (38.2)	1.00	
Hospitalization in year before index			
Yes	316 (28.2)	0.74 (0.66-0.83)	0.70 (0.62-0.79)
No	3722 (39.4)	1.00	1.00
Physician training			
Specialist	657 (41.5)	1.09 (0.96-1.23)	-
General practitioner	712 (32.5)	1.00	
Physician is active TB experienced§			
Yes	1361 (42.2)	1.05 (0.89-1.23)	-
No	2656 (36.6)	1.00	
Year of treatment start			
2007	782 (38.5)	1.06 (0.96-1.17)	-
2006	775 (38.8)	1.09 (0.99-1.18)	
2005	873 (40.5)	1.16 (1.05-1.28)	

2004	814 (37.9)	1.06 (0.96-1.17)
2003	794 (35.7)	1.00

Abbreviations: IQR=interquartile range, INH=isoniazid, RMP=rifampin, CI=confidence interval, RR=rate ratio

* Treatment completion=9INH: 270 doses dispensed in 365 days; 4RMP: 120 doses dispensed in 180 days.

† Missing data: treating physician (n=78), health region (n=39).

‡Log-binomial regression using GEE methods with compound symmetry correlation structure to account for clustering of patients within physicians.

§Active TB experienced=physician treated more than 10 active TB cases over the 10-year study period

Table 18: Predictors of LTBI treatment completion, Quebec, 2003-2007*, stratified models (4RMP only and 9INH only), univariable and multivariable log-binomial regression

Patient and physician characteristics†‡	4RMP			9INH		
	Number (%) completing treatment†	Crude RR (95% CI)	Adjusted RR (95% CI)	Number (%) completing treatment†	Crude RR (95% CI)	Adjusted RR (95% CI)
Sex						
Male	206 (44.0)	0.89 (0.76-1.05)	-	1653 (46.3)	1.15 (1.08-1.22)	1.11 (1.05-1.18)
Female	262 (56.0)	1.00		1917 (53.7)	1.00	1.00
Age group (years)						
1-19	34 (54.0)	1.13 (0.74-1.69)	0.98 (0.70-1.39)	941 (41.0)	1.27 (1.14-1.42)	1.26 (1.13-1.41)
20-34	200 (64.7)	1.00	1.00	982 (32.0)	1.00	1.00
35-64	206 (56.1)	1.03 (0.88-1.21)	1.04 (0.93-1.15)	1423 (37.6)	1.21 (1.10-1.34)	1.19 (1.08-1.32)
≥65	28 (20.6)	0.54 (0.34-0.87)	0.67 (0.45-0.99)	244 (41.2)	1.36 (1.19-1.55)	1.35 (1.18-1.55)
Health region of residence						
Intermediate/remote	22 (24.2)	0.50 (0.29-0.85)	-	356 (35.3)	1.01 (0.90-1.13)	-
Central/peripheral	446 (57.2)	1.00		3206 (37.0)	1.00	
Low Socioeconomic status						
Yes	111 (57.8)	1.11 (0.99-1.25)	-	976 (36.9)	1.00 (0.94-1.07)	-
No	357 (52.4)	1.00		2594 (36.9)	1.00	
HIV/AIDS						
Yes	2 (40.0)	1.56 (0.64-3.78)	-	53 (51.5)	1.46 (1.20-1.79)	1.53 (1.25-1.87)
No	466 (53.6)	1.00		3517 (36.7)	1.00	1.00
Cancer						
Yes	10 (20.0)	0.62 (0.34-1.11)	-	96 (31.9)	0.89 (0.75-1.05)	-
No	458 (55.5)	1.00		3474 (37.0)	1.00	
Diabetes						
Yes	15 (20.6)	0.57 (0.37-0.86)	-	157 (41.0)	1.14 (1.01-1.29)	-
No	453 (56.4)	1.00		3413 (36.7)	1.00	
Renal failure						
Yes	4 (10.0)	0.26 (0.10-0.68)	-	104 (43.3)	1.24 (1.04-1.46)	1.21 (1.00-1.46)
No	464 (55.6)	1.00		3466 (36.7)	1.00	1.00
Liver disease						
Yes	23 (50.0)	1.29 (0.86-1.93)	-	45 (34.9)	0.97 (0.75-1.23)	-
No	445 (53.7)	1.00		3525 (36.9)	1.00	
Substance abuse						
Yes	11 (31.4)	0.79 (0.45-1.40)	-	38 (28.8)	0.78 (0.60-1.03)	-
No	457 (54.4)	1.00		3532 (37.0)	1.00	
Any Charlson-Deyo co-morbidities						

Yes	12 (13.2)	0.36 (0.21-0.62)	0.54 (0.31-0.94)	88 (29.9)	0.82 (0.69-0.98)	0.85 (0.70-1.02)
No	456 (58.2)	1.00	1.00	3482 (37.1)	1.00	1.00
Any psychiatric diagnosis						
Yes	33 (29.5)	0.69 (0.46-1.02)	-	272 (34.5)	0.95 (0.85-1.05)	-
No	453 (57.0)	1.00		3298 (37.1)	1.00	
Physician specialist training						
Specialist	402 (55.8)	0.95 (0.68-1.33)	-	2903 (38.4)	1.13 (1.03-1.25)	1.10 (1.00-1.21)
General practitioner	64 (43.8)	1.00		648 (31.7)	1.00	1.00
Physician is active TB experienced§						
Yes	301 (68.1)	1.48 (1.03-2.13)	-	1060 (38.0)	1.00 (0.87-1.14)	-
No	165 (38.9)	1.00		2491 (36.5)	1.00	
Hospitalization in year prior						
Yes	47 (21.3)	0.44 (0.31-0.63)	0.59 (0.42-0.82)	269 (29.9)	0.80 (0.71-0.90)	0.79 (0.69-0.89)
No	421 (64.4)	1.00	1.00	3301 (37.6)	1.00	1.00
Year of treatment start						
2007	75 (53.2)	1.83 (1.27-2.65)	1.69 (1.26-2.28)	707 (37.4)	1.02 (0.92-1.12)	-
2006	119 (55.4)	1.91 (1.28-2.85)	1.72 (1.25-2.36)	656 (36.8)	1.09 (0.99-1.20)	
2005	121 (62.4)	1.65 (1.16-2.36)	1.53 (1.17-1.99)	752 (36.8)	1.04 (0.94-1.14)	
2004	100 (54.1)	1.56 (1.00-2.45)	1.48 (1.06-2.06)	714 (36.4)	1.07 (0.97-1.17)	
2003	53 (37.9)	1.00	1.00	741 (35.6)	1.00	

Abbreviations: IQR=interquartile range, INH=isoniazid, RMP=rifampin, CI=confidence interval, RR=rate ratio

* Treatment completion=9INH: 270 doses dispensed in 365 days; 4RMP: 120 doses dispensed in 180 days.

† Missing data: treating physician (n=78), health region (n=39).

‡Log-binomial regression using GEE methods with compound symmetry correlation structure to account for clustering of patients within physicians.

§Active TB experienced=physician treated more than 10 active TB cases over the 10-year study period

Table 19: Sensitivity analyses of relative risk estimates of LTBI treatment completion (INH vs RMP), Quebec, 2003-2007 (n=10,559)

Measures of LTBI treatment completion	Patients completing treatment	
	n	% (95% CI)
Dispensed 100% of doses, on-time (primary analysis)		
4RMP (120 doses/6 months)	468	53.5 (50.2-56.8)
9INH (270 doses/12 months)	3570	36.9 (35.9-37.8)
4RMP:9INH, RR (95% CI)		1.51 (1.31-1.75)*
Dispensed 100% of doses, ever (sensitivity analysis #1)		
4RMP (120 doses)	488	55.7% (52.4-59.0)
9INH (270 doses)	3796	39.2% (38.2-40.2)
4RMP:9INH, RR (95% CI)		1.52 (1.31-1.75)*
Dispensed 100% of doses, ever, and including hospitalizations with discharge within 15 days before index date or admission within 30 days after last drug dispensation date as LTBI treatment days (sensitivity analysis #2) ǂ		
4RMP (120 doses)	492	56.2% (52.9-59.5)
9INH (270 doses)	3825	39.5% (38.5-40.5)
4RMP:9INH, RR (95% CI)		1.49 (1.28-1.73)*
Dispensed 100% of doses, on-time, excluding patients with hospitalizations with discharge within 15 days before index date, or admission within 30 days after last drug dispensation date (sensitivity analysis #3)		
4RMP (120 doses/6 months)	446	61.6% (58.1-65.2)
9INH (270 doses/12 months)	3359	37.1% (36.1-38.1)
4RMP:9INH, RR (95% CI)		1.66 (1.46-1.88)*
Dispensed 100% of doses, on-time, excluding patients with switches between LTBI regimens (sensitivity analysis #4)		
4RMP (120 doses/6 months)	471	54.6% (51.3-58.0)
9INH (270 doses/12 months)	3576	38.5% (37.5-39.5)
4RMP:9INH, RR (95% CI)		1.52 (1.31-1.76)*
Dispensed 100% of doses, on-time, limited to RAMQ TB drug program codes (sensitivity analysis #5)		
4RMP (120 doses/6 months)	395	65.0% (61.2-68.8)
9INH (270 doses/12 months)	2328	29.2% (28.2-30.2)
4RMP:9INH, RR (95% CI)		2.23 (2.02-2.45)*

Abbreviations: RR= risk ratio, CI=confidence interval; RMP=rifampin, INH=isoniazid

* RR's and 95% CIs estimated using log-binomial regression with GEE methods to account for clustering of patients within physicians, adjusted for sex, age group, any Charlson co-morbidities, HIV, physician specialist, and hospitalization in the past year

Table 20: Sensitivity analysis comparing crude rates of treatment completion for 4RMP and 9INH*, between patients with and without a hospitalization before or during treatment†, stratified by year of treatment start (n=10,559)

	Year of treatment start				
4RMP	2003	2004	2005	2006	2007
No hospitalizations (n=1110)					
# of patients starting	139	138	167	192	114
% completing	45.5	64.0	69.5	60.9	61.4
With hospitalizations (n=309)					
# of patients starting	28	46	27	23	27
% completing	7.1	23.9	18.5	8.7	18.5
9INH					
No hospitalizations (n=17040)					
# of patients starting	1958	1824	1814	1664	1803
% completing	36.6	36.6	35.5	36.5	37.3
With hospitalizations (n=1314)					
# of patients starting	126	137	149	117	90
% completing	27.8	34.3	40.3	41.0	38.9

*Treatment completion=9INH: 270 doses dispensed in 365 days; 4RMP: 120 doses dispensed in 180 days.

†Hospitalization before and during treatment=discharge within 15 days before index date or admission up to 30 days after last TB drug dispensed

Table 21: Risk and rates of adverse outcomes occurring during LTBI treatment in Quebec, stratified by initial regimen, 2003-2007 (N=10,559)

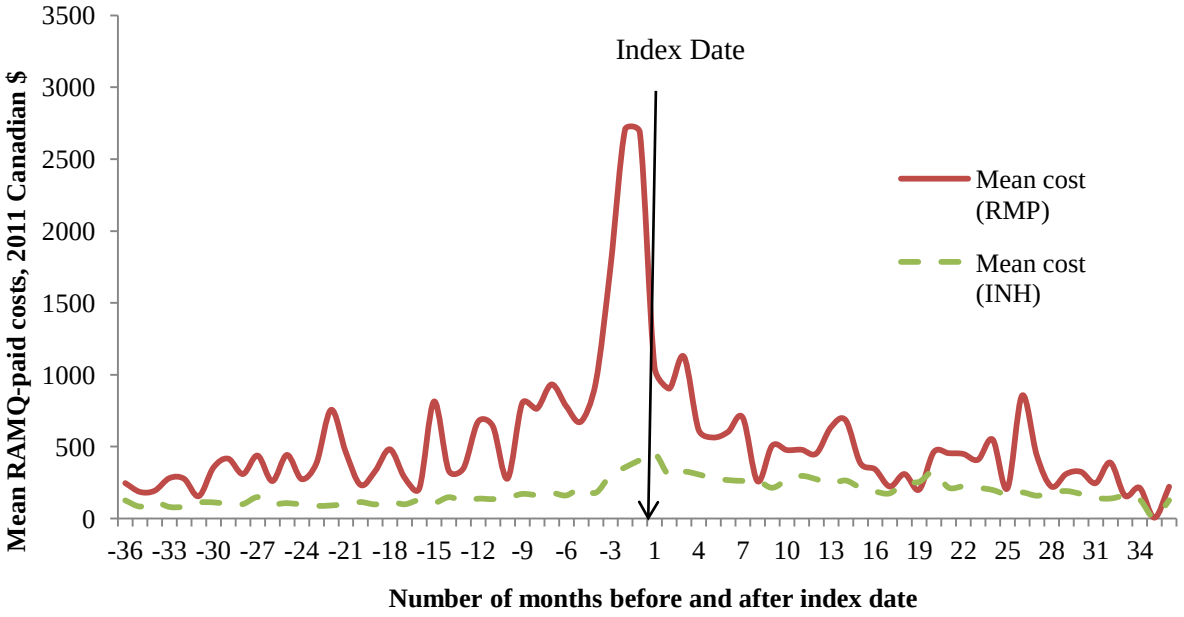
Type of event and LTBI regimen	n	% of patients starting regimen (95% CI)	Risk difference, 4RMP-9INH (95% CI)	Median time to event, in days	# events/ 10,000 person-doses dispensed	Incidence rate ratio (4RMP:9INH) †	
						Univariable RR (95% CI)	Multivariable RR (95% CI)
Switch in regimen							
4RMP	13	1.5% (0.8-2.5)	-2.6% (-3.5,-1.7)	30 (25-53)	1.53	0.71 (0.45-1.11)	0.72 (0.45-1.15)
9INH	394	4.1% (3.7-4.5)	0	58 (30-91)	2.18	1.00	1.00
Severe hepatotoxic							
4RMP	1	0.1% (0.0-0.6)	-0.1% (-0.1, 0.3)	31 (31-31)	0.12	1.07 (0.13-8.59)	0.73 (0.10-5.43)
9INH	20	0.2% (0.1-0.3)	0	151.5 (63.5-249.5)	0.11	1.00	1.00
Death							
4RMP	4	0.5% (0.1-1.2)	0.3% (-0.6, 0.3)	46.5 (32-58)	0.47	2.85 (0.88-9.28)	1.43 (0.49-4.20)
9INH	30	0.3% (0.2-0.4)	0	143.5 (42-227)	0.17	1.00	1.00

Abbreviations: IQR=interquartile range, INH=isoniazid, RMP=rifampin, CI=confidence interval, RR=rate ratio

* Follow-up censored at earliest of: event date, 30 days after last TB dose dispensed, or at time limits of regimens (365 days for 9INH, 180 days for RMP)

† Rate ratios estimated using Poisson regression with ln(doses) as offset and dscale option to account for underdispersion (SAS PROC GENMOD), and independent correlation structure to account for clustering by treating physician; multivariable models adjusted for: sex, age>65 years old, and hospitalization in year prior (any versus none)

Figure 8: Estimated mean health resource costs paid by RAMQ for LTBI patients*, stratified by number of months before and after index date, Quebec†



*Patients starting LTBI treatment with INH or RMP between 2003-2007
† Costs reported in 2011 Canadian dollars (rounded to the nearest dollar). Estimated total RAMQ-paid costs= sum of hospitalizations+ emergency department (ED) visits+ hospital day procedures+ physician billing + drugs dispensed. Unit costs assigned to hospitalizations ($1308/day), ED visits ($183.08/visit) and hospital day procedure ($183.08). Actual billed costs used for physician billing and drugs dispensed, adjusted to 2011 dollars using the Consumer Price Index. Drug costs include all amounts paid by RAMQ for drug dispensation, including sum of drug cost and pharmacist dispensing fee, minus deductable and co-pay by patients

Table 22: Estimated monthly RAMQ-paid costs for health service use during LTBI treatment period, stratified by LTBI regimen (INH or RMP), Quebec*†‡

		RMP, all costs ($)		RMP, TB drug costs ($)		RMP, other health service use costs ($)	
Month of treatment	N	Mean (sd)	Median (IQR)	Mean (sd)	Median (IQR)	Mean (sd)	Median (IQR)
Month 1	875	1052.0 (5556.6)	190 (125-354)	95.7 (41.1)	77 (73-145)	956 (5560)	80 (35-246)
Month 2	875	903.7 (4792.4)	113 (73-230)	46.8 (44.7)	69 (0-75)	857 (4798)	37 (0-178)
Month 3	874	459.7 (3615.2)	77 (0-135)	42.1 (42.6)	52 (0-75)	418 (3616)	35 (0-59)
Month 4	644	340.1 (2508.9)	74 (0-116)	36.1 (38.1)	10.5 (0-74.1)	304 (2511)	25 (0-57)
Month 5	584	383.7 (4868.5)	36 (0-82)	9.8 (25.4)	0 (0-0)	374 (4864)	35 (0-67)
Month 6	385	279.9 (1886.8)	0 (0-41)	6.4 (19.1)	0 (0-0)	274 (1886)	0 (0-37)
Total cost, per month	875	971.7 (3984.0)	105 (78-228)	46.5 (16.3)	51 (37-60)	925.2 (3986.6)	49 (25-183)
		INH, all costs ($)		INH, TB drug costs ($)		INH, other health service use costs ($)	
Month of treatment	N	Mean (sd)	Median (IQR)	Mean (sd)	Median (IQR)	Mean (sd)	Median (IQR)
Month 1	9684	453.2 (5716.8)	80 (31-152)	20.5 (26.7)	11 (10-21)	432 (5717)	53 (9-128)
Month 2	9684	297.4 (2480.7)	40 (11-95)	11.2 (19.1)	10 (0-11)	286 (2481)	29 (0-75)
Month 3	9684	299.5 (3580.9)	35 (10-84)	11.2 (19.9)	10 (0-11)	288 (3581)	16 (0-62)
Month 4	8460	313.3 (3015.1)	38 (10-91)	11.8 (20.4)	10 (0-11)	301 (3015)	23 (0-72)
Month 5	7935	297.7 (3570.1)	37 (10-89)	12.0 (19.8)	10 (0-11)	285 (3770)	18 (0-69)
Month 6	7471	291.1 (2706.3)	36 (10-88)	11.8 (19.2)	10 (0-11)	279 (2707)	16 (0-66)
Month 7	7091	270.0 (2456.7)	35 (10-84)	11.8 (20.3)	10 (0-11)	258 (2457)	13 (0-64)
Month 8	6626	275.4 (2753.0)	23 (10-81)	11.4 (19.1)	10 (0-11)	264 (2753)	9 (0-58)
Month 9	6101	229.9 (1604.9)	20 (0-76)	9.3 (17.9)	10 (0-11)	221 (1605)	9 (0-58)
Month 10	5533	270.4 (2773.6)	11 (0-67)	4.1 (12.7)	0 (0-0)	266 (2774)	8 (0-56)
Month 11	4213	322.3 (7011.4)	0 (0-37)	3.0 (11.2)	0 (0-0)	319 (7018)	0 (0-35)
Month 12	1770	369.1 (3669.9)	0 (0-57)	4.4 (13.2)	0 (0-0)	365 (3670)	0 (0-46)
Total cost, per month	9684	363.7 (3014.2)	49 (27-100)	11.7 (13.6)	8 (6-9)	352.0 (3014.4)	36 (17-84)

LTBI=latent tuberculosis infection; RMP=rifampin; INH=isoniazid, std=standard deviation; IQR=interquartile range

*Patients starting LTBI treatment with INH or RMP between 2003-2007

† Total costs during TB treatment period=from first date with a TB drug dispensed to 30 days after the last TB drug dispensed, limited to a period of up to 365 days for INH and 180 days for RMP.

‡ Costs reported in 2011 Canadian dollars. Estimated total RAMQ-paid costs= sum of hospitalizations+ emergency department (ED) visits+ hospital day procedures+ physician billing + drugs dispensed. Unit costs assigned to hospitalizations ($1308/day), ED visits ($183.08/visit) and hospital day procedure ($183.08). Actual billed costs used for physician billing and drugs dispensed, adjusted to 2011 dollars using the Consumer Price Index. Drug costs include all amounts paid by RAMQ for drug dispensation, including sum of drug cost and pharmacist dispensing fee, minus deductable and co-pay by patients.

