Evaluating the role of primary care physicians in the treatment of latent tuberculosis: a population study

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1. Abstract

Evaluating the role of primary care physicians in the treatment of latent tuberculosis: a population study

Background: Tuberculosis (TB) remains within the world’s most important infectious causes of morbidity and mortality among adults. There are close to 10 million new cases of TB annually and latent TB (LTBI) is the main source of new active cases. Treatment of LTBI is long and often results in poor treatment completion rates. Primary care physicians have been identified as playing an important role in LTBI treatment; however, how large a role they currently play and the impact of this have not been assessed.

Objective: To estimate the treatment completion rate in individuals receiving therapy for LTBI when the treatment is initiated by a primary care physician after controlling for initial health status and other patients characteristics.

Study design and population: The province of Quebec (Canada) provides TB treatment free of charge to all residents. The study population consists of all Quebec residents who have been prescribed, for 30 days or more, LTBI therapy between January 1, 1998 and December 31, 2005.

Data gathering: Using data from the regional health insurance board (Régie de l’Assurance Maladie du Québec), de-identified data was extracted from the beneficiaries database, the medical services database, the prescription claims database and the hospital services database (Med-Echo), all linked with a unique patient identifier. Basic descriptive statistics were done to describe the study population and determine the proportion of treatment initiated by primary care physicians. Regression modeling was used to determine what factors were significantly associated with completion rates including the type of prescribing physician.

Results: Twenty-six percent of all LTBI prescriptions during the study period were initiated by primary care physicians. This proportion decreased from 1998 (28.7%) until 2005 (21.1%). A total of 6 059 (41.1%) individuals completed the treatment. Individuals prescribed by primary care physicians were less likely to complete the LTBI treatment (OR: 0.80, 95% CI: 0.67-0.95).

Conclusions: More than half of patients treated for LTBI are still not completing the recommended regimen. Between a third and a quarter are initiated by primary care
physicians. The reasons why completion is less likely for those initiated by primary care physicians need to be investigated.
2. Résumé

Le Rôle du médecin de soins primaires dans le traitement de la tuberculose latent: une étude populaire

Contexte: La tuberculose (TB) est encore une des plus importantes causes d'infections de mortalité et morbidité entre des adultes. Il y a presque 10 millions de nouveaux cas de tuberculose annuellement, et la TB latente (LTBI) et la plus importante source des nouveaux cas actifs. Les médecins de famille ont été identifiés comme jouant un rôle important dans le traitement de la LTBI; cependant, le vrai rôle qu'ils jouent et son impact doit être analysé en profondeur.

Objectif: Estimer le taux d'achèvement du traitement chez les personnes recevant un traitement de la tuberculose latente lorsque le traitement est prescrit par un médecin de famille après contrôle de l'état de santé initial et d'autres caractéristiques des patients

Conception de l'étude et la population: La province de Québec (Canada) offre un traitement antituberculeux gratuitement à tous ces résidents. La population étudiée se compose de tous les résidents du Québec à qui ont été prescrits, pendant 30 jours ou plus, la thérapie LTBI entre le 1 janvier 1998 et le 31 décembre 2005.

La collecte des données: En utilisant les données de la Régie de l’Assurance Maladie du Québec, les données dépersonnalisées ont été extraites de la base de données de «Information personne assurée», le fichier des «Services médicaux», le fichier des «Services pharmaceutiques» et de le fichier des «Séjours-hospitaliers» (Med-Écho), tous liés à un identificateur unique du patient. Des statistiques descriptives de base ont été faites pour décrire la population à l'étude et pour déterminer la proportion du traitement initié par des médecins généralistes. Un modèle de régression logistique a été utilisé pour déterminer quels sont les facteurs qui étaient significativement associés à des taux d'achèvement, y compris le type de médecin prescripteur.