Table 23: Patterns and direct costs of health service use by LTBI patients in Quebec, during LTBI treatment period

Health service utilization and estimated RAMQ paid costs, per component	LTBI patients, 2003-2007†	
	RMP (n=875)	INH (n=9684)
Hospitalizations		
Mean cost, per patient starting treatment (sd)	$1687.1 (9079.2)	$1273.9 (11774.5)
Total number of hospitalizations events	76	722
Patients with any event, n (%)	59 (6.7%)	493 (5.1%)
Mean # of events/patient (sd) ‡	1.29 (0.70)	1.47 (0.90)
Median (IQR), max ‡	1 (1-2), 5	1 (1-2), 6
# days in-hospital per stay, mean (sd) ‡	15.1 (15.6)	11.6 (20.8)
# days in-hospital per stay, median (IQR)‡	10 (6-19)	5 (2-12)
Emergency department visits (ED)		
Mean cost, per patient starting treatment (sd)	$39.5 (120.1)	$54.7 (150.4)
Total number of ED visits	189	2895
Patients with any event, n (%)	131 (15.0%)	1853 (19.1%)
Mean # of events/patient (sd) ‡	1.60 (1.68)	1.60 (1.29)
Median (IQR), max ‡	1 (1-2), 16	1 (1-2), 26
Hospital day procedures		
Mean cost, per patient starting treatment (sd)	$2.9 (24.6)	$5.9 (38.8)
Total number of procedures	14	311
Patients with any event, n (%)	13 (1.5%)	259 (2.7%)
Mean # of events/patient (sd) ‡	1.08 (0.28)	1.20 (0.53)
Median (IQR), max ‡	1 (1-1), 2	1 (1-2), 6
Physician billing		
Mean cost, per patient starting treatment (sd)	$426.4 (1186.0)	$462.9 (1266.4)
Total number of physician contacts	6535	86628
Patients with any event, n (%)	820 (93.7%)	8986 (92.8%)
Mean # of events/patient (sd) ‡	8.0 (12.3)	9.6 (18.8)
Median (IQR), max ‡	5 (3-8), 1-109	5 (3-10), 1-314
First-line TB drug dispensations		
Mean cost, per patient starting treatment (sd)	$220.6 (118.2)	$99.0 (128.3)
Total number of TB drug dispensations	2755	60789
Patients with any event, n (%)	875 (100%)	9684 (100%)
Mean # of events/patient (sd) ‡	3.1 (1.6)	6.3 (3.7)
Median (IQR), max ‡	4 (2-4), 9	7 (3-9), 49
Other drugs dispensations		
Mean cost, per patient starting treatment (sd)	$668.0 (1864.8)	$789.1 (3106.7)
Total number of other drug dispensations	2950	57356
Patients with any event, n (%)	381 (43.5%)	6146 (63.4%)
Mean # of events/patient (sd) ‡	7.74 (7.11)	9.34 (12.51)
Median (IQR), max ‡	6 (2-11), 54	6 (2-10), 34
Total RAMQ-paid costs (mean, sd), per patient starting treatment	*$3044.5 (10486.2)*	*$2685.5 (13519.3)*
Total RAMQ-paid costs (mean, sd), per patient completing treatment	*$1172.9 (3151.7)*	*$3015.8 (12240.1)*

Abbreviations: sd=standard deviation; IQR=interquartile range; ED=emergency department

* Total costs during TB treatment period (from first date with a TB drug dispensed to 30 days after the last TB drug dispensed, limited to a period of up to 365 days for INH and 180 days for RMP).

†Total days of follow-up during TB treatment period= 142,499 (RMP); 2,481,775 (INH).

‡Among patients with one or more events

Table 24: Predictors of RAMQ-paid costs for health service use *(excluding TB drugs)** during LTBI treatment period (4RMP *vs* 9INH), Quebec, 2003-2007 (n=10,559)

Characteristics	Mean (sd) costs, $	Crude Cost Ratio † (95% CI)	Adjusted Cost Ratio† (95% CI)
Starting LTBI regimen			
RMP	2824.0 (10504.9)	1.11 (0.66-1.86)	0.87 (0.59-1.27)
INH	2586.5 (13520.4)	1.00	1.00
Sex			
Male	3461.1 (16965.7)	1.70 (1.53-1.89)	-
Female	1952.3 (9534.5)	1.00	
Age group (years)			
1-19	705.1 (6707.8)	0.72 (0.66-0.78)	0.69 (0.41-1.15)
20-34	997.1 (8755.7)	1.00	1.00
35-64	3193.0 (14155.8)	3.12 (2.91-3.36)	2.22 (1.58-3.12)
≥65	12726.7 (28237.4)	12.07 (10.62-13.71)	6.25 (3.89-10.03)
Remote health region			
Yes	4613.6 (11990.2)	2.01 (1.80-2.25)	-
No	2377.7 (13446.4)	1.00	
Low individual SES			
Yes	2882.6 (14714.4)	1.15 (1.06-1.24)	-
No	2504.6 (12735.2)	1.00	
HIV/AIDS			
Yes	17199.5 (46170.6)	4.50 (2.76-7.33)	5.27 (3.50-7.94)
No	2455.4 (12432.5)	1.00	1.00
Cancer			
Yes	19129.1 (10443.5)	5.62 (4.56-6.93)	4.27 (2.61-6.99)
No	2038.1 (43239.9)	1.00	1.00
Diabetes			
Yes	12089.2 (33156.6)	3.87 (3.09-4.85)	-
No	2178.2 (11446.1)	1.00	
Renal failure			
Yes	18716.5 (30177.3)	5.96 (5.64-7.65)	4.06 (3.01-5.47)
No	2167.3 (12232.1)	1.00	1.00
Liver disease			
Yes	18767.2 (48715.9)	7.63 (5.91-9.85)	-
No	2333.8 (11641.4)	1.00	
Substance abuse			
Yes	14715.7 (39010.5)	3.96 (2.73-5.74)	-
No	2411.6 (12366.3)	1.00	
Any Charlson co-morbidities			
2 or more	27852.2 (57216.4)	13.78 (10.73-17.69)	-
1	14599.4 (26826.6)	7.26 (5.79-9.08)	
0	1928.3 (9960.6)	1.00	
Any psychiatric diagnosis			
Yes	7839.5 (24170.0)	3.61 (3.21-4.06)	2.69 (1.84-3.94)
No	2118.0 (11663.9)	1.00	1.00
Physician training			
Specialist	2589.4 (13083.7)	0.94 (0.86-1.02)	1.51 (1.06-2.13)
General practitioner	2672.3 (14222.3)	1.00	1.00
Physician is active TB experienced‡			
Yes	1100.2 (7167.5)	0.33 (0.31-0.35)	0.56 (0.41-0.77)
No	3278.2 (15247.9)	1.00	1.00
Hospitalization in year before index			

Yes	11431.7 (31781.3)	7.13 (6.44-7.89)	2.89 (2.23-3.73)
No	1552.7 (8186.2)	1.00	1.00
Year of treatment start			
2007	2448.0 (14217.4)	1.03 (0.92-1.14)	-
2006	2914.6 (11706.6)	1.14 (1.02-1.26)	
2005	2705.2 (14423.8)	1.23 (1.10-1.37)	
2004	2595.3 (12223.3)	1.08 (0.97-1.20)	
2003	2388.2 (13622.7)	1.00	
Months of treatment completed, per month	399.5 (3110.4)	1.05 (1.05-1.06)	1.09 (1.06-1.12)

Abbreviations: IQR=interquartile range, INH=isoniazid, RMP=rifampin, CI=confidence interval, RR=rate ratio.
Missing data: treating physician (n=78), health region (n=39).
* Total costs during TB treatment period (from first date with a TB drug dispensed to 30 days after the last TB drug dispensed, limited to a period of up to 365 days for INH and 180 days for RMP.
† Gamma regression using GEE methods to account for clustering of patients within physicians (compound symmetric correlation structure).
‡ Active TB experienced=physician treated more than 10 active TB cases over the 10-year study period

Table 25: Estimated mean (sd) direct health system costs during LTBI treatment period in Quebec*, frequencies of treatment completion and severe hepatotoxic events, stratified by patient age group and co-morbidity level†‡§

Patient characteristics	N		TB drug costs		Other costs		Treatment completion (%)‖		Severe AE, hepatotoxic (%)	
	RMP	INH	RMP	INH	RMP	INH	RMP	INH	RMP	INH
Age group (years)										
0-19										
With co-morbidities	7	134	185.4 (168.5)	145.9 (166.6)	13684.0 (20289.1)	2504.9 (11184.00	28.6	19.4	0	0
No co-morbidities	56	2162	218.1 (144.6)	177.4 (202.4)	365.6 (866.9)	559.7 (6280.9)	61.6	33.8	0	0.1
20-34										
With co-morbidities	20	230	170.0 (101.6)	71.9 (105.1)	4434.2 (12345.6)	5761.6 (28093.3)	30.0	22.1	0	0.4
No co-morbidities	289	2775	252.6 (87.3)	73.2 (83.4)	227.8 (315.8)	657.5 (4817.2)	66.8	25.3	0	0
35-64										
With co-morbidities	87	358	150.8 (104.3)	76.0 (70.5)	6709.4 (16485.1)	6531.0 (12283.7)	18.7	28.2	0	1.4
No co-morbidities	280	3432	252.5 (94.3)	78.0 (80.7)	392.5 (1214.9)	1420.7 (5636.5)	63.5	28.3	0	0.2
65+										
With co-morbidities	108	182	131.2 (107.9)	61.2 (49.4)	8558.3 (14295.3)	25358.9 (46104.4)	16.4	27.7	0.9	2.2
No co-morbidities	28	411	181.8 (155.8)	72.0 (82.6)	9256.4 (28685.7)	8464.7 (16596.3)	39.4	34.0	0	0.2

*Patients starting LTBI treatment with INH or RMP between 2003-2007

† Total costs during TB treatment period (from first date with a TB drug dispensed to 30 days after the last TB drug dispensed, limited to a period of up to 365 days for INH and 180 days for RMP)

‡ Costs reported in 2011 Canadian dollars (rounded to the nearest dollar). Estimated total RAMQ-paid costs= sum of hospitalizations+ emergency department (ED) visits+ hospital day procedures+ physician billing + drugs dispensed. Unit costs assigned to hospitalizations ($1308/day), ED visits ($183.08/visit) and hospital day procedure ($183.08). Actual billed costs used for physician billing and drugs dispensed, adjusted to 2011 dollars using the Consumer Price Index. Drug costs include all amounts paid by RAMQ for drug dispensation, including sum of drug cost and pharmacist dispensing fee, minus deductable and co-pay by patients.

§Co-morbidities defined as having one or more hospital discharges in the year before the first TB drug dispensation (index date)

‖Treatment completion=9INH: 270 doses dispensed in 365 days; 4RMP: 120 doses dispensed in 180 days

CHAPTER 7: GENERAL DISCUSSION

7.1 Summary

The studies included in this thesis addressed a number of gaps in the literature important for assessing the cost-effectiveness of LTBI treatment programs in Quebec.

First, a systematic review was completed of studies which had validated methods for identifying TB patients in health administrative databases (Chapter 3). Results of this review suggested that TB case definitions based on diagnostic codes generally had low positive predictive value, particularly among using non-hospitalized populations. Positive predictive value generally improved with use of algorithms based on TB drug prescriptions data. The review concluded that drug prescription-based algorithms specifying initial use of 3 or more TB drugs, total treatment duration of more than 3 months, and markers to identify and exclude NTM cases should increase the PPV for capturing active TB cases in health administrative databases.

Following from this, using data from the Quebec provincial RAMQ health administrative database (Chapter 4), this thesis documented the high rates of health service utilization and direct costs by patients with active TB over a ten-year period in Quebec. Health service use costs were shown to begin to rise as much as eight months before the start of TB treatment, with a marked increase 3 months before and followed by a significant decline in health service use costs once treatment was started. Similar to other costing studies, hospitalizations of active TB cases accounted for the largest portion of estimated direct costs during the period of diagnosis and treatment of active TB patients, with more than half of all active TB patients hospitalized at least once.

A third follow-up thesis study (Chapter 5) evaluated the role of patient-level clinical and demographic factors in predicting hospitalization and hospital length of stay during diagnosis and treatment of active TB cases in the largest health region in the province (Montreal). More than one-third of active TB patients were diagnosed as inpatients. More than half of active TB patients were hospitalized initially, and roughly one in ten patients were hospitalized later during TB treatment. Patients who were older, Canadian-born, with more severe TB disease and co-

morbidities, and multi- or poly-drug resistant TB had the highest probability of being hospitalized initially. Having older age, symptomatic disease, co-morbidities including HIV infection, renal disease, and drug resistant TB, as well as being in a teaching hospital, were associated with longer hospital stays.

A final study (Chapter 6) compared completion rates, direct costs, and adverse event rates between two LTBI regimens, 9 months of INH and 4 months of RMP. Similar to previous studies, this study found that rates of treatment completion were higher for 4RMP than 9INH, with crude completion rates nearly double for the population of RMP treated patients (54%) than for INH treated patients (37%). Completion rates were lowest in RMP treated patients who were older and had multiple co-morbidities, while older age was not associated with lower completion rates in 9INH patients. TB drug costs were higher for 4RMP than 9INH patients, while costs for other health service use did not differ significantly after adjustment for age and comorbidities in multivariable models. Rates of severe hepatotoxic adverse events did not differ significantly between regimens.

7.2 Policy Implications

First, these thesis results reinforce previous findings, namely that active TB is a costly disease to the healthcare system, with a high health service use burden, in large part due to the high rates of hospitalization of active TB patients. These results also support the argument that shifting treatment from inpatient to outpatient care, wherever possible, could lead to substantial cost-savings and possibility of diversion of resources to TB prevention programs.

Interestingly, findings from this thesis suggested that Canadian-born patients and long-term foreign-born residents may be presenting with more advanced disease, on average, compared to recent immigrants. Among Canadian-born patients and foreign-born patients who have lived in Canada for a number of years, a low index of clinical suspicion by healthcare providers, diagnostic delays, and social marginalization of some patients may lead to more severe disease at the time of TB diagnosis. Earlier diagnosis and treatment of these patients should reduce treatment-related costs by reducing time spent in-hospital. As well, the finding of increasing health service use in the months leading up to treatment initiation for active TB suggests that

some patients are experiencing diagnostic delays. We could not determine definitively when the rise in health service use attributable to TB occurred, but our results suggested that costs increased markedly in the 3 months before the index date, and there was some TB related health service use may have started as early as 8 months before the index date. From an economic perspective, disease costs may be underestimated if these periods are not incorporated into costing studies.

For LTBI treatment, the generally low rates of treatment completion observed in this thesis, for both INH and RMP regimens, highlights the need to focus additional efforts on understanding and promoting LTBI treatment completion in Quebec. Completion rates were lower than observed in published randomized clinical trials comparing INH and RMP[8], and generally lower than most other previously published observational studies [8, 89, 91-93, 198, 211, 212]. While missing data and other data limitations in the Quebec health administrative database could have led to some underestimation of treatment completion rates, it should not have accounted for all of this effect. With regards to current LTBI treatment policy, the finding of lower rates of treatment completion for 9INH compared to 4RMP observed in this thesis, similar to other studies, suggests that switching to the shorter-course 4RMP regimen should lead to an increase in completion rates in the general population of patients treated for LTBI in Quebec.

A full cost-effectiveness analysis was not completed as part of this thesis. However evidence from published cost-effectiveness analyses suggests that, given the higher overall completion rates for 4RMP, and the fact that costs of other health service use for 4RMP patients were not significantly higher than for 9INH patients, it could be expected to be cost-effective to extend the use of 4RMP to the broader population of patients. It is important to consider that in current clinical practice, as observed in these thesis results, RMP appears to be utilized more frequently for patients who were older and with more co-morbidities. Though it was not possible from these data to determine the specific reasons for this discrepancy in prescribing patterns, these are likely patients who are predicted by clinicians to be a higher-risk of not completing treatment with the standard INH regimen, either due to probability of hepatotoxic adverse events or to patient drop-out. Thus, completion rates should be expected to increase by extending 4RMP to a population with fewer co-morbidities. Notably, the finding of reduced completion rates in the presence of co-morbidities, particularly for older-aged RMP-treated patients, needs further investigation and

may suggest that even shorter-course regimens (eg. 3HP) could be cost-effective for patients at high risk for treatment non-completion.

Lastly, this thesis provided some insight into the use of health administrative databases for TB research and surveillance. These types of databases may be useful for health service research of TB patients and for tracking outcomes among treated LTBI patients, particularly when no disease registries exist. They may also be useful for surveillance purposes of tracking TB disease rates and evaluating the completeness of current TB notification systems. But researchers need to be aware of the specific limitations of these types of databases, particularly due to missing inpatient treatment data and challenges with TB case definitions. Researchers should cautiously use ICD codes to identify TB; use of ICD diagnostic codes for identifying TB may have low diagnostic accuracy, particularly when derived from physician billing records. For identifying treated LTBI patients, researchers should focus on using drug prescriptions data. Developers of future versions of the ICD system should also consider incorporating new diagnostic codes which would differentiate LTBI from active TB, in order to improve coding accuracy and utility of these codes for research and surveillance purposes.

7.3 Next Steps: Areas of Future Research

Results of these four thesis studies suggest a number of areas for further research.

First, further studies should examine treatment completion and adverse event rates of RMP and other short-course regimens for LTBI treatment, compared to the standard INH regimen, within different settings and population groups. While these health administrative data allowed investigation of completion rates, our health administrative dataset was limited in availability of demographic, clinical and physician-related variables which may be important determinants of treatment completion[3]. The finding of a poor completion rate of 4RMP in older-aged patients with co-morbidities warrants further investigation. As well, larger scale studies of SAE's using clinical and health service use data may be needed to understand the adverse event risks of these drug regimens. When available, clinical trial results will also provide data on the efficacy of the 4RMP regimen.

Completing cost-effectiveness and/or cost-utility economic analyses of different LTBI treatment regimens within different settings and patient populations, including cohorts with older ages and co-morbidities, is an important next research step. Most economic evaluations of different LTBI treatment regimens to-date have focused on adult contacts, recent immigrants, and low-risk reactors. Although clinical trial results about efficacy of shorter-course RMP are not yet available, sensitivity analyses can provide insight into the cost-effectiveness of different regimens within different patient populations. This thesis contributed more detailed individual patient-level data about LTBI treatment completion rates, health service utilization and costs, which will be useful for improved economic analyses. Future economic evaluation models could also consider using discrete event simulation models in order to fully incorporate the variability of individual-level patient data available in health administrative and clinical databases[213].

Third, future studies of the Quebec population should incorporate a more comprehensive approach to disease costing. This thesis used an average daily cost estimate for hospitalizations based on estimated costs in urban Montreal hospitals. However, it is unlikely that all hospitalizations would have similar resource use[214]. Future studies should consider incorporating resource intensity weights (NIRRUs) in the RAMQ data to better estimate hospitalization costs[215]. Additionally, given that the recommended base-case analysis for cost-effectiveness evaluations is to use a societal approach[216], future studies for the Quebec population should evaluate additional direct and indirect costs to the healthcare system that were not available in the RAMQ database. Additional direct costs would include laboratory tests, nursing visits, visits to salaried (non fee-for-service) physicians, ambulance services, and visits to other allied health care professionals. Indirect costs may also add substantially to the true cost of active TB and future costing studies of TB in Quebec should incorporate costs such as time lost from work, travel time and transportation costs, caregiver time, etc. Future TB costing studies should also estimate the cost impact of diagnostic delay and of longer-term pulmonary impairment after TB treatment is completed. More detailed regression models of costs using individual-level data would also provide more insight into the timing and drivers of disease costs in active TB patients. Future costing studies should also consider the health service use and costs of diagnosing and initiating treatment for suspected active TB cases, as these also contribute to TB control program costs.

Fourth, additional studies should focus on developing a clearer understanding of the determinants and timing of health service use by active TB patients. Detecting cases earlier should theoretically help to reduce costs and improve health outcomes in TB patients, by identifying and treating TB cases before they develop greater morbidity and are more contagious. While this thesis did not set out to identify patient trajectories through the healthcare system, the finding that a high proportion of active TB patients visited the ED at least once during the six months before the start of community-based treatment suggests that many Quebec patients may have had ED contact before TB diagnosis, with resulting missed opportunities for earlier diagnosis. Health administrative data would allow further investigation of the timing of service use. The higher rates of hospitalization observed in Canadian-born active TB patients and foreign-born patients who have lived in Canada for a number of years, compared to more recent immigrants, also warrants further investigation.