Résultats: Vingt-six pour cent des prescriptions LTBI ont été initiées par des médecins généralistes. Cette proportion a diminué à partir de 1998 (28,7%) jusqu'en 2005 (21,1%). Un total de 6 059 (41,1%) personnes ont répondu au traitement. Les individus qui ont reçu des prescriptions par les médecins de famille étaient moins susceptibles de terminer le traitement de LTBI (OR: 0,80, IC 95%: 0,67- 0,95).
Conclusions: Plus de la moitié des patients traités pour l'infection tuberculose latente ne finissent pas le traitement recommandé. Entre un tiers et un quart des prescriptions sont initiées par des médecins de famille. Les raisons pour lesquelles l'achèvement du traitement est moins probable chez des patients qui ont consulté un médecin de famille doit être recherché.
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4. Introduction

4.1. The Global Burden of Tuberculosis (TB)

Today in the twenty-first century, tuberculosis is still a highly prevalent infectious disease and it continues to be a major threat to the world population.\(^1\) v TB, HIV and malaria are major global causes of morbidity and mortality; and the three are responsible of more than 3.5 million deaths per year.\(^4, 5, 6, 7\) TB disease ranks second only to human immunodeficiency virus (HIV) infection as an infectious cause of death.\(^8\) The WHO also estimates that each year there are close to 10 million new cases of TB and that several million die regardless of the existence of a highly effective therapy.\(^9, 10, 11\) In the 2010 Global TB Control report, it was declared that TB has caused 1.3 million deaths in HIV-negative individuals and 380,000 deaths in HIV-positive individuals, representing approximately 25% of all deaths in HIV-infected persons.\(^12\) Currently, TB infects up to 100 million people worldwide annually with approximately 8 million developing active disease.\(^13\) Unfortunately, of all the TB cases detected around the world, only around 20% are successfully treated.\(^13\)

The World Health Organization announced a worsening of the global TB situation for the years to come if an improvement in funding and political commitment is not evident.\(^14\) This organization has estimated that between 2010 and 2015, 50 million people will develop active TB, 10 million will die (4 million of them will be women and children), millions of children will be orphaned, and over 2 million cases of multi drug resistant-TB will surface demanding appropriate care.\(^14\)

4.2. Aetiology and Treatment of Tuberculosis

After an individual has contact with the infectious agent, *Mycobacterium tuberculosis*, different scenarios may occur. The infected person can either develop an active disease or a latent or inactive infection.\(^15\) Individuals whose immune system can successfully control the infection and do not develop the disease, have what is referred to as latent tuberculosis infection (LTBI).\(^15\) These people are not clinically ill and have no evidence of active tuberculosis disease (TB), they cannot spread the disease at this stage and the infection may remain inactive for a lifetime. Nevertheless, people with LTBI have a lifetime risk of disease reactivation that ranges from 5-10% for otherwise healthy individuals up to 20% or higher for those with specific health conditions\(^16-18\) such as
diabetes, HIV/AIDS, chronic renal failure, etc. If re-activation takes place, these individuals become sick with signs and symptoms of active TB disease and are able to spread this disease.

The treatment of LTBI is essential for controlling and eliminating active TB by reducing the risk that tuberculosis infection will progress to active disease. As long as those individuals with a latent infection do not receive or complete the required treatment, there will be a continuous pool of infected people acting as a constant source of potential cases. Nearly 30% of the worldwide population is infected with the mycobacterium tuberculosis. In countries where TB disease is not highly incident, such as the US and Canada; these individuals currently represent the main source of almost all the TB cases that are diagnosed. As long as this continues to be the case, the goal set by the Centers for Disease Control and Prevention and the Advisory Committee for the Elimination of Tuberculosis to eliminate the tuberculosis disease cannot be achieved, where elimination is defined as an incidence rate of less than one TB case per 1 million persons per year.

The therapeutic regimens currently recommended by the WHO have been found to be highly efficacious not only for treating, but also for preventing TB if treatment is completed. However completion is often poor, leading to low effectiveness. Before starting the treatment for LTBI, active disease must be ruled out as the treatment for LTBI is not adequate for active TB and may increase the risk of developing a drug-resistant strain of TB. The existing regimens to treat LTBI are the following: Isoniazid (INH) for 6, 9 or 12 months, Rifampin for 4 months or Rifampin plus Pyrazinamide for 2 months. Current American Thoracic Society guidelines recommend a 9-month regimen of INH taken daily as the regimen of choice. INH was commercially released in 1952 and since then many clinical trials have shown that a 6 to 12 month course of INH therapy is effective in preventing reactivation of disease in tuberculin reactors. While this drug has been shown to be safe, cheap, easy to take and well tolerated, its effectiveness has been shown to be dependent on adherence to treatment and adequate duration. If taken properly, this regimen may reduce the risk of developing active disease by about 50% and has shown to be highly efficacious in preventing future active TB. It has been demonstrated that when patients took at least 80% of the
recommended doses of daily INH for at least one year, they achieved a 93% protection rate against reactivation.\textsuperscript{29}

4.3. LTBI Treatment Completion

Currently, poor adherence to LTBI treatment has become a major barrier for the control of tuberculosis disease in low incidence countries.\textsuperscript{23, 33, 34, 35, 36} Treatment completion rates have been found to be overall between 50-60\%\textsuperscript{37}, but it actually may be lower for the commonly recommended regimen with INH for 9 months.\textsuperscript{16, 33}

Several studies have been conducted with the goal of identifying different strategies that may increase adherence and treatment completion for latent tuberculosis.\textsuperscript{38-40, 41, 42, 43} Some of the factors that have been found to be associated with low rates of treatment completion include the quality of health care delivery, the physician-patient relationship, physician accessibility, and cultural and linguistic barriers.\textsuperscript{43, 44, 45} Directly Observed Prophylactic Therapy (DOPT), a method of drug delivery thought to improve adherence consisting of observing the person to actually take the medication,\textsuperscript{46} is recommended in all intermittent regimens and in individuals at very high risk of developing TB disease, such as co-infection with HIV and in children less than 5 years old.\textsuperscript{47} Nevertheless, a strong rapport between the patient and the health-care worker is mandatory in order for this strategy be effective.\textsuperscript{47}

4.4 The Role of the Primary Care Physician

One area that has not sufficiently been explored is the role of different types of health professionals who are involved with the management of LTBI. Many health care professionals may be dispensing, monitoring, and following up in an adequate and effective manner; yet, individuals with LTBI may find that their first source of care is their primary care physician.\textsuperscript{48, 49} By definition,“…a primary care physician is a generalist physician who provides definitive care to the undifferentiated patient at the point of first contact and takes continuing responsibility for providing the patient’s care. Such a physician must be specifically trained to provide primary care services. Primary care physicians devote the majority of their practice to providing primary care services to a defined population of patients. The style of primary care practice is such that the personal primary care physician serves as the entry point for substantially all of the patient's medical and health care needs - not limited by problem origin, organ system, or
diagnosis. Primary care physicians are advocates for the patient in coordinating the use of the entire health care system to benefit the patient…” 21 The Institute of Medicine states that primary care is “the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients and practicing within the context of family and community”. 50

The cornerstone of primary care is an ongoing, integrative and personal patient-physician relationship which also extends to the patient’s family, health care system, and community. This relationship guides and helps the physician to prioritize and deliver care according to the different patient needs. 51 This special integrated approach has an effect on important outcomes 51 and regardless of innovation in medical technology and the fragmented nature of the current medicine, the healing relationship between physicians and patients remains indispensable to ensure a good and deserved quality of care. 52 Rothman et al. found that primary care clinicians, especially more recent graduates, usually have more training in areas such as behavioural and life-style change and self-management support than other specialists. 53 Therefore, primary care physicians may play a significant role in the treatment of latent tuberculosis. 18, 54 They also see their patients more often than other specialists, providing more opportunities to discuss issues that might arise around LTBI treatment. 55