Lastly, more work needs to be completed to validate health administrative databases for identifying TB cases, for understanding the validity of different TB-relevant codes, and for understanding the impact of missing data. In Quebec, the RAMQ database could be linked to provincial MADO files to enable direct validation of TB case definitions. While there are eighteen different health regions in the province (and thus eighteen different MADO files), linkage of the TB Resource cohort would be a logical next step (given that the Montreal health region accounts for a majority of TB cases in the province). Results from this thesis also suggest that ICD codes for NTM may be useful for identifying NTM within health administrative databases, but more validation work is needed. As there are generally no disease registries for NTM, and given the reported increasing prevalence of NTM infections[217], health administrative databases could provide a useful data source for NTM surveillance and research. As well, while health administrative databases in Canada share many common characteristics (given universal healthcare coverage), there are differences between provinces, both in data availability and in provision of health services. Therefore, it is not entirely clear how generalizable these results will be to other provinces. Similarly, there may be also differences between Canadian and US databases and health systems. Therefore, more work to assess comparability of these thesis findings to other jurisdictions is needed.

7.4 Final Conclusions

This thesis addressed several gaps in the literature important for assessing the cost-effectiveness of LTBI treatment in Quebec. It provided real-world data about health service use and costs of active TB patients, as well as treatment completion rates, adverse events and costs for two different LTBI regimens. These population datasets included data for all treated patients in the general population, without being limited to patients only eligible for enrollment in a clinical trial or who were being treated solely at specialized public health or respiratory medicine clinics. Since in Quebec any physician can prescribe TB drugs, these population datasets captured the wide range of providers and clinics providing TB treatment.

The use of the provincial health administrative database was a strength of this thesis in that it allowed assessment of the types, timing and costs of health service use in active TB patients and in treated LTBI patients, across the entire province. The key feature of the Quebec RAMQ database, that all TB drugs have been paid for by the RAMQ since 1997, allowed the assumption that the dataset was near complete for capturing treated LTBI patients. Given that no LTBI registries exist in the province of Quebec, the use of the RAMQ thus allowed us to thus track LTBI treatment outcomes across the province. Different jurisdictions may have other policies regarding coverage of TB drugs, thus usefulness of health administrative databases to track LTBI treatment outcomes may differ in different regions. The use of the Montreal Resource cohort database was a further strength of this thesis in that it allowed us to evaluate hospitalization patterns across multiple hospitals in the largest health region of the province, incorporating data that are not normally available in health administrative data or public health charts alone.

These thesis results will be useful for health planners and policy makers for better understanding the resource needs and timing of health service use of TB patients in Quebec. This thesis documented the high rates of health service use and costs of diagnosing and treating active TB in the Quebec general population, with a marked rise in costs the months prior to the start of TB treatment and a high cost burden of hospitalizations. Policy-makers need to consider the full costs of diagnosing and treating active TB when making resource planning decisions, including costs due to diagnostic delays, potential long-term disability, and investigation of suspected active TB which is later ruled out.

Finally, LTBI treatment guidelines which have been developed based on clinical and economic evidence will help clinicians and policymakers to more efficiently target these shorter-course but more expensive regimens to those patients at highest risk of INH treatment complications and non-completion. Results from this thesis supported previous evidence that LTBI treatment completion rates were higher with the shorter 4RMP regimen compared to the 9INH regimen, with higher drug costs and similar costs of other health service use. Future studies should thus investigate the cost-effectiveness of standard and short-course LTBI treatment regimens within different patient populations, including cohorts of patients with different ages and co-morbidity levels.

APPENDIX 1: LITERATURE REVIEW TABLES

Table 26: Recommended Treatment Regimens for Active TB, LTBI, and Non-tuberculosis Mycobacteria (NTM)

Type	Specific Indication	Regimen options	Minimum duration
		Induction phase for Active TB	Continuation phase for Active TB
Active TB	Pulmonary, culture (+)	H+R+Z+E: Daily or 5x/week (8 wks)	H+R: Daily or 5x/week (18 wk) H+R: 2x/week (18 wks) H+P: 1x/week (18 wks) H+R: 2x/wk (18 wks)
		H+R+Z+E: Daily (2 wks), then 2x/wk (6 wks); or 5x/wk (2 wks) then 2x/wk (6 wks) H+R+Z+E: 3x/wk (8 wks) H+R+E: Daily (8 wks) or 5x/wk (8 wks)	H+P: 1x/wk (18 wks) H+R: 3x/wk (18 wks) H+R: Daily or 5x/wk (31 wk) H+R: 2x/wk (31 wks)
	Pulmonary, culture (−)	Standard regimens, including H+R in continuation H+R	6 months 39 wks
	Extra-pulmonary TB with liver disease	Standard regimens, including H+R in continuation Standard regimens as above, where possible R+Z+E H+R+E (until H+R susceptibility confirmed)	6-12 months 6 months 9 months
	TB in pregnancy	Standard regimens as above, where possible H+R+E	9 months 6 months
	H resistant pulmonary R resistant pulmonary H+R resistant pulmonary H+R+(E or Z) resistant	R+Z+E(+/- FQN) H+Z+E(+/-FQN) Z+E+F+IA(+/- alternative agent) F+(E or Z if active)+IA+2 alternative agents	9-12 months 18-24 months 24 months
Latent TB (LTBI)	Standard is daily Alternative Alternative Alternative for HIV+ on ARV No longer recommended UK & Canada alternative, HIV- cases	H: Daily (270 doses) or 2x/wk (76 doses) H: Daily (180 doses) or 2x/wk (52 doses) R: Daily (120 doses) B: Daily R+Z H+R	9 months (complete in 12) 6 months (complete in 9) 4 months 4 months 2 months 3 months
NTM	*M. avium* pulmonary disease Severe *M. avium* *M. kansaii* pulmonary Prophylaxis *M. avium*	M+R+E: 3x weekly M +(R or B)+E: Daily + S or AMIK 3x weekly H+R+E: Daily M or B	Min 1 year

H= INH; R=RIF; Z=Pyrazinamide; E=Ethambutol; B=RIFabutin; P=RIFapentine; M=macrolide (clarithromycin, azithromycin); S=streptomycin; AMIK=amikacin; FQN=fluroquinolone; IA=injectable agent

Sources: American Thoracic Society (2003) [66]; Mayo Clinic Proceedings (2011)[218]; UK National Institute for Clinical Evaluation (2011)[219]; Canadian Thoracic Society (2013)[2]

Note: Canadian TB Standards 7th edition advises daily or 3x/week during continuation phase of active TB treatment[2]

Table 27: Recommended candidates for treatment of LTBI

Category of person tested	TST<5 mm	TST 5-9 mm	TST 10-14 mm	TST ≥15 mm	IGRA+
Contacts who are: children <5 years and HIV-infected or otherwise immunosuppressed persons	CONSIDER TREAT	TREAT	TREAT	TREAT	TREAT
HIV-infected; Immunosuppressed persons; Contact of TB case (not immunosuppressed); Fibrotic changes on chest x-ray (adults)	Do not treat	TREAT	TREAT	TREAT	TREAT
Recent arrival from endemic country; Injection drug user; Resident/employee institutional setting†; Mycobacteria lab personnel; High-risk clinical conditions‡; Child< 4 years; Persons aged<18 years exposed to high-risk adults	Do not treat	Do not treat	TREAT	TREAT	TREAT
No risk factors (testing discouraged)	Do not treat	Do not treat	TREAT*	TREAT	TREAT

*In areas of the US where non-tuberculosis mycobacteria is more prevalent, treatment is recommended starting at TST≥15 mm
†TST conversion: increase in reaction size of ≥10 mm within 2 years should be considered a TST conversion indicative of recent infection with *M. tuberculosis*
‡Silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (eg. leukemias and lymphomas), other specific malignancies (eg. carcinoma of health and neck or lung), weight loss ≥10% of ideal body weight, gastrectomy, and jejunoileal bypass

Table 28: Summary of studies reporting LTBI treatment adherence, comparing regimens of INH and RMP

Reference	N	Design	Population	Results (% of patients completing treatment)
Pina, 2013, Spain	1002 (863 9H, 139 4R)	Retrospective, clinical database	All patients (contacts) aged ≥15 years and without HIV, treated for LTBI at a clinic in Catalonia (years 1986-2006 9H prescribed; 2007-2009 4R prescribed). *Adherence definition:* 120 doses in 4-4.5 months (4R); 270 doses in 9-12 months (9H)	4R (90.6%); 9H (71.0%)
Rivest, 2013, Canada[195]	2895 H; R 373	Retrospective, health administrative database	All patients aged ≥20 years in Quebec RAMQ database with filled prescriptions for 300mg H or 600 mg R (excluded: patients with prescriptions for 100mg tablets, INH syrup or RMP 150 mg tablets; patients with switches between regimens), 2006-2009, first prescription within 6 month period; completion measured within 12 months of initial prescription. *Adherence definition:* dispensed ≥270 doses in 12 months (9H), ≥180 doses in 12 months (6H); ≥120 doses in 12 months	4R (64.9%); 9H (31.3%), 6H (56.1%).
Fresard, 2011, Switzerland[2][11]	624 (426 6H, 198 4R)	Retrospective, clinical database	All patients treated for LTBI at a TB clinic, 1993-2002 (H) and 2005-2007 (R). *Adherence definition:* 9 months H, 4 months R	R (83%) vs H (74%) Adjusted odds ratio: 1.74 (95% CI, 1.11-2.72), adjusted for sex, age, alcohol, history of liver disorder
Horsburgh, 2010, US and Canada[89]	1994 (1674 9H, 181 6H, 91 4R)	Retrospective, cross-sectional	Stratified sample of LTBI patients in public and private clinics in the US and Canada in 2002. *Adherence definition:* 270 doses in 12 months (9H); 180 doses in 9 months (6H); 120 doses in 6 months (4R)	4R (68.8%); 6H (55.2%); 9H (45.2%) Adjusted odds ratio of non-completion, 9H vs 4R: 2.08 (95% CI, 1.23–3.57), adjusted for residence in a congregate setting (nursing home, shelter, or jail); injection drug use; age ≥ 15 years, and employment at a health-care facility
Li, 2010, US[198]	15035 (14030 H, 1005 R)	Retrospective, clinical database	All patients treated for LTBI in New York City chest clinics, 2002-2004. *Adherence definition:* ≥18 years old patients (6-9 months of H daily or twice-weekly in 12 months, or ≥4 months of daily R in 6 months); <18 years old patients (≥9 months of H in 12 months, or ≥6 months of R in 9 months)	R (60%); H (44%) Crude risk ratio: 1.36 (1.29-1.44) Adjusted risk ratio: 1.20 (1.14-1.26), adjusted for age, race/ethnicity, country of birth, risk group, and ever on directly observed preventive treatment
Trajman 2010, Canada/ Brazil/ Saudi Arabia[212]	847 (427 9H, 420 4R)	Randomized controlled trial	LTBI patients randomized to treatment. Eligibility: TST positive, treating physician had recommended LTBI treatment, signed informed consent; no absolute contraindications to the use of H or R. *Adherence definition:* took at least 80% of doses within 180 days for 4R and in 365 days for 9H	R (81%) vs H (64%); Adjusted relative risk: 4.3(2.7-6.8), adjusted for age, sex, country of birth, recruitment centre
Young, 2009, US[93]	777 (639 9H, 138 4R)	Retrospective chart review	LTBI patients at a county health clinic, 2003-2007 (excluding: patients with unavailable medical records, <18 years old, prisoners, who declined treatment or who were lost to follow-up after <1 month, previously treated for either active tuberculosis or LTBI, or began treatment for LTBI at another facility but transferred care to the study clinic). *Adherence*	R (90.6%); 9H (65%); 6H (73%) Adjusted odds ratio: 4.4 (1.9-9.9), adjusted for age, race, HIV status, chest x-ray abnormalities, and hepatitis history

			definition: dispensed 9H in 12 months or 4H in 6 months	
Cook, 2006, US[90]	310 2RZ or 4R; 149 9H	Prospective observational study	All LTBI patients at county health department, 2000-2006. Eligibility: TST positive, written informed consent, no clinical or radiographic evidence of active TB. Patients offered PZA+R unless they had contraindications (i.e., active hepatitis or were receiving medications metabolized through cytochrome P450) or if H was preferred (e.g., for contact lens users, jail inmates, and some oral contraceptive users). *Adherence definition:*4-6 months of R or 2 months of PZA+R or 9 months of H	RZ/R (77.7%); H (65.8%)
Lardizabal, 2006, US[91]	213 9H; 2614 R	Retrospective chart review	All LTBI patients at a county chest clinic, 2000-2003. *Adherence definition*: received ≥270 doses in 12 months (9H) or ≥180 doses (6H); ≥120 doses in 6 months (4R)	R (80.5%); H (53.1%); Adjusted odds ratio, R vs H=5.1 (3.3-8.1), adjusted for employment status, time in the US.
Page, 2006, US[92]	770 9H; 1379 4R	Retrospective chart review	All LTBI patients at a county health department, 1999-2004. *Adherence definition*: took 80% or more of the prescribed doses within 43 weeks (9H) or within 20 weeks (4R)	R (71.6%); H (52.6%); Adjusted odds ratio, R vs H=2.88 (2.27-3.66), adjusted for age, region, baseline liver enzymes, adverse event. Failure to complete 1 month of treatment: R (13.6%); H (12.7%) Completed 4 months of treatment: R (75.3%); H (73.9%)
Menzies, 2004, Canada/ Brazil/ Saudi Arabia[8]	58H, 58R	RCT	LTBI patients randomized to treatment. Eligibility: TST positive, treating physician had recommended LTBI treatment, signed informed consent; no absolute contraindications to the use of H or R. *Adherence definition:* took more than 80% of total prescribed doses within 20 weeks for 4R, or 43 weeks for 9H (measured with an electronic pill monitoring device)	4R: 80% of doses (91%), 90% of doses (86%) 9H: 80% of doses (76%), 90% of doses (62%) RR: 80% of doses: 1.2 (1.02, 1.4); 90% of doses: 1.4 (1.1, 1.7)

Abbreviations: 9H=9 months of INH; 6H=6 months of INH; 4R=4 months of Rifampin; 2RZ=2 months of rifampin+pyrazinamide

Table 29: Summary of studies reporting adverse drug events of LTBI treatment, comparing regimens of INH and RMP

Reference	N	Design	Population	Results (% of patients with an adverse event, AE)
Pina, 2013, Spain	1002 (863 9H, 139 4R)	Retrospective, clinical database	All patients (contacts) aged ≥15 years and without HIV, treated for LTBI at a clinic in Catalonia	Any hepatotoxicity leading to treatment interruption: R (1.4%); H (5.4%)
Fresard, 2011, Switzerland[211]	624 (426 6H, 198 4R)	Retrospective, clinical database	All patients treated for LTBI at a TB clinic	Any hepatotoxicity leading to treatment interruption: R (2.0%); H (6.1%) Other side effect leading to treatment interruption: R (5.6%); H (4.0%)
Smith, 2011, Canada[94]	9145 (8487 9H; 430 4R)	Retrospective, secondary data, Canada	All patients in Quebec with a filled prescription for 1+ months of LTBI treatment	Any severe AE= 1.3% Any severe hepatotoxicity= R (0.2%); H (0.3%)
Young, 2009, US[93]	639 9H; 138 4R	Retrospective, chart review, US	Adults at a public health clinic (2003-2007), treatment for >1 month	Hepatitis (symptomatic elevation of ALT, 2.5 times above normal)= R (0.72%); H (2.2%)
Menzies, 2008[8]	427 9H; 420 4R	RCT (Canada/ Brazil /Saudi Arabia)	Adults, TST+, normally would be recommended for LTBI treatment. Excluded: contacts of drug-resistant TB cases, allergic to H or R, possible drug interactions with other concurrent medications	Any AE= R (3.8%); H (5.7%) Severe AE + stop treatment= R (1.7%); H (4.0%) Hepatotoxicity= R (0.7%); H (3.8%) Hematologic AE= R (0.5%); H (0.2%) Rash AE= R (0.2%); H (0%)
Cook, 2006, US[90]	149 9H; 310 2RZ or 4R	Prospective observational study	All LTBI patients at a county health department (2000-2006)	Moderate-severe hepatotoxicity= R (0%), RZ (6.1%), H (2.0%)
Lardizabal, 2006, US[91]	213 9H; 261 4R	Retrospective, chart review	Patients put on LTBI treatment in 2000 and 2003 at a county Chest clinic	Discontinuation of therapy due to complaints of side effects/drug reactions= R (3.1%), H (6.1%) Hepatitis= R (0%), H (1.4%)
Page, 2006, US[92]	770 9H; 1379 4R	Retrospective, chart review	All people prescribed LTBI at a county health department (1999-2004)	Any adverse reaction= R (8.3%), H (11.3%) Stopped treatment due to AE= R (1.9%), H (4.6%) Clinical hepatotoxicity= R (0.08%), H (1.8%)

Abbreviations: 9H=9 months of isoniazid; 6H=6 months of isoniazid; 4R=4 months of Rifampin; 2RZ=2 months of rifampin+pyrazinamide; AE=adverse event; RCT=randomized controlled trial

Table 30: Summary of cost-effectiveness studies comparing LTBI treatment regimens, INH versus RMP

Reference	Type	View point	Target population	Comparator	Costs included	Source of Parameters	Model Type	Effectiveness Measure	Main Conclusions
Pina, 2013, Spain	CE	Health system	Contacts	9H; 4R	Direct medical (inpatient, outpatient, physician fees, other laboratory, drugs)	Observational study: LTBI completion, average 2009 costs for LTBI multiplied by assumed visit rates Literature: active TB costs	None	TB cases averted over 5 years	RMP more cost-effective when efficacy ≥75%.
Esfahani, 2011, Canada[111]	CE	Society	Aged ≥36 years, TST positive, HIV negative. Either contacts or low risk reactors	9H; 4R	Direct medical (inpatient, outpatient, physician fees, nursing care, other laboratory, drugs); indirect (lost productivity)	Literature: all estimates	Markov; 4 states; 1 year cycles; 20 year horizon	TB cases averted	RMP more cost-effective than INH if RMP efficacy ≥69%. Results sensitive to RMP efficacy.
Aspler, 2010, Canada[112]	CE	Health system	Recent close contacts (age ≥18)	9H; 4R	Direct medical (RCT, Montreal Chest Hospital)	RCT: all estimates except efficacy Literature: Efficacy	None	TB cases averted over 2 years	RMP more cost-effective than INH. Results sensitive to RMP cost and efficacy.
Ziakas, 2009, USA[113]	CE	Not stated	Not stated	9H; 4R	Direct medical (crude estimates)	Meta-analysis	None	% completing treatment	RMP more cost-effective. Sensitive to RMP cost.
Holland, 2009, USA[103]	CU/ CE	Not stated	Recent contacts (average age 39 years)	No treatment; 9H; 9H-DOT; 3HP-DOT; 4R	Direct medical (inpatient, outpatient, drugs, DOT); contact tracing; indirect (patient time)	Literature: Drug effect, AE rates, AE hospitalization; Extended TB treatment, TB death, QALY weights, costs	Markov; 5 states: 1 month cycles; 20 year horizon	Future TB cases averted, QALYs gained	RMP dominated all except HP (more effective, but more costly)
Khan, 2009, USA[114]	CU/ CE	Society	New immigrants to US (18+ years)	No screen/tmt Screen+9H Screen+4R Screen+2RZ	Direct (medical, TST, transport, translator, drugs);	Literature: TST sensitivity/ specificity; Drug efficacy; AE rates; TB morbidity/ mortality, costs; Experts: QALY weights	Decision analysis; lifetime	Future TB cases averted, QALYs gained	RMP not cost-effective compared to INH (except in cases of INH resistance). Sensitive to RMP cost.