We have been unable to find any studies that have specifically looked at the implications of a primary care physician being the health professional initiating the treatment of latent tuberculosis infection. This is despite the fact that guidelines for LTBI treatment targeting primary care physicians are currently being developed in the United States. 56 The existent Canadian guideline gives recommendations for refugees and new immigrants and does not particularly look at primary care physicians. 57 Therefore, the objective of this study is to estimate the treatment completion rate in individuals receiving therapy for latent tuberculosis infection when the treatment is initially prescribed by a primary care physician in comparison with other types of physicians.
5. Literature Review:

Even though tuberculosis (TB) is a preventable and treatable disease, it remains within the world’s most important infectious causes of morbidity and mortality among adults.1, 54, 58 Since TB has a long period of latent infection, each new infection is added to the pool of existing infections which represents a source for potential TB cases for years, even decades.54, 59, 22 Any person from the general population with a positive tuberculin skin test has a lifetime risk of reactivation of 5-10%1, 9, 16, 17, 18, 33 with about half of that risk in the first 2 years after infection in otherwise healthy individuals.9, 60 That risk of reactivation fluctuates according to age, size of the skin test reaction, and whether the person has an underlying medical condition33 reaching up to 10% annually for the high risk population such as patients with HIV infection.1, 9, 16, 17, 18 The experience of the past 15 years has demonstrated that resurgence of TB can occur as long as affected groups remain.61 Because patients with latent tuberculosis infection (LTBI) are acting as hidden reservoirs of the disease, this represents a major obstacle for its eradication.17 Treating those patients could be a strategy; however, this cannot be successfully done since the LTBI treatment completion rates are still very low.16, 17, 26, 62 The lowest rate reported was around 20%,63, 64 furthermore the overall completion rate lays between 50-60%.37 Despite these low rates, it has been estimated that the targeted screening and treatment of LTBI prevented between 4 000 and 11 000 active TB cases in the United States and Canada in 2002 alone.65 And it has been a cornerstone of national programs to reduce the burden of TB in these two countries.35

Given that primary care physicians may be the first source of care for patients with LTBI, they may play a significant role in detection and treatment of LTBI. As poor adherence to anti-tuberculosis therapy is known to be an issue,36, 66, 67 improving treatment completion would make a significant contribution to public health17 by achieving the objective of tuberculosis eradication.18, 54

5.1. TB worldwide

In 1993, the World Health Organization (WHO) declared tuberculosis as a “global emergency”.13, 68, 69, 70 In 2003 WHO reported a continued TB pandemic.13 It was estimated that in 2009 there were 9.4 million new TB cases in the world and that 1.8 million people died from TB. There are more than 2 billion people infected with the
tubercle bacillus (the bacterium causing the disease), meaning that approximately one third of the entire world population is a carrier of the latent (dormant) form of the disease. Of these infected individuals, between 8 and 9 million will develop TB disease each year, 200 million will develop the disease during their lifetime, and 30 million will die from TB over the next decade. The WHO also estimates that each person with untreated active TB infects on average 10 to 15 people every year.

5.2. TB in Canada

Despite the high prevalence in developing countries, in North America many consider TB to be a disease of the past, with little current significance or importance. That being said, TB has important implications for Canada due to the large amount of international travel and the continuous immigration from TB-endemic countries. Over the last 30 years, the epidemiology of tuberculosis infection and disease has changed dramatically in Canada. The incidence of TB disease has declined steadily from the beginning of this century until the mid 1980's, when incidences levelled off. In 2000, Canada had one of the world’s lowest reported rates of active TB, with five new active cases per 100 000 people, but this low overall rate masks the much higher incidence in certain populations such as high-risk, disadvantaged and marginalized groups. Over two-thirds (>65%) of all active cases occur among foreign-born Canadians, with an incidence of TB twenty times higher than in the non-Aboriginal Canadian born population (16 vs. 0.8 cases/100 000 population). The highest TB rates reported in Canada in 2008 were 99.2, 34.5 and 10.6, (per 100 000 population) corresponding to Nunavut, Northwest Territories and Saskatchewan respectively.