Abbreviations: CU=cost-utility analysis; CE=cost-effectiveness analysis; QALY=quality-adjusted life years; 9H=9 months of INH; 4R=4 months of rifampin; 3HP=3 months INH+rifapentine; 2RZ=2 months of rifampin+pyrazinamide; AE=adverse event; TST=tuberculin skin test; DOT=directly observed therapy

Table 31: Summary of published cost-of-illness studies of active TB in high income countries

Place and year of publication	Patient type	N (people)	% in- hospital	Average # days hospitalized (range)	Hospital costs as a proportion of total	Average cost for active TB (2009 CDN dollars)*	Factors associated with higher cost	Length of follow-up
Menzies, 2008, Canada[122]	Any TB	1,574	50%	20.6	40.5%	$51,996	Region	Diagnosis to end of treatment
Bocchino, 2006, Italy[120]	TB, HIV-	92	n/a (all)	*treat success:* 42 *died:* 29 *lost:* 43 *transferred:* 32	67.2% 100% 84.7% 86.8%	$29,366 $15,796 $23,850 $49,977	Severity, MDR-TB	Diagnosis to end of treatment
Diel, 2004, Germany[121]	Lung TB	5,964	80%	49.6	n/a	$32,529 (Direct)	Age	Diagnosis to end of treatment, productivity loss
Rajbhandary, 2004, USA[68]	MDR	13	71%	27.6 (5-90)	57.6% (direct costs only) 3.8% (including indirect costs)	$65,713 (direct costs only) $1,004,973 (including indirect costs)	Treatment completers, HIV+ or HIV unknown status	Diagnosis to end of treatment, productivity loss
Taylor, 2000, USA[118]	Any TB	1493	49% 45% (initial) 8% (during treatment)	11	100%	$11,568	Substance abuse, homeless, region, MDR, age 65+, HIV	Hospitalization
Wurtz, 1999, USA[119]	Culture+	92	99% (initial) 16% (TB readmissions)	20.2 14.9 (for TB readmissions)	32.5%	$105,922	HIV, Age<60, Completers	Diagnosis to end of treatment
Brown, 1995, USA[116]	Any TB	26,283	79%	19.9	60%	$45,658	Drug resistance	Diagnosis to end of treatment
Rosenblum, 1994, USA[117]	Any TB	n/a	n/a (all)	14.3	100%	$24,578	HIV, HIV-TB severity	Hospitalization
Arno, 1993, USA[115]	Any TB	n/a	n/a (all)	25	100%	$39,852	HIV	Hospitalization

*Costs converted to 2009 Canadian dollars using the Bank of Canada Currency Convertor (http://www.bankofcanada.ca/en/rates/exchform.html) and the Bank of Canada Inflation Calculator (http://www.bankofcanada.ca/en/rates/inflation_calc.html)

Note: not including single-clinic studies of active TB costs that have been estimated as part of cost-effectiveness evaluations

APPENDIX 2: TB-RELEVANT DIAGNOSTIC, PROCEDURE, AND DRUG IDENTIFICATION CODES

Table 32: List of Codes Used to Identify TB Drugs and Macrolides in the RAMQ Databases

Drug description	AHFS codes	Health Canada DINs
First-line TB drugs		
Isoniazid (INH)	816:04	00261270, 00265500, 00272655, 00577782, 00577790, 00577804, 00577812
Pyrazinamide (PZA)	816:04	00283991, 00618810
Ethambutol (EMB)	816:04	00127957, 00127965, 00247960, 00247979, 02170078
Rifampin (RIF)	816:04	00343617, 00393444, 00580384, 02091887, 02092808
Rifabutin (RFB)	816:04	02063786
Rifater (INH-PZA-RIF)	816:04	02148625
Second-line TB drugs		
Para-aminosalicylic *acid* (PAS)	816:04	00236691
Cycloserine (CYC)	816:04	02032414
Fluoroquinolone (FLQ)	812:18, 8:22:00	
Aminoglycoside (GLY)	812:02	02243660, 02015862, 02242971, 00397415
Other drugs		
Macrolide	812:12	

* AHFS=American Hospital Formulary Service; DIN=Drug Identification Number

Table 33: List of Dose Codes for TB Drugs and Macrolides in the RAMQ Database

Dose code	Dose description
36234	50 mg
41602	100 mg
45872	150 mg
47702	200 mg
49776	250 mg
51240	300 mg
52399	333 mg
53192	400 mg
54412	500 mg
55876	600 mg
56364	750 mg
97736, 57096	1000 mg
545	120mg-50mg-300mg
13176	2 mg/mL
24522	10 mg/mL
34770	40 mg/mL
37088	50 mg/mL
41968	100 mg/mL
50264	250 mg/mL
470	400 mg/mL
36143	50 mg/5 mL
41541	100 mg/5 mL
44247	125 mg/5mL
47611	200 mg/5 mL
49715	250 mg/5 mL
51149	300 mg/5mL
53131	400 mg/5 mL
54336	500 mg/5 mL

Table 34: ICD9/10 Diagnostic Codes Relevant to TB and Other Mycobacterial Infections

ICD9	ICD10	Description
TB		
010	A15.7	Primary tuberculosis infection[1]
011	A15-A16	Pulmonary tuberculosis
012	A15-A16	Other respiratory tuberculosis
013	A17	Tuberculosis of meninges and central nervous system
014	A18.3	Tuberculosis of intestines, peritoneum, and mesenteric glands
015	A18.0	Tuberculosis of bones and joints
016	A18.1	Tuberculosis of genitourinary system
017	A18.4-18.8	Tuberculosis of other organs
018	A19	Miliary tuberculosis
137	B90	Late effects of tuberculosis
Non-TB Mycobacteria (NTM)		
031.0	A31.0	Pulmonary (including infections by *Mycobacterium avium, M. intracellulare, M. kansai*)
031.1	A31.1	Cutaneous (including infections by *M. balnei, M. ulcerans*)
031.2	-	Disseminated (including *M. avium-intracellulare,* MAC)
031.8	A31.8	Other unspecified
031.9	A31.9	Unspecified, Atypical mycobacterium infection NOS

Table 35: ICD9/10 Diagnostic Codes for Other Possible Indications for Long-Term Rifampin Treatment (30 days or longer)

ICD9	ICD10	Description
030	A30	Leprosy
730	M86	Osteomyelitis
023	A23	Brucellosis
041.11, 014.12, 038.12, 482.42	A49.0, B95.6, A41.0, G00.3, P36.2, Z22.3, J15.2, L00, P23.2	Multidrug resistant *Staphylococcus aureus*-MRSA

Table 36: Charlson-Deyo Comorbidity Index, Quan Adaptation (ICD9 and ICD10)

ICD-9/ ICD-10 Codes	Description	Weight
410.x, 412.x, I21.x, I22.x, I25.2	Myocardial Infarction	1
428.x, I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0	Congestive heart failure	1
443.9, 441.x, 785.4, V43.4, I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	Peripheral vascular disease	1
430.x-438.x, G45.x, G46.x, H34.0, 160.x-169.x	Cerebrovascular disease	1
290.x, F00.x-F03.x, F05.1, G30.x, G31.1	Dementia	1
490.x-505.x, 506.x, 127.8, 127.9, J04.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3	Chronic pulmonary disease	1
710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725.x, M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0	Rheumatic disease	1
531.x-534.x	Peptic ulcer disease	1
571.2, 571.4-571.6, B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.2-K76.4, K76.8, K76.9, Z94.4	Mild liver disease	1
250.0-250.3, 250.7, E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	Diabetes without chronic complication	1
250.4-250.6, E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7	Diabetes with chronic complication	2
344.1, 342.x, G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9	Hemiplegia or paraplegia	2
582.x, 583.x-583.7, 585.x, 586.x, 588.x, I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N26.0, Z49.0-Z49.2, Z94.0, Z99.2	Renal disease	2
140.x-172.x, 174.x-195.8, 200.x-208.x, C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x	Any malignancy, including leukemia and lymphoma	2
456.0-456.21, 572.2-572.8, I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K71.9, K76.5, K76.6, K76.7	Moderate or severe liver disease	2
196.x-199.1, C77.x-C80.x	Metastatic solid tumor	3
042.x-044.x, B20.x, B22.x, B24.x	HIV/AIDS	6

Source: Quan et al (2005) [199]

Table 37: ICD9/10 Diagnostic Codes and American Hospital Formulary Code used for identifying baseline TB-related risk factors, psychiatric diagnosis, and liver disease in RAMQ

ICD9 /ICD10/AHFS codes *	Description
140-172, 174-195.8, 200-208, 238.6, C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C81-C85, C88, C90-C97	Cancer (malignant neoplasms)
250, E10-E14	Diabetes
042-044, V08, B20-B22, B24, Z21, AHF=81808	HIV/AIDS
403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582, 583, 585-586, 588, V42.0, V45.1, V56.1, I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18, N19, N25.0, Z49.0-Z49.2, Z94.0, Z99.2	Renal Disease
291, 292, 303, 304, 305.0, 305.2-305.9, 357.5, F10-F16, F18-F19, G62.1	Substance Abuse (Alcohol or drugs, excluding tobacco)
V42.0,V 42.1, V42.6, V42.7, V42.81,V42.83, V42.84, Z94.0-Z94.4, Z94.6, Z94.8	Solid organ (liver, kidney, heart, lung, pancreas, intestine) or bone marrow transplant recipient
502, J62	Silicosis
260-263, E40-E46	Malnutrition
DIN= 2242903,2274728,2258595,2244016	Treatment with TNF-alpha inhibitors
070, 456.0-456.2, 570-573, V42.7, B18, I85.0, I85.9, I86.4, I98.2, K70-K74, K76, Z94.4	Liver disease (including viral hepatitis)
290-319, F10-F19	Psychiatric diagnosis

*AHFS=American Hospital Formulary Service; DIN=Health Canada Drug Identification Number
Source: Cancer, diabetes, HIV, liver disease and renal disease codes derived from Quan adaptation of the Charlson-Deyo score (2005) [199]

Table 38: RAMQ Codes and Characteristics of the 18 Quebec Health Regions, 2006-2007

	Population characteristics			
Quebec Health Region	Population density: people/ km^2	Total population	% Recent Immigrants[1]	% Aboriginal[2]
Central				
03- Capitale-Nationale	35.2	678,169	1.3	0.6
05- Estrie	29.3	304,525	1.4	0.8
06- Montreal	3714.9	1,892,751	7.5	0.5
13- Laval	1492.2	384,351	2.4	0.4
Peripheral				
12- Chaudiere-Appalaches	26.1	401,002	0.3	0.4
14- Lanaudiere	34.6	451,078	0.4	1.1
15- Laurentides	24.6	534,947	0.6	0.8
16- Monteregie	122.0	1,412,485	1.4	0.6
Intermediate/remote				
01- Bas-Saint-Laurent	9.0	201,128	0.3	0.9
02- Saguenay-Lac-Saint-Jean	2.8	272,419	0.4	2.8
04- Mauricie et Centre-du-Quebec	11.3	490,208	0.6	1.4
07- Outaouais	11.1	352,717	1.6	4.0
08- Abitibi-Temiscamingue	2.5	144,934	0.2	4.6
09- Cote-Nord	0.4	95,652	0.2	13.4
11- Gaspesie-Iles-de-la-Madeleine	4.6	94,612	0.2	2.5
10/17/18- Nord-du-Quebec, Nunavik, Terres-Cries-de-la-Baie-James	0.05	41,059	0.1	59.1
MeanValue for Quebec	5.6	7,752,037	0.5	5.9

1. Recent immigrant=reported on census to have immigrated to Quebec within past 5 years
2. Aboriginal= self-defined as identifying with at least one Aboriginal group (North American Indian, Métis or Inuit) and/or those who reported being a Treaty Indian or a Registered Indian, as defined by the *Indian Act* of Canada, and/or those who reported they were members of an Indian band or First Nation.

Source: 2006 Canadian Census ; Quebec MSSS

APPENDIX 3: RAMQ/MED-ECHO DATABASE FILES

RAMQ BENEFICIARY FILE

Variable Name	Variable Description	
ID	Unique patient ID number (scrambled)	
Age group	Cohorts 1 and 2 (extraction 1998-2002): 17=0-4 years 16=5-9 years 15=10-14 years 14=15-19 years 13=20-24 years 12=25-29 years 11=30-34 years 10=35-39 years 9=40-44 years 8=45-49 years 7=50-54 years 6=55-59 years 5=60-64 years 4=65-69 years 3=70-74 years 2=75-79 years 1=80 years or older	Cohorts 3 and 4 (extraction 2003-2007): 1=<1 year 2=1-4 years 3=5-9 years 4=10-14 years 5=15-19 years 6=20-24 years 7=25-29 years 8=30-34 years 9=35-39 years 10=40-44 years 11=45-49 years 12=50-54 years 13=55-59 years 14=60-64 years 15=65-69 years 16=70-74 years 17=75-79 years 18=80-84 years 19=85 years or older 99=missing
Region	Health region of residence at index date 1= Bas-Saint-Laurent 2= Saguenay-Lac-Saint-Jean 3= Capitale-Nationale 4= Mauricie et Centre-du-Quebec 5= Estrie 6=Montreal 7= Outaouais 8= Abitibi-Temiscamingue 9= Cote-Nord 10= Nord-du-Quebec 11= Gaspesie-Iles-de-la-Madeleine 12= Chaudiere-Appalaches 13= Laval 14= Lanaudiere 15= Laurentides 16= Monteregie 17= Nunavik 18= Terres-Cries-de-la-Baie-James	
Death date	Death date (Month and year only)	
Median income	Median income for the postal region of residence (ie. first 3 digits of postal code) from 2001 Statistics Canada Census	
% individuals with university education	% of individuals with a university diploma in the postal region of residence, from 2001 Statistics Canada Census	
% individuals with college diploma	% of individuals with a college diploma in the postal region of residence, from 2001 Statistics Canada Census	
% individuals with high school diploma	% of individuals with a high school diploma in the postal region of residence, from 2001 Statistics Canada Census	
Index date	Date of the first filled prescription for a TB drug for a duration of 30 days or longer, between January 1, 1998-December 31, 2007	
Cohort number	Number assigned to each cohort data extraction	

	1=Case (years 1998-2002) 2=Controls (years 1998-2002) 3=Case (years 2003-2007) 4=Controls (years 2003-2007)

RAMQ DRUG PLAN FILE

Variable Name	Variable Description
ID	Unique patient ID number (scrambled)
Drug plan category	General category of RAMQ Drug Plan PS=Receiving Employment Insurance (EI) PA=Person aged 65 years and older AD=Member AL=Purchase of beds DE=Deassured 01=Sexually transmitted diseases 02=TB 04=Urgent oral contraception Blank= Not determined
Drug plan code	Name of specific RAMQ drug plan 10= Employment Insurance (EI), adult, 18-65 years old 11= Employment Insurance, senior, 65+ 12= Dependent of EI recipient (<18) 13= Dependent of EI recipient (18-25, full-time student) 16= Beneficiary of a spouse allowance (60-64 years) 17= EI adult, with severe constraints to employment 18= Beneficiary of a spouse allowance (60-64 years), severe constraints to employment 20= Senior 65+, no Guaranteed Income Supplement (GIS) 21= Senior 65+, max GIS 22= Senior 65+, partial GIS 23= Senior 65+, max (94%) GIS 30= Adult 31= Dependent of adult or senior (<18) 32= Dependent of adult or senior (18-25, full-time student) 33= Dependent of adult or senior (18-25, functional disabled) 50= Program to purchase beds in private Long-term care facility 96= Refugee status 97= Long-term care facility resident 98= 65+ not covered by public system 1= Sexually transmitted disease 2= TB (02L=preventive treatment and 02K=active treatment) 4= Emergency contraception- pill
Start date of drug plan coverage	Start date of an individual's registration in a specific drug plan (Year, month)
End date of drug plan coverage	End date of an individual's registration in a specific drug plan (Year, month)

RAMQ DRUG PRESCRIPTIONS BILLING FILE

Variable Name	Variable Description
ID	Unique patient ID number (scrambled)
Drug plan category	See RAMQ DRUG PLAN REGISTRATION FILE
Drug plan code	See RAMQ DRUG PLAN REGISTRATION FILE
Category of listed medications	1=Sexually transmitted diseases 2=TB

	3=Medications in-pharmacy 4=Urgent oral contraception 5=Parenteral treatment 40=Medications for patient with pharmacy exception 41=Drug exception 43=Magistral (non-official) drug permitted without authorization 44=Anti-smoking treatment
Date of service	Date when prescription filled (Year, month, day)
DIN	Health Canada Drug Identification Number
AHF	American Hospital Formulary Service code
Common name	Commonly used name of drug (eg. isoniazid) 0=Information missing
Form	Detailed description of form of drug (eg. oral gel, etc) 0=Information missing
Dose	Dose of drug 0=Information missing
Renewal	Nature of prescription NS=New prescription, written NV=New prescription, verbal RS=Prescription renewal, written RV=Prescription renewal, oral Blank=not listed
Substitution	If the original drug prescribed is substituted for another E=Choice of pharmacist to dispense an equivalent medication P=Choice of prescriber to substitute Blank=As prescribed
Duration	Number of days of treatment dispensed 0=Information missing
Quantity	Number of doses of drug dispensed
Pharmacy fee	Amount paid by RAMQ to pharmacy for dispensing the drug
Drug cost	Amount paid by RAMQ for the drug
Co-pay amount	Amount paid by patient
Deductable	Amount paid by patient
Amount paid by RAMQ	Total amount paid by RAMQ=(Pharmacy fee + Drug cost) - (Co-pay + Deductable)
Intervention code1	Detailed RAMQ codes describing reasons why drug exception or intervention requested
Intervention code2	As above
Intervention code3	As above
Intervention code4	As above
Service code 1	RAMQ codes describing what intervention was given to the patient
Service code 2	As above
Service code 3	As above
Prescribing physician ID	Unique physician ID number (scrambled)
Pharmacist ID	Unique pharmacist ID number (scrambled)
Pharmacy ID	Unique pharmacy ID number (scrambled)

RAMQ MEDICAL REGISTRATION FILE

Variable Name	Variable Description
Class of professional	1=Physician in Quebec 2=Dentist in Quebec 3=Optometrist in Quebec 4=Pharmacist in/outside Quebec 5=Medical resident in Quebec 6=Physician outside Quebec

	7=Dentist outside Quebec 8=Optometrist in Quebec 9=Other (Podiatrist, midwife, audiologist)
Physician ID	Unique physician ID number (scrambled)
Year of graduation	Year of graduation from professional program 0=Not available 1=Before 1950 2=1950-1959 3=1960-1969 4=1970-1979 5=1980-1989 6=1990-1999 7=After 1999

RAMQ MEDICAL SERVICES BILLING FILE

Variable Name	Variable Description
Class of professional	See RAMQ MEDICAL REGISTRATION FILE
Physician ID	Billing physician, unique physician ID number (scrambled)
Specialty	RAMQ-assigned physician specialty code 0= General practitioner (non-specialist) 1= Allergy and immunology 2= Pathology 3= Anesthesiology 4= Medical microbiology and infectious diseases 5= Medical biochemistry 6= Cardiology 7= General surgery 8= Orthopedic surgery 9= Plastic surgery 10= Thoracic surgery 11= Dermatology 12= Gastroenterology 13= Gynecology 14= Obstetrics/gynecology 15= Hematology 16= Hygiene/public health 17= Respirology 18= Internal medicine 19= Physical/rehab medicine 20= Neurosurgery 21= Neuropsychiatry 22= Neurology 23= Obstetrics 24= Ophthalmology 25= Oto-rhino-laryngology 26= Clinical pathology 27= Pediatrics 28= Psychiatry 29= Diagnostic radiology 30= Radio-oncology 31= Urology 32= Cardiovascular and thoracic surgery 33= Nuclear medicine 34= Nephrology 35= Endocrinology 36= Rheumatology 37= Electroencephalography 38= Community health 39= Family medicine 40= Ultrasonography 41= Internal rotation 42= Mixed rotation 43= Neuro-opthalmology 44= Neonatology 45= Geriatrics 46= Medical oncology 47= Neuro-pathology 48= Medical genetics 49= Emergency medicine 50= Cardiac surgery 51= Geriatrics
Act code	RAMQ assigned codes according to RAMQ billing manuals - General practitioners: http://www.ramq.gouv.qc.ca/fr/professionnels/medecins-omnipraticiens/manuels/Pages/facturation.aspx - Specialists: http://www.ramq.gouv.qc.ca/fr/professionnels/medecins-specialistes/manuels/Pages/facturation.aspx
Role	Physician's role in the execution of the act

	1=responsible for the act 2/3=anaesthesia 4=assistant 7=radiology lab honorarium 8=responsible for interpretation of results	
Date of service	Billing date (Year, month, day)	
Diagnostic code	ICD9 diagnostic code assigned as reason for visit/procedure Blank or V999=missing	
Type of establishment	Type of facility where medical visit or procedure took place	
	61X, 51X, 52X, 53X, 54X, 55X, 56X, 57X	Private office
	0X0, 0X1, 4X1	Hospital Centre- outpatient
	0X3	Hospital Centre- inpatient
	0X2, 0X4, 0X5	Extended Care Unit
	0X6, 4X6	Intensive Care Unit
	0X7	Emergency Department
	0X8	Psychiatry Unit
	30X, 31X, 32X, 33X	Diagnostic laboratories and radiology
	0X9, 589, 599	Out of province
	1X3,1X5,2X5,34X,340,341,4X7, 4X9,509,503,582,592,7X0,7X1,7 X2,7X3,7X4,7X5,7X6,8X5,9X0, 9X1,9X2, 9X3,9X6,9X7,9X9	Other locations (eg. Nursing homes, physiotherapy, CLSCs, federal detention centres)
Amount billed	Amount billed by physician to the RAMQ as specified in the RAMQ billing manuals (above)	
Renumeration rate	% increase in RAMQ's renumeration rate based on location of physician within province, ie, for practicing in a more remote health region: http://www.ramq.gouv.qc.ca/SiteCollectionDocuments/professionnels/manuels/150-facturation-specialistes/006_localites_acte_spec.pdf	
Class of referring physician	See RAMQ MEDICAL REGISTRATION FILE	
Referring physician ID	Referring physician, unique physician ID number (scrambled)	
Specialty of referring physician	See above	

MED-ECHO HOSPITAL DISCHARGE ABSTRACT (DIAGNOSES) FILE

Variable Name	Variable Description
Hospitalization ID	Unique ID number of hospitalization record
ID	Unique patient ID number (scrambled)
Diagnosis type	A=Admission (in use since 2006) D=Death (in use since 1986) P=Principal (mandatory) S=Secondary (optional)
Diagnosis number	Sequential number of diagnoses included in a single hospital record
Diagnosis classification	1=ICD10 (in use since April 1, 2006) 4=ICD9 (in use before April 1, 2006)
Diagnosis code	Diagnostic code (ICD9 or ICD10), to 5 digits
Nature of diagnosis	0-No complications or infections 1=Complications 2=Infection 3-Precision (in use since April 1, 2006 to describe complication diagnosis) A=External cause of injury

MED-ECHO HOSPITAL DISCHARGE ABSTRACT (DATES) FILE

Variable Name	Variable Description
Hospitalization ID	Unique ID number of hospitalization record
ID	Unique patient ID number (scrambled)
Date of admission	Date that an individual occupied a bed or date of day surgery (Year, month, day)
Date of discharge	Date that an individual left facility, living or dead (Year, month, day)
Type of care	Type of care provided by hospital 1=Physical and psychiatric, short duration 2=Convalescent care 3=Long duration (public) 4=Short duration (public) 6= Long duration (private) 27=Day surgery 29=Post-mortem Note: Since 2000-2001, only codes 1, 27, and 29 are used
Accident date	Date of accident as reported by the hospital (Year, month, day) Blank=not applicable
Accident diagnosis system	Classification system of accident diagnosis 1=ICD10 4=ICD9
Cause of accident code	Diagnostic code indicating cause of accident Blank=not applicable
Number of days absent	Number of days absent from the hospital due to a temporary leave or medical treatment and with a hospitalization at a different facility
Length of hospital stay	Total number of days of hospital stay
Destination ID	Unique ID number of destination from hospital
Type of destination	Type of place where the patient was discharged to after the hospital stay 1=Acute care hospital 3=Extended care hospital/nursing home 9=Acute care hospital, outside Quebec 10=Extended care hospital/nursing home, outside Quebec 13=Rehabilitation centre 17=CLSC 21=Home 23=Day care centre 26=Day hospital 27=Day surgery 30/34=Funeral home 31=Left without authorization 33=Day medical treatment
Type of death	1=Pre-operative death 2=Post-operative death 5=Maternal death 6=Other type of death 7=Early neonatal death 8=Late neonatal death Blank=not applicable

MED-ECHO HOSPITAL DISCHARGE ABSTRACT (PROCEDURES) FILE

Variable Name	Variable Description
Hospitalization ID	Unique ID number of hospitalization record
ID	Unique patient ID number (scrambled)
Procedure number	Sequential number of procedure (up to 20)
Date of procedure	Date the procedure was completed, or if repeated multiple times, date of the first time the procedure was completed (Year, month, day)
Location of procedure	1=Operating room

	2=Delivery room 6=Outside facility 9=Other location inside the facility
Procedure code system	System of procedure coding 2=Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures: CCP (in use to March 31st, 2006) 5=Canadian Classification of Health Interventions: CCI (in use since April 1, 2006)
Procedure outcome	Detailed indicator of outcome of procedure (eg. abandoned, late, etc; see procedure code systems for detailed lists) Blank=not applicable
Body location of procedure	Detailed location in the body where the procedure was performed (see procedure code systems for detailed lists)
Quantity of procedure	Detailed description of quantity of body parts undergoing procedure (see procedure code systems for detailed lists)
Procedure number	Number of times procedure completed
Class-procedure	Class of professional conducting procedure
Specialty-procedure	Specialty of professional conducting procedure

APPENDIX 4: SUPPLEMENTAL MATERIAL

Data Extraction Form:
VALIDATED METHODS FOR IDENTIFYING TUBERCULOSIS IN HEALTH ADMINISTRATIVE DATABASES

Review Date: _____ Reviewer: _____

I. Study details

First Author		
Year of publication		
Country		
Study objective		
Test sample	Data source description	
	Population description	
	Sample size	
Reference standard	Data source description	☐ Chart review: ☐ TB Registry: ☐ Physician recall: ☐ Other:
	Population description	
Notes about false positives		
Author's conclusion		

II. Calculating diagnostic accuracy of decision rules:

		Reference standard +	-	
Test population	+	a	b	t1
	-	c	d	t2
		r1	r2	N

Sensitivity=a/(a+c)

PPV=a/(a+b)

RESULTS (decision rules tested)	# TPs (a)	# FPs (b)	# FNs (c)	# FNs (d)	Sensitivity	PPV
1.						
2.						
3.						
4.						
5.						
6.						
7.						
8.						
9.						
10.						

Possible bias assessment	Yes/No/Unknown (describe)
1. Were the linkage methods clearly described (ie. not an ecologic study)?	
2. If chart review, did reviewers know result of algorithm before chart review completed?	
3. Did the authors define the time window or follow-up period in which algorithm was applied?	
4. Reference standard- confirmed TB vs reported TB? If confirmed, how was it confirmed? Was it complete?	
5. Were there any patient exclusions from the test dataset?	
6. Were there any patient exclusions from the reference dataset?	

Detailed summary of included studies

Fiske et al (2012) validated TB case definitions in adult rheumatoid arthritis patients registered in Medicaid. They tested five algorithms in physician billing and pharmacy claims files, and confirmed screening results against confirmed active TB cases in the state TB registry. They found a low PPV for all algorithms tested. The lowest PPV was found for any TB-related ICD-9 code (1.3%). The majority of false positives were found when algorithms were based solely on ICD-9 codes or TB drug prescriptions (either an algorithm of 2 or more TB drugs, or algorithms based on dispensing of specific TB drugs isoniazid plus rifampin, or pyrazinamide). No false positives were found among patients who had received at least three months of TB drugs[147].

Winthrop et al (2011) validated case definitions for both active TB and NTM in two patient populations: rheumatoid arthritis patients at an HMO, and the entire population in a Veterans' Affairs database. Among veterans, algorithms were tested in clinical inpatient/outpatient, microbiologic, and pharmacy dispensing data from electronic health records, and validated against chart review (with confirmation of active TB disease using Centers for Disease Control and Prevention (CDC) criteria). Among rheumatoid arthritis patients, algorithms were tested in inpatient, outpatient, and pharmacy records in a claims database, validated against chart review. PPVs and sensitivity tended to be lower in the veteran population than in the arthritis cohort, for comparable algorithms (ie. an algorithm of any ICD-9 code had a low PPV (9%) and moderate sensitivity (77%) in the veteran population, which rose to 54% and 100%, respectively, in the arthritis cohort). The authors concluded that TB diagnostic codes alone are not reliable and are useful only in combination with TB drug dispensing data.

Calderwood et al (2010) validated case definitions for active TB in outpatient records, written drug prescriptions and diagnostic test orders of the entire population of a large ambulatory group practice. Algorithms were validated by chart review using CDC criteria. They found a high PPV (84%) for their composite algorithm, which included any prescription for pyrazinamide, an ICD-9 code for TB plus a TB (acid fast bacilli) test order, or an ICD-9 code for TB plus an order for two or more TB drugs. All false positives were due to LTBI[146].

Sickbert-Bennett et al (2010) validated case definitions for active TB in inpatient/outpatient records from six non-federal acute care health systems. They confirmed active TB cases using CDC criteria applied during chart review. They found a low PPV (23.4%) for an algorithm of any ICD-9 code for TB, and concluded that while use of ICD-9 codes may have acceptable PPV for identifying other reportable infectious diseases, TB was a notable exception[159].

Schneeweiss et al (2007) validated case definitions for active TB and NTM in inpatient records of a Veterans' Affairs database, compared against chart review using CDC criteria. They found a high PPV (77%) for a primary ICD-9 code for TB, which increased when limited to an ICD-9 code for pulmonary TB only (85%). They also found a relatively high PPV (70%) to identify NTM cases using a primary ICD-9 diagnosis for NTM[140].

Yokoe et al (2004) validated a case definition for active TB in pharmacy dispensing records of patients of three US health plans in three states. Algorithms were validated against confirmed or clinically suspected active TB cases reported to state TB registries. An algorithm with 2 or more TB drugs dispensed had a PPV of 25%[148].

Yokoe et al (1999) validated case definitions for active TB in inpatient, emergency department, outpatient claims and pharmacy dispensing records of patients with HMO pharmacy coverage. Algorithms were validated by chart review using CDC criteria. The lowest PPV/highest sensitivity was found with an ICD-9 diagnosis for TB: 2% and 100%, respectively. PPV was higher for TB drug-based algorithms (ie. dispensing of 2 or more first- or second-line TB drugs: PPV=30%, 3 or more drugs: 50%). False positives were due to suspected active TB, other mycobacterial infections, LTBI, active TB being diagnosed outside of the study period, and treatment for other conditions (eg. mono-rifampin for *Staphylococcus aureus* infection or mono-ethambutol for NTM prophylaxis). The authors suggested that PPV could be improved by using more rigorous criteria for pharmacy dispensing data, including a rule of three or more drugs, restricting timing (eg. two or more TB drugs be dispensed on the same date), excluding patients also receiving medications used to treat NTM (eg. clarithromycin), and requiring that TB drugs be dispensed over a minimum time interval (eg. at least 4 months). They did not test any of these proposed strategies[148].

Maggini et al (1991) validated case definitions for having 'a TB indication' in pharmacy dispensing records of the Italian national prescription drug plan. They tested algorithms based on specific TB drugs dispensed (isoniazid, rifampin, ethambutol, and/or streptomycin), and validated these algorithms by asking prescribing physicians to recall if their patient had had a TB-indication (including active TB and LTBI). The authors reported that all three-TB

drug combinations had a high PPV, with the PPV decreasing according to the number of drugs included in the algorithm (and subsequent increase in sensitivity)[144].

Figure 9: Availability of RAMQ data at the time of study data extraction

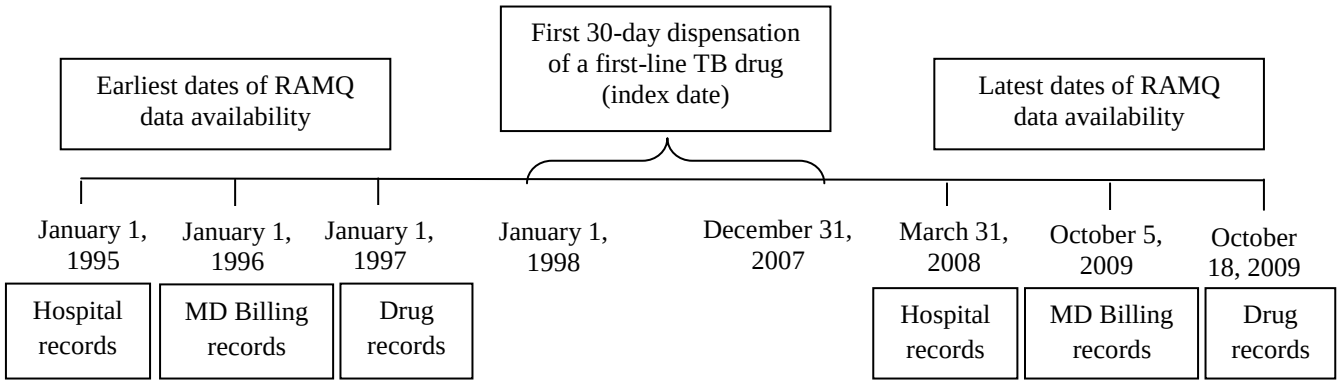


Figure 10: Identification of an individual patient's TB drug treatment period

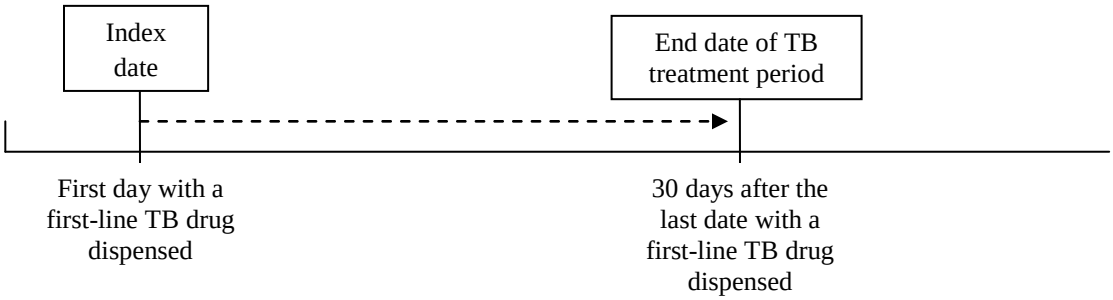
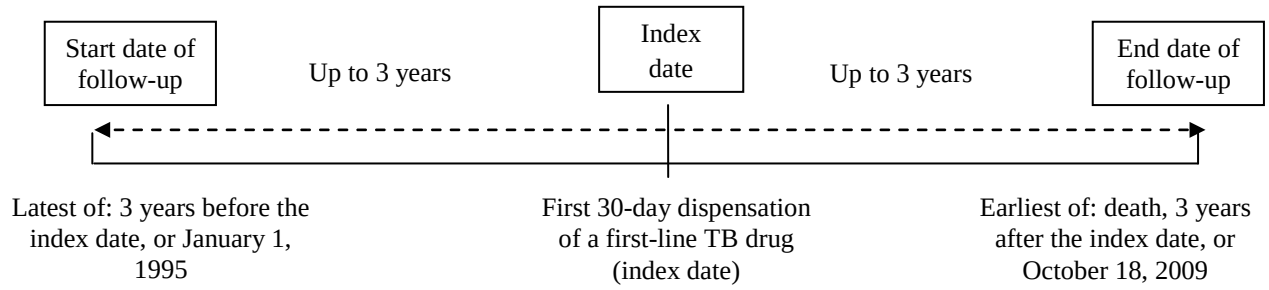


Figure 11: Identification of an individual patient's study follow-up period



Examples of data programming steps to set up arrays for calculating timing of TB drug exposures and outcomes

Example 1. Calculating drug dispensation days in the raw RAMQ data extraction file, calibrated as number of days from the index date (sindex)*

*For this patient, the index date is defined as the first date that a first-line TB drug was dispensed (ie. the start date of the TB treatment period), and recalculated as sindex=1. All other dates were calibrated as the number of days from this index date, ie. the second day of the TB treatment period recalculated as sindex=2, etc.

Raw data file

ID	Index date	Drug dispense date	Duration	DIN	AHFS	Quantity	Dose code	Form code	Drug	sindex	sindex
1684491033	2002-09-11	2002-09-11	30	577804	81600	30	51240	203	INH	1	30
1684491033	2002-09-11	2002-10-17	30	577804	81600	30	51240	203	INH	37	66
1684491033	2002-09-11	2002-10-25	30	577804	81600	30	51240	203	INH	45	74
1684491033	2002-09-11	2002-11-19	30	577804	81600	30	51240	203	INH	70	99
1684491033	2002-09-11	2002-12-19	30	577804	81600	30	51240	203	INH	100	129
1684491033	2002-09-11	2003-01-23	30	577804	81600	30	51240	203	INH	135	164

Example 2. Setting up TB drug arrays to identify days with TB drugs dispensed

* For every patient in the study, we set up the following arrays to track their patterns of TB drug dispensation over their follow-up period. For example #1 (above), the patient would have had the following array. This patient would be classified as an LTBI patient, with dispensing of 180 doses of INH.

# days from index (sindex)	1	2	3	4	5	6	→	36	37	38	39	40	41	42	43	44	45	46	→	160	161	162	163	164
Cumulative # of INH doses dispensed	1	2	3	4	5	6		30	31	32	33	34	35	36	37	38	40	42		176	177	178	179	180
Cumulative # of RIF doses dispensed	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0
Cumulative # of PZA doses dispensed	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0
Cumulative # of EMB doses dispensed	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0
# different first-line drugs dispensed	1	1	1	1	1	1		0	1	1	1	1	1	1	1	1	1	1		1	1	1	1	1
Any 2nd-line TB drug dispensed	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0
Any MAC doses dispensed	0	0	0	0	0	0	→	0	0	0	0	0	0	0	0	0	0	0	→	0	0	0	0	0
Cumulative # days with ≥3 first-line TB drugs dispensed	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0
Cumulative # days with ≥2 first-line and ≥second-line TB drugs dispensed	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0
Cumulative # days with ≥2 first-line TB drugs dispensed	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0
Cumulative # days with (RIF and/or EMB) + MAC	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0
Cumulative # days with RIF+INH	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0
Cumulative # days with RIF+PZA	0	0	0	0	0	0		0	0	0	0	0	0	0	0	0	0	0		0	0	0	0	0

Example 3. Applying case identification rules using TB drug arrays with multiple drugs dispensed

* This patient would have be identified as a standard active TB case (ie. meets rule #2 for 30 days of 3 or more first-line TB drugs dispensed, and meets rule #3 for 120 days of 2 or more first-line TB drugs)

Raw data file

ID	Duration	Drug	sindex	sindex
182106710	30	INH	1	30
182106710	30	RIF	1	30
182106710	30	PZA	1	30
182106710	30	EMB	1	30
182106710	30	INH	36	65
182106710	30	RIF	36	65
182106710	30	PZA	36	65
182106710	30	EMB	36	65

ID	Duration	Drug	sindex	sindex
182106710	30	INH	58	87
182106710	30	RIF	58	87
182106710	30	INH	82	111
182106710	30	RIF	82	111
182106710	30	INH	117	146
182106710	30	RIF	117	146
182106710	30	INH	148	177
182106710	30	RIF	148	177

Array file

# days from index (sindex)	1	2	3	4	5	6	35	36	37	38	39	40	41	42	43	44	45	173	174	175	176	177
Cumulative # of INH doses dispensed	1	2	3	4	5	6	30	31	32	33	34	35	36	37	38	39	40	176	177	178	179	180
Cumulative # of RIF doses dispensed	1	2	3	4	5	6	30	31	32	33	34	35	36	37	38	39	40	176	177	178	179	180
Cumulative # of PZA doses dispensed	1	2	3	4	5	6	30	31	32	33	34	35	36	37	38	39	40	0	0	0	0	0
Cumulative # of EMB doses dispensed	1	2	3	4	5	6	30	31	32	33	34	35	36	37	38	39	40	0	0	0	0	0
# different first-line drugs dispensed	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	2	2	2	2	2
Any 2nd-line TB drug dispensed	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Any MAC doses dispensed	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative # days with ≥3 first-line TB drugs dispensed	1	2	3	4	5	6	30	31	32	33	34	35	36	37	38	39	40	60	60	60	60	60
Cumulative # days with ≥2 first-line and ≥1second-line TB drugs dispensed	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative # days with ≥2 first-line TB drugs dispensed	1	2	3	4	5	6	30	31	32	33	34	35	36	37	38	39	40	176	177	178	179	180
Cumulative # days with (RIF and/or EMB) + MAC	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Cumulative # days with RIF+INH	1	2	3	4	5	6	30	31	32	33	34	35	36	37	38	39	40	176	177	178	179	180
Cumulative # days with RIF+PZA	1	2	3	4	5	6	30	31	32	33	34	35	36	37	38	39	40	60	60	60	60	60

Example 4. Array for calculating switches in LTBI regimens

* This would be identified as an LTBI case, with a switch from INH to RIF at day 21 (ie. patient was only prescribed INH and RIF, and on day 21 there was a switch from INH to RIF, with permanent discontinuation of the INH regimen). In the LTBI adherence study, this patient would have been classified as starting INH and stopping INH at day 21 due to regimen switch.

Raw data file

ID	Duration	Drug	sindex	eindex
957760992	30	INH	1	30
957760992	30	RIF	21	50
957760992	30	RIF	49	78
957760992	30	RIF	77	106
957760992	30	RIF	112	142

Array file

# days from index (sindex)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Cumulative # of INH doses dispensed	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Cumulative # of RIF doses dispensed	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	3	4	5	6	7
Switch date																					X						

Example 5. Array for calculating concurrent INH+RIF regimens

*This patient would be identified as HR only (ie. the patient only received concurrent dispensation of INH+RIF)

Raw data file

ID	Duration	Drug	sindex	eindex
1108040673	30	INH	1	30
1108040673	30	RIF	1	30
1108040673	30	INH	33	62
1108040673	30	RIF	33	62

Array file

# days from index (sindex)	1	2	3	4	5	6	7	8	9	10	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50
Cumulative # of INH doses dispensed	1	2	3	4	5	6	7	8	9	10	28	29	30	30	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	47	47	48
Cumulative # of RIF doses dispensed	1	2	3	4	5	6	7	8	9	10	28	29	30	30	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Cumulative # days with RIF+INH	1	2	3	4	5	6	7	8	9	10	28	29	30	30	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48

Table 39: Number of First- and Second-Line TB Drug and macrolide dispensation records in RAMQ dataset, January 1998-December 2007 (N=242,816 records from 23,220 people)

	Number of prescriptions dispensed	Median duration of prescription record in days (IQR)*	Median number of prescription records per person (IQR)*	Median daily dose of first-line drugs, in mg (IQR)*†
Any first-line TB drug				
Isoniazid	127,959	30 (30-30)	6 (3-9)	300 (300-300)
Rifampin	31,078	30 (30-30)	4 (2-7)	600 (450-600)
Ethambutol	16,185	30 (18-30)	3 (2-9)	800 (600-1200)
Pyrazinamide	7036	30 (30-30)	2 (2-3)	1500 (1000-1500)
Rifabutin	2518	30 (7-30)	5 (2-11)	300 (150-300)
Rifapentine	0	n/a	0	n/a
Rifater	90	30 (30-30)	2 (1-7)	-
Any second-line TB drug				
Fluoroquinolone	12,320	10 (7-30)	2 (1-3)	-
Aminoglycoside	848	10 (7-28)	2 (1-6)	-
Para-aminosalicylic acid	58	29 (25-35)	14.5 (10.5-18.5)	-
Cycloserine	0	n/a	0	-
Ethionamide	0	n/a	0	-
Any macrolide	14,123	10 (7-30)	1 (1-2)	-

Abbreviations: IQR: interquartile range; Rifater=combined isoniazid+pyrazinamide+rifampin

* Among people with one or more records for that drug type

† calculated in RAMQ drug records as (quantity x dose)/duration

Table 40: Number of First- and Second-Line TB drug and macrolide dispensation records in RAMQ dataset, by year of drug dispensation record, January 1998-December 2007 (N=242,816 records from 23,220 people)

Drug	Year drug dispensed												Total
	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	records
First-line TB drugs													
Isoniazid	7889	10535	11229	10723	13608	14536	13845	14309	13310	13704	4126	145	127,959
Rifampin	781	2949	2817	2563	3332	3197	2901	3313	3292	3438	1263	202	31,078
Ethambutol	8321	1230	1392	1443	1583	1808	1346	1648	1609	2204	923	167	16,185
Pyrazinamide	648	880	824	849	837	723	521	556	461	625	96	16	7036
Rifabutin	53	77	115	111	251	392	313	271	336	362	140	97	2518
Rifapentine	0	0	0	0	0	0	0	0	0	0	0	0	0
Rifater	15	31	10	8	0	3	10	1	2	1	1	8	90
Second-line TB drugs													
Fluoroquinolone	313	697	971	1258	1277	1806	1157	1305	1379	1494	840	323	12,320
Aminoglycoside	55	80	85	120	118	106	65	59	25	49	66	20	848
Para-aminosalicylic acid	0	2	36	18	2	0	0	0	0	0	0	0	58
Cycloserine	0	0	0	0	0	0	0	0	0	0	0	0	0
Ethionamide	0	0	0	0	0	0	0	0	0	0	0	0	0
Other drugs													
Macrolide	325	740	1213	1335	1336	1496	1384	1486	1472	1881	1048	407	14,123

Abbreviations: Rifater=combined isoniazid+pyrazinamide+rifampin

Table 41: Number of first-line TB drug records dispensed in RAMQ extraction dataset, by age group and RAMQ drug plan which provided coverage, January 1998-December 2007 (N=184,866 records from 23,220 people)

RAMQ Drug Plan that covered TB drug*	Number of first-line TB drug dispensation records, by age group							Total records
	0-4 years	5-19 years	20-34 years	35-49 years	50-64 years	65-79 years	≥80 years	
All first-line TB drugs								
02	3464 (72.3%)	17150 (67.3%)	35236 (83.9%)	34617 (74.2%)	17523 (59.5%)	10828 (40.1%)	3861 (40.6%)	122699 (66.4%)
AD	777 (16.2%)	4730 (18.6%)	4153 (18.6%)	3981 (8.5%)	5869 (19.9%)	609 (2.3%)	0	20119 (10.9%)
PA	0	0	0	0	386 (1.3%)	14998 (55.6%)	5628 (59.1%)	21012 (11.4%)
PS	550 (11.5%)	3594 (14.1%)	3594 (14.1%)	8082 (17.3%)	5653 (19.3%)	542 (2.0%)	32 (0.3%)	21056 (11.4%)
Isoniazid								
02	3277 (75.5%)	15574 (67.6%)	27746 (84.2%)	26117 (78.9%)	12031 (65.2%)	5329 (41.9%)	1341 (40.3%)	91415 (71.4%)
AD	595 (13.7)	4128 (17.9%)	3236 (9.8%)	2669 (8.1%)	3372 (18.3%)	321 (2.5%)	0	14321 (11.2%)
PA	0	0	0	0	53 (0.3%)	6767 (53.2%)	1974 (59.3%)	8794 (6.9%)
PS	467 (10.8%)	3340 (14.5%)	1978 (6.0%)	4321 (13.1%)	2995 (16.2%)	313 (2.5%)	15 (0.5%)	13429 (10.5%)
Rifampin								
02	148 (54.8%)	1096 (66.5%)	5059 (87.9%)	5236 (73.9%)	3375 (58.8%)	3108 (42.7%)	1428 (43.3%)	19450 (62.6%)
AD	61 (22.6%)	369 (22.4%)	464 (8.1%)	624 (8.8%)	1112 (19.4%)	133 (1.8%)	0	2763 (8.9%)
PA	0	0	0	0	107 (1.9%)	3904 (53.7%)	1859 (56.3%)	5870 (18.9%)
PS	61 (22.6%)	183 (11.1%)	231 (4.0%)	1228 (17.3%)	1146 (20.0%)	132 (1.8%)	14 (0.4%)	2995 (9.6%)
Ethambutol								
02	6 (10.7%)	277 (63.1%)	1285 (74.1%)	1691 (45.8%)	1302 (37.2%)	1418 (28.4%)	580 (32.7%)	6559 (40.5%)
AD	42 (75.0%)	136 (31.0%)	252 (14.5%)	386 (10.5%)	1013 (28.9%)	98 (2.0%)	0	1927 (11.9%)
PA	0	0	0	0	172 (4.9%)	3403 (68.3%)	1195 (67.3%)	4770 (29.5%)
PS	8 (14.3%)	26 (5.9%)	197 (11.4%)	1615 (43.7%)	1016 (29.0%)	67 (1.3%)	0	2929 (18.1%)
Pyrazinamide								
02	29 (42.7%)	203 (71.7%)	1113 (87.2%)	1484 (76.3%)	796 (71.0%)	948 (67.0%)	502 (54.2%)	5075 (72.1%)
AD	27 (39.9%)	48 (17.0%)	97 (9.7%)	130 (6.7%)	119 (10.6%)	333 (2.3%)	0	454 (6.5%)
PA	0	0	0	0	0	404 (28.6%)	422 (45.5%)	826 (11.7%)
PS	12 (17.7%)	32 (11.3%)	67 (5.3%)	332 (17.1%)	206 (18.4%)	29 (2.1%)	3 (0.3%)	681 (9.7%)

*RAMQ Drug Plans: 02=Tuberculosis; AD=Adult members and their dependants, not otherwise specified; PA= Person aged 65 years and older; PS= Persons receiving employment insurance and their dependants

Table 42: Number (%) of patients with first-line TB drug records containing a RAMQ TB program code (02), RAMQ dataset, January 1998-December 2007 (N=23,220 people)

Type of first-line TB drug	Number (%) of patients with first-line TB drug records containing a RAMQ TB program code (02), stratified by the proportion of their records with a TB program code				Total patients
	0% of the patient's records	1-49% of the patient's records	50-99% of patient's records	100% of the patient's records	
Any first-line TB drug	5240 (22.6%)	1459 (6.3%)	1978 (8.5%)	14543 (62.6%)	23220 (100%)
Isoniazid	4165 (19.8%)	1091 (2.5%)	1937 (9.2%)	13819 (65.8%)	21012 (100%)
Rifampin	1609 (31.2%)	178 (3.4%)	375 (7.3%)	3003 (58.1%)	5165 (100%)
Pyrazinamide	437 (21.4%)	49 (2.4%)	166 (8.1%)	1390 (68.1%)	2042 (100%)
Ethambutol	757 (36.2%)	92 (4.4%)	191 (9.1%)	1056 (50.4%)	2096 (100%)

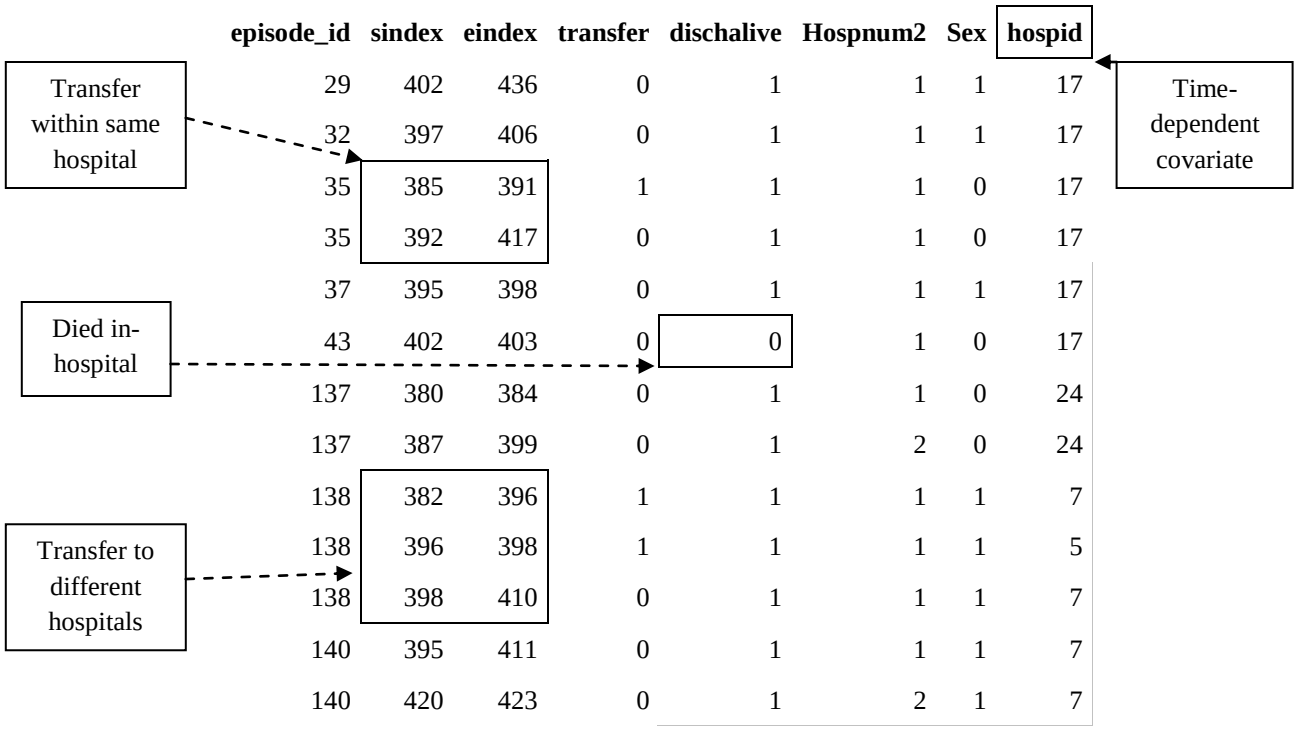
Table 43: Summary of TB drug treatment patterns, active TB cases, Montreal Resource Cohort (January 1996-May 2007), N=1852

	N	%
Pattern of first-line TB drugs prescribed		
Isonazid/Rifampin/Pyrazinamide/Ethambutol (HRZE)	1400	75.6%
Isoniazid/Rifampin/Pyrazinamide (HRZ)	267	14.4%
Isoniazid/Rifampin/Ethambutol (HRE)	88	4.8%
Isoniazid/Rifampin (HR)	35	1.9%
Other	24	1.3%
No treatment recorded	38	2.1%
Number of first- and second-line TB drugs prescribed*		
≥four different drugs	1458	78.7%
Three	318	17.2%
Two	36	1.9%
One	2	0.1%
Zero	38	2.1%
Number of cases with concurrent macrolide	4	0.2%

sd=standard deviation, IQR=interquartile range.

* First-line (isoniazid, rifampin, pyrazinamide, ethambutol, rifapentine, rifabutin) and second- line (fluoroquinolone, streptomycin, ethionamide, cycloserine, para-aminosalicylic acid (PAS), or injectable agent (eg. amikacin, kanamycin, capreomycin))

Table 44: Setting up hospital length of stay analyses



episode_id	sindex	eindex	transfer	dischalive	Hospnum2	Sex	hospid
29	402	436	0	1	1	1	17
32	397	406	0	1	1	1	17
35	385	391	1	1	1	0	17
35	392	417	0	1	1	0	17
37	395	398	0	1	1	1	17
43	402	403	0	0	1	0	17
137	380	384	0	1	1	0	24
137	387	399	0	1	2	0	24
138	382	396	1	1	1	1	7
138	396	398	1	1	1	1	5
138	398	410	0	1	1	1	7
140	395	411	0	1	1	1	7
140	420	423	0	1	2	1	7

Model statement in SAS:

```
proc phreg data=during covs(aggregate) covm ;

class sex hospid;

model (sindex eindex)*dischalive(0)= sex age aget hospid/ risklimits ties=efron
selection=backward slstay=0.2 details;

id episode_id ;

strata hospnum2; where hospnum2<3;

if log(los)>2.5 then time=1;
if log(los)<=2.5 then time=0;
aget=age*time;

output OUT=outp XBETA=xb RESDEV=dev RESMART=mart RESSCH =ressch LD=leverage
DFBETA=dfbeta;
run;
```

Table 45: Indirect Validation of RAMQ coding algorithms for *Montreal Health Region*: Number of active TB cases identified in RAMQ compared with number of confirmed Active TB Cases in the Montreal TB Cohort, *1998-2006*

Index year	TB Resource Cohort, all notified cases (n=1421)	TB Resource Cohort, patients with reported RAMQ registration (n=1134)	RAMQ database, estimated active TB cases using algorithm (n=981)	Estimated % of all notified cases (RAMQ/ Resource)
1998	149	124	117	94%
1999	164	136	131	96%
2000	199	156	133	85%
2001	156	131	123	94%
2002	175	126	106	84%
2003	173	133	97	73%
2004	132	112	90	80%
2005	133	108	93	86%
2006	140	108	73	68%

REFERENCES

1. WHO. Global tuberculosis report 2012. http://apps.who.int/iris/bitstream/10665/75938/1/9789241564502_eng.pdf. 2012.
2. Canadian Thoracic Society. Canadian Tuberculosis Standards, 7th edition. 2013 http://www.respiratoryguidelines.ca/tb-standards-2013.
3. Hirsch-Moverman Y, Daftary A, Franks J, Colson PW. Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2008;12(11):1235-54. Epub 2008/10/18.
4. Kunst H, Khan KS. Age-related risk of hepatotoxicity in the treatment of latent tuberculosis infection: a systematic review. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2010;14(11):1374-81. Epub 2010/10/13.
5. Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventive therapy: a 7-year survey from a public health tuberculosis clinic. JAMA : the journal of the American Medical Association. 1999;281(11):1014-8. Epub 1999/03/23.
6. Reichman LB, Lardizabal A, Hayden CH. Considering the role of four months of rifampin in the treatment of latent tuberculosis infection. American journal of respiratory and critical care medicine. 2004;170(8):832-5. Epub 2004/08/07.
7. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control. 2000;49(RR-6):1-51. Epub 2000/07/06.
8. Menzies D, Dion MJ, Rabinovitch B, Mannix S, Brassard P, Schwartzman K. Treatment completion and costs of a randomized trial of rifampin for 4 months versus isoniazid for 9 months. American journal of respiratory and critical care medicine. 2004;170(4):445-9. Epub 2004/06/03.
9. Menzies D, Long R, Trajman A, Dion MJ, Yang J, Al Jahdali H, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Annals of internal medicine. 2008;149(10):689-97. Epub 2008/11/20.
10. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. The American review of respiratory disease. 1992;145(1):36-41. Epub 1992/01/01.
11. Chavan S, Newlands D, Smith C. A systematic review of economic evaluations of chemoprophylaxis for tuberculosis. Journal of tropical medicine. 2011;2011:130976. Epub 2011/12/02.
12. Crystal S, Akincigil A, Bilder S, Walkup JT. Studying prescription drug use and outcomes with medicaid claims data: strengths, limitations, and strategies. Medical care. 2007;45(10 Supl 2):S58-65. Epub 2007/10/25.
13. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. Journal of clinical epidemiology. 2005;58(4):323-37. Epub 2005/05/03.
14. Sorensen HT, Sabroe S, Olsen J. A framework for evaluation of secondary data sources for epidemiological research. International journal of epidemiology. 1996;25(2):435-42. Epub 1996/04/01.

15. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects--advantages and disadvantages. Nature clinical practice Rheumatology. 2007;3(12):725-32. Epub 2007/11/27.
16. WHO. WHO Report 2009- Global Tuberculosis Control. Epidemiology, Strategy, Financing. . Geneva, Switzerland: World Health Organization, 2009.
17. Maartens G, Wilkinson RJ. Tuberculosis. Lancet. 2007;370(9604):2030-43. Epub 2007/08/28.
18. Kwan CK, Ernst JD. HIV and Tuberculosis: a Deadly Human Syndemic. Clin Microbiol Rev.24(2):351-76. Epub 2011/04/13.
19. Wells CD, Cegielski JP, Nelson LJ, Laserson KF, Holtz TH, Finlay A, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. J Infect Dis. 2007;196 Suppl 1:S86-107. Epub 2007/08/30.
20. Yoon CJ. HIV-TB: a perfect storm. AIDS Read. 2007;17(6):302-6, 9. Epub 2007/07/18.
21. World Health Organization. Global tuberculosis control: surveillance, planning, financing. WHO report 2005. Geneva, World Health Organization

(WHO/HTM/TB/2005.349).
22. UNAIDS. HIV and TB Fact Sheet. http://data.unaids.org/pub/factsheet/2006/tb_hiv_qa.pdf (accessed April 29, 2011). 2006.
23. World Health Organization/ Stop TB Partnership. 2010/2011 Tuberculosis Global Facts. www.who.int/tb (accessed February 2012).
24. Alexander PE, De P. The emergence of extensively drug-resistant tuberculosis (TB): TB/HIV coinfection, multidrug-resistant TB and the resulting public health threat from extensively drug-resistant TB, globally and in Canada. Can J Infect Dis Med Microbiol. 2007;18(5):289-91. Epub 2008/10/17.
25. Public Health Agency of Canada. Tuberculosis in Canada 2010 – Pre-release. Ottawa (Canada): Minister of Public Works and Government Services Canada; 2012. http://publications.gc.ca/collections/collection_2012/aspc-phac/HP37-5-1-2010-eng.pdf.
26. Harris T, Panaro L, Phypers M, Choudhri Y, Archibald CP. HIV Testing among Canadian Tuberculosis Cases from 1997 to 1998. Can J Infect Dis Med Microbiol. 2006;17(3):165-8. Epub 2008/04/18.
27. Phypers M. Special report of the Canadian Tuberculosis Committee. Tuberculosis and HIV co-infection in Canada. Can Commun Dis Rep. 2007;33(8):77-83. Epub 2007/07/18.
28. Public Health Agency of Canada and Canadian Lung Association/Canadian Thoracic Society. Canadian Tuberculosis Standards. Sixth ed. Long R, Ellis E, editors; 2007.
29. Haddad MB, Wilson TW, Ijaz K, Marks SM, Moore M. Tuberculosis and homelessness in the United States, 1994-2003. JAMA : the journal of the American Medical Association. 2005;293(22):2762-6. Epub 2005/06/09.
30. Barnes PF, Yang Z, Preston-Martin S, Pogoda JM, Jones BE, Otaya M, et al. Patterns of tuberculosis transmission in Central Los Angeles. JAMA : the journal of the American Medical Association. 1997;278(14):1159-63. Epub 1997/10/27.
31. Hernandez-Garduno E, Kunimoto D, Wang L, Rodrigues M, Elwood RK, Black W, et al. Predictors of clustering of tuberculosis in Greater Vancouver: a molecular epidemiologic study. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2002;167(4):349-52. Epub 2002/08/29.
32. Lienhardt C. From exposure to disease: the role of environmental factors in susceptibility to and development of tuberculosis. Epidemiologic reviews. 2001;23(2):288-301. Epub 2002/08/24.

33. Smith A, Miller RF, Story A, Booth HL. A&E department: a missed opportunity for diagnosis of TB? Thorax. 2006;61(4):364-5. Epub 2006/03/28.
34. Hopewell PC. Targeting tuberculosis prevention. American journal of respiratory and critical care medicine. 2000;162(6):2017-8. Epub 2000/12/09.
35. Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. The New England journal of medicine. 2004;350(20):2060-7. Epub 2004/05/14.
36. Ziv E, Daley CL, Blower SM. Early therapy for latent tuberculosis infection. American journal of epidemiology. 2001;153(4):381-5. Epub 2001/02/24.
37. Oursler KK, Moore RD, Bishai WR, Harrington SM, Pope DS, Chaisson RE. Survival of patients with pulmonary tuberculosis: clinical and molecular epidemiologic factors. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2002;34(6):752-9. Epub 2002/02/19.
38. Rao VK, Iademarco EP, Fraser VJ, Kollef MH. The impact of comorbidity on mortality following in-hospital diagnosis of tuberculosis. Chest. 1998;114(5):1244-52. Epub 1998/11/21.
39. Erbes R, Oettel K, Raffenberg M, Mauch H, Schmidt-Ioanas M, Lode H. Characteristics and outcome of patients with active pulmonary tuberculosis requiring intensive care. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2006;27(6):1223-8. Epub 2006/02/17.
40. Pasipanodya JG, McNabb SJ, Hilsenrath P, Bae S, Lykens K, Vecino E, et al. Pulmonary impairment after tuberculosis and its contribution to TB burden. BMC public health. 2010;10:259. Epub 2010/05/21.
41. Long R, Maycher B, Dhar A, Manfreda J, Hershfield E, Anthonisen N. Pulmonary tuberculosis treated with directly observed therapy: serial changes in lung structure and function. Chest. 1998;113(4):933-43. Epub 1998/04/29.
42. Vecino M, Pasipanodya JG, Slocum P, Bae S, Munguia G, Miller T, et al. Evidence for chronic lung impairment in patients treated for pulmonary tuberculosis. Journal of infection and public health. 2011;4(5-6):244-52. Epub 2011/11/29.
43. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control. 2005;54(RR-15):1-47. Epub 2005/12/17.
44. Prevention and control of tuberculosis in correctional and detention facilities: recommendations from CDC. Endorsed by the Advisory Council for the Elimination of Tuberculosis, the National Commission on Correctional Health Care, and the American Correctional Association. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control. 2006;55(RR-9):1-44. Epub 2006/07/11.
45. Public Health Agency of Canada. Nationally notifiable diseases in Canada: Tuberculosis. http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/09vol35/35s2/Tuberc-eng.php (accessed April 25, 2012).
46. Mor Z, Migliori GB, Althomsons SP, Loddenkemper R, Trnka L, Iademarco MF. Comparison of tuberculosis surveillance systems in low-incidence industrialised countries. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2008;32(6):1616-24. Epub 2008/08/08.
47. Ries NM. Public health law and ethics: lessons from SARS and quarantine. Health law review. 2004;13(1):3-6. Epub 2005/04/21.

48. El-Sadr WM, Tsiouris SJ. HIV-associated tuberculosis: diagnostic and treatment challenges. Seminars in respiratory and critical care medicine. 2008;29(5):525-31. Epub 2008/09/24.
49. Getahun H, Harrington M, O'Brien R, Nunn P. Diagnosis of smear-negative pulmonary tuberculosis in people with HIV infection or AIDS in resource-constrained settings: informing urgent policy changes. Lancet. 2007;369(9578):2042-9. Epub 2007/06/19.
50. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis. Common errors and their association with the acquisition of drug resistance. JAMA : the journal of the American Medical Association. 1993;270(1):65-8. Epub 1993/07/07.
51. Stout JE, Holland DP. Treating latent tuberculosis with rifampin: is it the cheaper option? Thorax. 2010;65(7):572-3. Epub 2010/07/16.
52. Davies PD. TB in the elderly in industrialised countries. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2007;11(11):1157-9. Epub 2007/10/26.
53. Greenaway C, Menzies D, Fanning A, Grewal R, Yuan L, FitzGerald JM. Delay in diagnosis among hospitalized patients with active tuberculosis--predictors and outcomes. American journal of respiratory and critical care medicine. 2002;165(7):927-33. Epub 2002/04/06.
54. Khan K, Campbell A, Wallington T, Gardam M. The impact of physician training and experience on the survival of patients with active tuberculosis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2006;175(7):749-53. Epub 2006/09/27.
55. Rao VK, Iademarco EP, Fraser VJ, Kollef MH. Delays in the suspicion and treatment of tuberculosis among hospitalized patients. Annals of internal medicine. 1999;130(5):404-11. Epub 1999/03/06.
56. Lam PK, Lobue PA, Catanzaro A. Clinical diagnosis of tuberculosis by specialists and non-specialists. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2009;13(5):659-61. Epub 2009/04/23.
57. Rao SN, Mookerjee AL, Obasanjo OO, Chaisson RE. Errors in the treatment of tuberculosis in Baltimore. Chest. 2000;117(3):734-7. Epub 2000/03/14.
58. Sumartojo EM, Geiter LJ, Miller B, Hale BE. Can physicians treat tuberculosis? Report on a national survey of physician practices. American journal of public health. 1997;87(12):2008-11. Epub 1998/02/07.
59. Gardam M, Verma G, Campbell A, Wang J, Khan K. Impact of the patient-provider relationship on the survival of foreign born outpatients with tuberculosis. Journal of immigrant and minority health / Center for Minority Public Health. 2009;11(6):437-45. Epub 2009/01/08.
60. Landry J, Menzies D. Preventive chemotherapy. Where has it got us? Where to go next? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2008;12(12):1352-64. Epub 2008/11/20.
61. Schaaf HS, Collins A, Bekker A, Davies PD. Tuberculosis at extremes of age. Respirology. 2010;15(5):747-63. Epub 2010/06/16.
62. Minion J, Sohn H, Pai M. Light-emitting diode technologies for TB diagnosis: what is on the market? Expert Rev Med Devices. 2009;6(4):341-5. Epub 2009/07/04.
63. Hanekom WA, Lawn SD, Dheda K, Whitelaw A. Tuberculosis research update. Trop Med Int Health.15(8):981-9. Epub 2010/06/22.

64. Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M, et al. Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. The Cochrane database of systematic reviews. 2013;1:CD009593. Epub 2013/02/27.
65. Mitchison DA. Antimicrobial therapy of tuberculosis: justification for currently recommended treatment regimens. Seminars in respiratory and critical care medicine. 2004;25(3):307-15. Epub 2005/08/10.
66. Blumberg HM, Burman WJ, Chaisson RE, Daley CL, Etkind SC, Friedman LN, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. American journal of respiratory and critical care medicine. 2003;167(4):603-62. Epub 2003/02/18.
67. Nahid P, Pai M, Hopewell PC. Advances in the diagnosis and treatment of tuberculosis. Proc Am Thorac Soc. 2006;3(1):103-10. Epub 2006/02/24.
68. Rajbhandary SS, Marks SM, Bock NN. Costs of patients hospitalized for multidrug-resistant tuberculosis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2004;8(8):1012-6. Epub 2004/08/13.
69. McIlleron H, Meintjes G, Burman WJ, Maartens G. Complications of antiretroviral therapy in patients with tuberculosis: drug interactions, toxicity, and immune reconstitution inflammatory syndrome. J Infect Dis. 2007;196 Suppl 1:S63-75. Epub 2007/08/30.
70. Kwara A, Flanigan TP, Carter EJ. Highly active antiretroviral therapy (HAART) in adults with tuberculosis: current status. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2005;9(3):248-57. Epub 2005/03/25.
71. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. American journal of respiratory and critical care medicine. 2003;167(11):1472-7. Epub 2003/02/06.
72. Marra F, Marra CA, Bruchet N, Richardson K, Moadebi S, Elwood RK, et al. Adverse drug reactions associated with first-line anti-tuberculosis drug regimens. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2007;11(8):868-75. Epub 2007/08/21.
73. Guo N, Marra F, Fitzgerald JM, Elwood RK, Marra CA. Impact of adverse drug reaction and predictivity of quality of life status in tuberculosis. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2010;36(1):206-8. Epub 2010/07/03.
74. Saukkonen JJ, Cohn DL, Jasmer RM, Schenker S, Jereb JA, Nolan CM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. American journal of respiratory and critical care medicine. 2006;174(8):935-52. Epub 2006/10/06.
75. Chang KC, Leung CC, Yew WW, Lau TY, Tam CM. Hepatotoxicity of pyrazinamide: cohort and case-control analyses. American journal of respiratory and critical care medicine. 2008;177(12):1391-6. Epub 2008/04/05.
76. Davern TJ. Drug-induced liver disease. Clinics in liver disease. 2012;16(2):231-45. Epub 2012/05/01.
77. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1996;9(10):2026-30. Epub 1996/10/01.

78. Hussaini SH, Farrington EA. Idiosyncratic drug-induced liver injury: an overview. Expert opinion on drug safety. 2007;6(6):673-84. Epub 2007/10/31.
79. Francis J. Curry National Tuberculosis Center and California Department of Public Health, 2009. Tuberculosis Drug Information Guide. pp 1-41.
80. Sterling TR, Bethel J, Goldberg S, Weinfurter P, Yun L, Horsburgh CR. The scope and impact of treatment of latent tuberculosis infection in the United States and Canada. American journal of respiratory and critical care medicine. 2006;173(8):927-31. Epub 2006/01/21.
81. Menzies D, Gardiner G, Farhat M, Greenaway C, Pai M. Thinking in three dimensions: a web-based algorithm to aid the interpretation of tuberculin skin test results. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2008;12(5):498-505. Epub 2008/04/19.
82. Farhat M, Greenaway C, Pai M, Menzies D. False-positive tuberculin skin tests: what is the absolute effect of BCG and non-tuberculous mycobacteria? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2006;10(11):1192-204. Epub 2006/11/30.
83. Moreno S, Baraia-Etxaburu J, Bouza E, Parras F, Perez-Tascon M, Miralles P, et al. Risk for developing tuberculosis among anergic patients infected with HIV. Annals of internal medicine. 1993;119(3):194-8. Epub 1993/08/01.
84. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. American journal of respiratory and critical care medicine. 2000;161(4 Pt 2):S221-47. Epub 2000/04/14.
85. NICE. UK National Institute for Health and Clinical Effectiveness. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control (March 2011). Web site: http://publications.nice.org.uk/tuberculosis-cg117. [Accessed: March 31, 2012].
86. Preventive therapy of tuberculous infection. The American review of respiratory disease. 1974;110(3):371-4. Epub 1974/09/01.
87. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 1999;3(10):847-50. Epub 1999/10/19.
88. Gordin F, Chaisson RE, Matts JP, Miller C, de Lourdes Garcia M, Hafner R, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. JAMA : the journal of the American Medical Association. 2000;283(11):1445-50. Epub 2000/03/25.
89. Horsburgh CR, Jr., Goldberg S, Bethel J, Chen S, Colson PW, Hirsch-Moverman Y, et al. Latent TB Infection Treatment Acceptance and Completion in the United States and Canada. Chest.137(2):401-9. Epub 2009/10/02.
90. Cook PP, Maldonado RA, Yarnell CT, Holbert D. Safety and completion rate of short-course therapy for treatment of latent tuberculosis infection. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2006;43(3):271-5. Epub 2006/06/29.

91. Lardizabal A, Passannante M, Kojakali F, Hayden C, Reichman LB. Enhancement of treatment completion for latent tuberculosis infection with 4 months of rifampin. Chest. 2006;130(6):1712-7. Epub 2006/12/15.
92. Page KR, Sifakis F, Montes de Oca R, Cronin WA, Doherty MC, Federline L, et al. Improved adherence and less toxicity with rifampin vs isoniazid for treatment of latent tuberculosis: a retrospective study. Arch Intern Med. 2006;166(17):1863-70. Epub 2006/09/27.
93. Young H, Wessolossky M, Ellis J, Kaminski M, Daly JS. A retrospective evaluation of completion rates, total cost, and adverse effects for treatment of latent tuberculosis infection in a public health clinic in central massachusetts. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2009;49(3):424-7. Epub 2009/06/25.
94. Smith BM, Schwartzman K, Bartlett G, Menzies D. Adverse events associated with treatment of latent tuberculosis in the general population. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2011;183(3):E173-9. Epub 2011/01/12.
95. Comstock GW. Prevention of tuberculosis among tuberculin reactors: maximizing benefits, minimizing risks. JAMA : the journal of the American Medical Association. 1986;256(19):2729-30. Epub 1986/11/21.
96. Dolan JG, Bordley DR. Isoniazid prophylaxis: the importance of individual values. Medical decision making : an international journal of the Society for Medical Decision Making. 1994;14(1):1-8. Epub 1994/01/01.
97. Sorresso DJ, Mehta JB, Harvill LM, Bentley S. Underutilization of isoniazid chemoprophylaxis in tuberculosis contacts 50 years of age and older. A prospective analysis. Chest. 1995;108(3):706-11. Epub 1995/09/01.
98. Lobue P. People aged above 65 treated for latent tuberculosis are at increased risk of admission for a hepatic event compared with untreated controls. Evidence-based medicine. 2011;16(6):169-70. Epub 2011/06/08.
99. Taylor Z, O'Brien RJ. Tuberculosis elimination: are we willing to pay the price? American journal of respiratory and critical care medicine. 2001;163(1):1-2. Epub 2001/02/24.
100. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the Economic Evaluation of Health Care Programmes. Third ed. New York: Oxford University Press; 2005. 379 p.
101. Floyd K. Costs and effectiveness--the impact of economic studies on TB control. Tuberculosis (Edinb). 2003;83(1-3):187-200. Epub 2003/05/22.
102. Sarasin FP, Perrier A, Rochat T. Isoniazid preventive therapy for pulmonary tuberculosis sequelae: which patients up to which age? Tuber Lung Dis. 1995;76(5):394-400. Epub 1995/10/01.
103. Holland DP, Sanders GD, Hamilton CD, Stout JE. Costs and cost-effectiveness of four treatment regimens for latent tuberculosis infection. American journal of respiratory and critical care medicine. 2009;179(11):1055-60. Epub 2009/03/21.
104. Tan MC, Marra CA, Sadatsafavi M, Marra F, Moran-Mendoza O, Moadebi S, et al. Cost-effectiveness of LTBI treatment for TB contacts in British Columbia. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2008;11(5):842-52. Epub 2008/05/21.
105. Dasgupta K, Schwartzman K, Marchand R, Tennenbaum TN, Brassard P, Menzies D. Comparison of cost-effectiveness of tuberculosis screening of close contacts and foreign-born populations. American journal of respiratory and critical care medicine. 2000;162(6):2079-86. Epub 2000/12/09.

106. Schwartzman K, Menzies D. Tuberculosis screening of immigrants to low-prevalence countries. A cost-effectiveness analysis. American journal of respiratory and critical care medicine. 2000;161(3 Pt 1):780-9. Epub 2000/03/11.
107. Tan M, Menzies D, Schwartzman K. Tuberculosis screening of travelers to higher-incidence countries: a cost-effectiveness analysis. BMC public health. 2008;8:201. Epub 2008/06/07.
108. Gourevitch MN, Alcabes P, Wasserman WC, Arno PS. Cost-effectiveness of directly observed chemoprophylaxis of tuberculosis among drug users at high risk for tuberculosis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 1998;2(7):531-40. Epub 1998/07/14.
109. Linas BP, Wong AY, Freedberg KA, Horsburgh CR, Jr. Priorities for screening and treatment of latent tuberculosis infection in the United States. American journal of respiratory and critical care medicine. 2011;184(5):590-601. Epub 2011/05/13.
110. Pina JM, Clotet L, Ferrer A, Sala MR, Garrido P, Salleras L, et al. Cost-effectiveness of rifampin for 4 months and isoniazid for 9 months in the treatment of tuberculosis infection. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology. 2013;32(5):647-55. Epub 2012/12/15.
111. Esfahani K, Aspler A, Menzies D, Schwartzman K. Potential cost-effectiveness of rifampin vs. isoniazid for latent tuberculosis: implications for future clinical trials. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2011;15(10):1340-6. Epub 2012/01/31.
112. Aspler A, Long R, Trajman A, Dion MJ, Khan K, Schwartzman K, et al. Impact of treatment completion, intolerance and adverse events on health system costs in a randomised trial of 4 months rifampin or 9 months isoniazid for latent TB. Thorax. 2010;65(7):582-7. Epub 2010/07/16.
113. Ziakas PD, Mylonakis E. 4 months of rifampin compared with 9 months of isoniazid for the management of latent tuberculosis infection: a meta-analysis and cost-effectiveness study that focuses on compliance and liver toxicity. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2009;49(12):1883-9. Epub 2009/11/17.
114. Khan K, Muennig P, Behta M, Zivin JG. Global drug-resistance patterns and the management of latent tuberculosis infection in immigrants to the United States. The New England journal of medicine. 2002;347(23):1850-9. Epub 2002/12/06.
115. Arno PS, Murray CJ, Bonuck KA, Alcabes P. The economic impact of tuberculosis in hospitals in New York City: a preliminary analysis. J Law Med Ethics. 1993;21(3-4):317-23. Epub 1993/01/01.
116. Brown RE, Miller B, Taylor WR, Palmer C, Bosco L, Nicola RM, et al. Health-care expenditures for tuberculosis in the United States. Arch Intern Med. 1995;155(15):1595-600. Epub 1995/08/07.
117. Rosenblum LS, Castro KG, Dooley S, Morgan M. Effect of HIV infection and tuberculosis on hospitalizations and cost of care for young adults in the United States, 1985 to 1990. Annals of internal medicine. 1994;121(10):786-92. Epub 1994/11/15.
118. Taylor Z, Marks SM, Rios Burrows NM, Weis SE, Stricof RL, Miller B. Causes and costs of hospitalization of tuberculosis patients in the United States. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2000;4(10):931-9. Epub 2000/10/31.
119. Wurtz R, White WD. The cost of tuberculosis: utilization and estimated charges for the diagnosis and treatment of tuberculosis in a public health system. The international journal of

tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 1999;3(5):382-7. Epub 1999/05/20.
120. Bocchino M, Greco S, Rosati Y, Mattioli G, Marruchella A, De Mori P, et al. Cost determinants of tuberculosis management in a low-prevalence country. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2006;10(2):146-52. Epub 2006/02/28.
121. Diel R, Rappenhoner B, Schaberg T. The cost structure of lung tuberculosis in Germany. Eur J Health Econ. 2004;5(3):243-51. Epub 2005/02/17.
122. Menzies D, Lewis M, Oxlade O. Costs for tuberculosis care in Canada. Canadian journal of public health Revue canadienne de sante publique. 2008;99(5):391-6. Epub 2008/11/18.
123. Marks SM, Taylor Z, Miller BI. Tuberculosis prevention versus hospitalization: taxpayers save with prevention. Journal of health care for the poor and underserved. 2002;13(3):392-401. Epub 2002/08/03.
124. MacIntyre CR, Plant AJ, Hendrie D. Shifting the balance between in-patient and out-patient care for tuberculosis results in economic savings. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2001;5(3):266-71. Epub 2001/05/01.
125. Liu C, Watts B, Litaker D. Access to and utilization of healthcare: the provider's role. Expert review of pharmacoeconomics & outcomes research. 2006;6(6):653-60. Epub 2006/12/01.
126. Martens P, Brownell M, Au W, MacWilliam L, Prior H, Schultz J, et al. Health Inequities in Manitoba: Is the Socioeconomic Gap Widening or Narrowing Over Time? Winnipeg, MB: Manitoba Centre for Health Policy: 2010.
127. Gaeta TJ, Webheh W, Yazji M, Ahmed J, Yap W. Respiratory isolation of patients with suspected pulmonary tuberculosis in an inner-city hospital. Acad Emerg Med. 1997;4(2):138-41. Epub 1997/02/01.
128. Marks SM, Taylor Z, Burrows NR, Qayad MG, Miller B. Hospitalization of homeless persons with tuberculosis in the United States. American journal of public health. 2000;90(3):435-8. Epub 2000/03/08.
129. Hansel NN, Merriman B, Haponik EF, Diette GB. Hospitalizations for tuberculosis in the United States in 2000: predictors of in-hospital mortality. Chest. 2004;126(4):1079-86. Epub 2004/10/16.
130. Shulkin DJ, Brennan PJ. The cost of caring for patients with tuberculosis: planning for a disease on the rise. American journal of infection control. 1995;23(1):1-4. Epub 1995/02/01.
131. Rodriguez-Monguio R, Otero MJ, Rovira J. Assessing the economic impact of adverse drug effects. PharmacoEconomics. 2003;21(9):623-50. Epub 2003/06/17.
132. Riley GF. Administrative and claims records as sources of health care cost data. Medical care. 2009;47(7 Suppl 1):S51-5. Epub 2009/06/19.
133. Marko NF, Weil RJ. The role of observational investigations in comparative effectiveness research. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2010;13(8):989-97. Epub 2010/12/09.
134. Manitoba Centre for Health Policy. Administrative Health Data / Databases. http://mchp-appserv.cpe.umanitoba.ca/viewDefinition.php?definitionID=102210. Accessed June 14, 2013.
135. Saydah SH, Geiss LS, Tierney E, Benjamin SM, Engelgau M, Brancati F. Review of the performance of methods to identify diabetes cases among vital statistics, administrative, and survey data. Annals of epidemiology. 2004;14(7):507-16. Epub 2004/08/11.

136. van Walraven C, Austin P. Administrative database research has unique characteristics that can risk biased results. Journal of clinical epidemiology. 2012;65(2):126-31. Epub 2011/11/15.
137. Schneeweiss S, Maclure M. Use of comorbidity scores for control of confounding in studies using administrative databases. International journal of epidemiology. 2000;29(5):891-8. Epub 2000/10/18.
138. Lix LM, Neufeld SM, Smith M, Levy A, Dai S, Sanmartin C, et al. Quality of Administrative Data in Canada: A Discussion Paper. University of Saskatchewan: http://www.usaskhealthdatalab.ca/wp-content/uploads/2012/09/Workshop_Background-Document-updated-AppendixD.pdf. 2002.
139. Hornbrook MC, Goodman MJ, Fishman PA, Meenan RT, O'Keeffe-Rosetti M, Bachman DJ. Building health plan databases to risk adjust outcomes and payments. International journal for quality in health care : journal of the International Society for Quality in Health Care / ISQua. 1998;10(6):531-8. Epub 1999/02/03.
140. Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. Journal of clinical epidemiology. 2007;60(4):397-409. Epub 2007/03/10.
141. Brassard P, Lowe AM, Bernatsky S, Kezouh A, Suissa S. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis and rheumatism. 2009;61(3):300-4. Epub 2009/02/28.
142. Clancy L, Rieder HL, Enarson DA, Spinaci S. Tuberculosis elimination in the countries of Europe and other industrialized countries. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 1991;4(10):1288-95. Epub 1991/11/01.
143. Tang PC, Ralston M, Arrigotti MF, Qureshi L, Graham J. Comparison of methodologies for calculating quality measures based on administrative data versus clinical data from an electronic health record system: implications for performance measures. Journal of the American Medical Informatics Association : JAMIA. 2007;14(1):10-5. Epub 2006/10/28.
144. Maggini M, Salmaso S, Alegiani SS, Caffari B, Raschetti R. Epidemiological use of drug prescriptions as markers of disease frequency: an Italian experience. Journal of clinical epidemiology. 1991;44(12):1299-307. Epub 1991/01/01.
145. Winthrop KL, Baxter R, Liu L, McFarland B, Austin D, Varley C, et al. The reliability of diagnostic coding and laboratory data to identify tuberculosis and nontuberculous mycobacterial disease among rheumatoid arthritis patients using anti-tumor necrosis factor therapy. Pharmacoepidemiology and drug safety. 2011;20(3):229-35. Epub 2011/02/26.
146. Calderwood MS, Platt R, Hou X, Malenfant J, Haney G, Kruskal B, et al. Real-time surveillance for tuberculosis using electronic health record data from an ambulatory practice in eastern Massachusetts. Public Health Rep. 2010;125(6):843-50. Epub 2010/12/03.
147. Fiske CT, Griffin MR, Mitchel E, Sterling TR, Grijalva CG. Accuracy of pharmacy and coded-diagnosis information in identifying tuberculosis in patients with rheumatoid arthritis. Pharmacoepidemiology and drug safety. 2012. Epub 2012/04/26.
148. Yokoe DS, Subramanyan GS, Nardell E, Sharnprapai S, McCray E, Platt R. Supplementing tuberculosis surveillance with automated data from health maintenance organizations. Emerging infectious diseases. 1999;5(6):779-87. Epub 1999/12/22.
149. Lix LM, Yogendran MS, Shaw SY, Burchill C, Metge C, Bond R. Population-based data sources for chronic disease surveillance. Chronic diseases in Canada. 2008;29(1):31-8. Epub 2008/11/28.

150. Campbell SE, Campbell MK, Grimshaw JM, Walker AE. A systematic review of discharge coding accuracy. Journal of public health medicine. 2001;23(3):205-11. Epub 2001/10/05.
151. Hennessy DA, Quan H, Faris PD, Beck CA. Do coder characteristics influence validity of ICD-10 hospital discharge data? BMC health services research. 2010;10:99. Epub 2010/04/23.
152. Yokoe DS, Coon SW, Dokholyan R, Iannuzzi MC, Jones TF, Meredith S, et al. Pharmacy data for tuberculosis surveillance and assessment of patient management. Emerging infectious diseases. 2004;10(8):1426-31. Epub 2004/10/22.
153. Manangan LP, Moore M, Macaraig M, MacNeil J, Shevick G, Northrup J, et al. Health department costs of managing persons with suspected and noncounted tuberculosis in New York City, Three Texas counties, and Massachusetts. Journal of public health management and practice : JPHMP. 2006;12(3):248-53. Epub 2006/04/15.
154. Mitruka K, Winston CA, Navin TR. Predictors of failure in timely tuberculosis treatment completion, United States. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2012;16(8):1075-82. Epub 2012/06/07.
155. Alberg AJ, Park JW, Hager BW, Brock MV, Diener-West M. The use of "overall accuracy" to evaluate the validity of screening or diagnostic tests. Journal of general internal medicine. 2004;19(5 Pt 1):460-5. Epub 2004/04/28.
156. NA VANH, Story A, Grant AD, Antoine D, Crofts JP, Watson JM. Record-linkage and capture-recapture analysis to estimate the incidence and completeness of reporting of tuberculosis in England 1999-2002. Epidemiology and infection. 2008;136(12):1606-16. Epub 2008/03/19.
157. van Hest NA, Smit F, Baars HW, De Vries G, De Haas PE, Westenend PJ, et al. Completeness of notification of tuberculosis in The Netherlands: how reliable is record-linkage and capture-recapture analysis? Epidemiology and infection. 2007;135(6):1021-9. Epub 2006/12/13.
158. Suissa S. Immeasurable time bias in observational studies of drug effects on mortality. American journal of epidemiology. 2008;168(3):329-35. Epub 2008/06/03.
159. Sickbert-Bennett EE, Weber DJ, Poole C, MacDonald PD, Maillard JM. Utility of International Classification of Diseases, Ninth Revision, Clinical Modification codes for communicable disease surveillance. American journal of epidemiology. 2010;172(11):1299-305. Epub 2010/09/30.
160. White VL, Paliwalla M, Steves CJ, Jadhav D, Moore-Gillon J. Management of tuberculosis in a British inner-city population. Journal of public health medicine. 2002;24(1):49-52. Epub 2002/04/10.
161. Etzioni R, Riley GF, Ramsey SD, Brown M. Measuring costs: administrative claims data, clinical trials, and beyond. Medical care. 2002;40(6 Suppl):III63-72. Epub 2002/06/18.
162. RAMQ (www.prod.ramq.gouv.qc.ca); Institut de la statistique du Quebec (www.bdso.gouv.qc.ca). [April 22, 2009].
163. RAMQ Prescription Drug Insurance http://www.ramq.gouv.qc.ca/en/citizens/prescription-drug-insurance/Pages/description.aspx.
164. Cree Board of Health and Social Services of James Bay. http://www.creehealth.org/services/cree-non-insured-health-benefits-cnihb (Accessed April 25, 2015).
165. Nunavik Board of Health and Social Services Insured/Non-Insured Health Benefits (INIHB) Program. http://www.hc-sc.gc.ca/fniah-spnia/pubs/nihb-ssna/yhb-vss-inuit/4-nihb-ssna-eng.php (Accessed April 26, 2015).

166. Wilchesky M, Tamblyn RM, Huang A. Validation of diagnostic codes within medical services claims. Journal of clinical epidemiology. 2004;57(2):131-41. Epub 2004/05/06.
167. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. Journal of clinical epidemiology. 1995;48(8):999-1009. Epub 1995/08/01.
168. Dendukuri N, McCusker J, Bellavance F, Cardin S, Verdon J, Karp I, et al. Comparing the validity of different sources of information on emergency department visits: a latent class analysis. Medical care. 2005;43(3):266-75. Epub 2005/02/24.
169. Bank of Canada. Inflation Calculator. Accessed March 2, 2014. http://www.bankofcanada.ca/rates/related/inflation-calculator/.
170. McGill University Health Centre (MUHC). Estimated average costs of inpatient days in McGill University Health Centre (MUHC) hospital. Personal communication (September 2011). 2011.
171. Sante et Services sociaux Quebec. Tarifs des services rendus en extreme. Anneve a la circulaire 2011-016 (03.01.42.19). Published 2011-05-01. http://msssa4.msss.gouv.qc.ca/fr/document/d26ngest.nsf/LienParId/7A6B2DD033ACF1288525788C004B4E6E?opendocument.
172. Gilbride SJ, Wild C, Wilson DR, Svenson LW, Spady DW. Socio-economic status and types of childhood injury in Alberta: a population based study. BMC pediatrics. 2006;6:30. Epub 2006/11/11.
173. Lichtenberg FR, Grootendorst P, Van Audenrode M, Latremouille-Viau D, Lefebvre P. The impact of drug vintage on patient survival: a patient-level analysis using Quebec's provincial health plan data. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2009;12(6):847-56. Epub 2009/06/06.
174. Breton JJ, Plante MA, St-Georges M. Challenges facing child psychiatry in Quebec at the dawn of the 21st Century. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2005;50(4):203-12. Epub 2005/05/19.
175. Dart AB, Martens PJ, Sellers EA, Brownell MD, Rigatto C, Dean HJ. Validation of a pediatric diabetes case definition using administrative health data in manitoba, Canada. Diabetes care. 2011;34(4):898-903. Epub 2011/03/08.
176. Long R, Zielinski M, Kunimoto D, Manfreda J. The emergency department is a determinant point of contact of tuberculosis patients prior to diagnosis. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2002;6(4):332-9. Epub 2002/04/09.
177. Thomas JA, Laraque F, Munsiff S, Piatek A, Harris TG. Hospitalizations for tuberculosis in New York City: how many could be avoided? The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2010;14(12):1603-12. Epub 2010/12/15.
178. Young TA. Estimating mean total costs in the presence of censoring: a comparative assessment of methods. PharmacoEconomics. 2005;23(12):1229-42. Epub 2005/12/13.
179. Wicks CA. Tuberculosis: Hospitalization and Outpatient Treatment. Canadian Medical Association journal. 1964;91:380-4. Epub 1964/08/22.
180. Taylor Z, Nolan CM, Blumberg HM. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control. 2005;54(RR-12):1-81. Epub 2005/11/04.

181. Oscherwitz T, Tulsky JP, Roger S, Sciortino S, Alpers A, Royce S, et al. Detention of persistently nonadherent patients with tuberculosis. JAMA : the journal of the American Medical Association. 1997;278(10):843-6. Epub 1997/09/18.
182. Singleton L, Turner M, Haskal R, Etkind S, Tricarico M, Nardell E. Long-term hospitalization for tuberculosis control. Experience with a medical-psychosocial inpatient unit. JAMA : the journal of the American Medical Association. 1997;278(10):838-42. Epub 1997/09/18.
183. Edlin BR, Tokars JI, Grieco MH, Crawford JT, Williams J, Sordillo EM, et al. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. The New England journal of medicine. 1992;326(23):1514-21. Epub 1992/06/04.
184. Nutini S, Fiorenti F, Codecasa LR, Casali L, Besozzi G, Di Pisa G, et al. Hospital admission policy for tuberculosis in pulmonary centres in Italy: a national survey. AIPO Tuberculosis Study Group. Italian Association of Hospital Pulmonologists. The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 1999;3(11):985-91. Epub 1999/12/10.
185. http://www.msss.gouv.qc.ca/sujets/santepub/mado.php. [September 1, 2009].
186. MSSS. Épidémiologie de la tuberculose au Québec de 2004 à 2007 (2009-04-03). Sante and services sociaux Quebec, 2009.
187. Langlois-Klassen D, Wooldrage KM, Manfreda J, Sutherland K, Ellis E, Phypers M, et al. Piecing the puzzle together: foreign-born tuberculosis in an immigrant-receiving country. The European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology. 2011;38(4):895-902. Epub 2011/03/26.
188. Fenn P, Davies P. Variations in length of stay. A conditional likelihood approach. Journal of health economics. 1990;9(2):223-34. Epub 1990/08/07.
189. Therneau T, Grambsch P. Modeling Survival Data: Extending the Cox Model. New York: Springer Science + Business Media; 2000. 1-356 p.
190. Dehghani K, Allard R, Gratton J, Marcotte L, Rivest P. Trends in duration of hospitalization for patients with tuberculosis in Montreal, Canada from 1993 to 2007. Canadian journal of public health Revue canadienne de sante publique. 2011;102(2):108-11. Epub 2011/05/26.
191. Laifer G, Widmer AF, Simcock M, Bassetti S, Trampuz A, Frei R, et al. TB in a low-incidence country: differences between new immigrants, foreign-born residents and native residents. The American journal of medicine. 2007;120(4):350-6. Epub 2007/04/03.
192. Ng E. The healthy immigrant effect and mortality rates. Health reports / Statistics Canada, Canadian Centre for Health Information = Rapports sur la sante / Statistique Canada, Centre canadien d'information sur la sante. 2011;22(4):25-9. Epub 2012/02/23.
193. Lemke KW, Weiner JP, Clark JM. Development and validation of a model for predicting inpatient hospitalization. Medical care. 2012;50(2):131-9. Epub 2011/10/18.
194. Pomey MP, Forest PG, Palley HA, Martin E. Public/private partnerships for prescription drug coverage: policy formulation and outcomes in Quebec's universal drug insurance program, with comparisons to the Medicare prescription drug program in the United States. The Milbank quarterly. 2007;85(3):469-98. Epub 2007/08/28.
195. Rivest P, Street MC, Allard R. Completion rates of treatment for latent tuberculosis infection in quebec, Canada from 2006 to 2010. Canadian journal of public health Revue canadienne de sante publique. 2013;104(3):e235-9. Epub 2013/07/05.

196. Suissa S, Ernst P, Hudson M, Bitton A, Kezouh A. Newer disease-modifying antirheumatic drugs and the risk of serious hepatic adverse events in patients with rheumatoid arthritis. The American journal of medicine. 2004;117(2):87-92. Epub 2004/07/06.
197. Myers RP, Leung Y, Shaheen AA, Li B. Validation of ICD-9-CM/ICD-10 coding algorithms for the identification of patients with acetaminophen overdose and hepatotoxicity using administrative data. BMC health services research. 2007;7:159. Epub 2007/10/04.
198. Li J, Munsiff SS, Tarantino T, Dorsinville M. Adherence to treatment of latent tuberculosis infection in a clinical population in New York City. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2010;14(4):e292-7. Epub 2009/08/07.
199. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical care. 2005;43(11):1130-9. Epub 2005/10/15.
200. Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. American journal of epidemiology. 2001;154(9):854-64. Epub 2001/10/30.
201. Schneeweiss S, Wang PS, Avorn J, Maclure M, Levin R, Glynn RJ. Consistency of performance ranking of comorbidity adjustment scores in Canadian and U.S. utilization data. Journal of general internal medicine. 2004;19(5 Pt 1):444-50. Epub 2004/04/28.
202. Pachi A, Bratis D, Moussas G, Tselebis A. Psychiatric morbidity and other factors affecting treatment adherence in pulmonary tuberculosis patients. Tuberculosis research and treatment. 2013;2013:489865. Epub 2013/05/22.
203. Gellad WF, Grenard J, McGlynn EA. A Review of Barriers to Medication Adherence: A Framework for Driving Policy Options. RAND Corporation: Santa Monica, USA. pp1-52. http://www.rand.org/content/dam/rand/pubs/technical_reports/2009/RAND_TR765.pdf. 2009.
204. Osterberg L, Blaschke T. Adherence to medication. The New England journal of medicine. 2005;353(5):487-97. Epub 2005/08/05.
205. Rivest F, Bosse P, Nedelca S, Simard A. Access to physician services in Quebec: Relative influence of household income and area of residence. Can Public Pol. 1999;25(4):453-81.
206. Rubinowicz A, Bartlett G, MacGibbon B, Greenaway C, Ronald L, Munoz M, et al. Evaluating the role of primary care physicians in the treatment of latent tuberculosis: a population study. Manuscript submitted to Annals of Family Medicine (2013).
207. McNutt LA, Wu C, Xue X, Hafner JP. Estimating the relative risk in cohort studies and clinical trials of common outcomes. American journal of epidemiology. 2003;157(10):940-3. Epub 2003/05/15.
208. Fitzmaurice GM, Laird NM, Ware JH. Applied Longitudinal Analysis. Hoboken, New Jersey: John Wiley & Sons; 2004. 506 p.
209. Hanley JA, Negassa A, Edwardes MD. GEE analysis of negatively correlated binary responses: a caution. Statistics in medicine. 2000;19(5):715-22. Epub 2000/03/04.
210. Dodd S, Bassi A, Bodger K, Williamson P. A comparison of multivariable regression models to analyse cost data. Journal of evaluation in clinical practice. 2006;12(1):76-86. Epub 2006/01/21.
211. Fresard I, Bridevaux PO, Rochat T, Janssens JP. Adverse effects and adherence to treatment of rifampicin 4 months vs isoniazid 6 months for latent tuberculosis: a retrospective analysis. Swiss medical weekly. 2011;141:w13240. Epub 2011/08/16.
212. Trajman A, Long R, Zylberberg D, Dion MJ, Al-Otaibi B, Menzies D. Factors associated with treatment adherence in a randomised trial of latent tuberculosis infection treatment. The

international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease. 2010;14(5):551-9. Epub 2010/04/16.
213. Caro JJ, Moller J, Getsios D. Discrete event simulation: the preferred technique for health economic evaluations? Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2010;13(8):1056-60. Epub 2010/09/10.
214. CIHI. The Cost of Hospital Stays: Why Costs Vary. Canadian Institute for Health Information. Ottawa, Ontario: 2008.
215. Eco-Santé. Annexe 15: Les NIRRU http://www.ecosante.fr/QUEBFRA/11500.html . Accessed December 15, 2013.
216. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA : the journal of the American Medical Association. 1996;276(15):1253-8. Epub 1996/10/16.
217. Philley JV, Griffith DE. Management of nontuberculous mycobacterial (NTM) lung disease. Seminars in respiratory and critical care medicine. 2013;34(1):135-42. Epub 2013/03/06.
218. Sia IG, Wieland ML. Current concepts in the management of tuberculosis. Mayo Clin Proc.86(4):348-61. Epub 2011/04/02.
219. National Institute for Health and Clinical Excellence, UK National Health Service (NHS). Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control (NICE clinical guideline 117). . March 2011.