LTBI prevalence is higher for foreign-born Canadians coming from Asia (50-80%), Africa (50-80%), Central America (30-50%), or South America (30-50%), regions that currently still have high rates of TB disease. For the last four decades, most new immigrants to Canada have been arriving from high-TB-incidence countries and 30-50% of them are infected with LTBI. The prevalence of LTBI in Aboriginal communities has been estimated to be as high as 45%. These high rates of LTBI places Canada in the difficult position of having a reservoir of approximately 1.5 million people with LTBI who are at risk of and eventually may develop active disease.
5.3. TB in Quebec

The annual TB incidence rate in Quebec is one of the lowest in Canada after the Maritimes and is situated within the lowest rates of the industrialized countries.\(^{85}\) As in the rest of Canada, the prevalence and incidence of TB in the province of Quebec has progressively decreased since 2003.\(^{85}\) The annual incidence rate has decreased from 4.3 cases per 100,000 people in 2000 to 3.1 cases per 100,000 people in 2008.\(^{82}\) However, there are individuals that are more vulnerable to this disease such as the aboriginal Canadians, in particular the Inuit community and those individuals coming from countries with a high incidence rate of TB.\(^{85, 86}\) The first group has rates 20 to 50 times higher (mean incidence, 77 cases per 100,000) than the non-Aboriginal Canadian-born population.\(^{86}\) And the immigrant groups showed an incidence rate three times higher than the rest of the Canadian population.\(^{85}\)

In Montreal, the incidence rate of active TB cases decreased from 11.6 per 100,000 in 1994 (209 reported cases) to 6.0 per 100,000 in 2010 (123 reported cases). In those years, approximately 80% of all the cases involved foreign-born individuals.\(^{82}\) In 1998, a study found that overall the annual incidence in foreign-born population living in Montreal reflected the reported incidence of TB in their regions of origin.\(^{61}\) Data consistently demonstrates a parallel between incidence rates in countries of origin and destination country after arrival (especially during the first five years).\(^{82}\) These surveillance data may help physicians in their clinical decision-making and may also guide public health agencies targeting their prevention and control strategies to particular situations.\(^{61}\)

5.4. Latent TB infection (LTBI)

The *Mycobacterium tuberculosis* is transmitted from person to person by inhalation of infectious aerosol droplets.\(^{17, 58}\) Once infected with the bacillus, between 3% and 5% of immunocompetent individuals will develop active disease within 2 years and an additional 3% to 5% later on during their lifetime.\(^{13}\) The majority (more than 95%) of the immune competent individuals who are infected for the first time (primary infection) develop an effective acquired immune response and the *Mycobacterium tuberculosis* bacillus enters a latent or dormant state, a condition that may last anywhere from six months to a lifetime.\(^{58, 87, 88}\) These people are referred to as having LTBI and have no
clinical illness. They have a positive tuberculin skin test, but are not contagious and have no symptoms or signs of disease. However, sometimes this latent state can develop into active disease referred to as reactivation which may be triggered at any time. There are certain medical conditions that put individuals at high risk of reactivation. These conditions include AIDS, HIV infection, transplantation, pulmonary silicosis, chronic renal failure/hemodialysis, recent TB infection within the last 2 years, Diabetes mellitus, using immunosuppressive drugs (such as corticosteroids or transplant anti-rejection drugs), genetic defects of the receptors for some of the mediators in the immune response to the mycobacterium tuberculosis (TNF-α receptor, IFN-γ receptor or IL-12 β1 receptor defects), older age, malnutrition, cancer (especially carcinoma of head and neck), recent contacts with a TB case, presence of fibrotic changes on chest X-ray consistent with old TB, children under 4 years of age.

Once reactivated, the disease is usually progressive with signs and symptoms and an abnormal chest X-ray (80% of active disease is pulmonary). Patients with pulmonary disease will become progressively more contagious as the disease advances and spreads to new hosts. Since TB transmission occurs before diagnosis in the index case, even when an optimal TB control program is in place, new and undiagnosed cases are the driving force behind the current epidemic.

5.5. Detecting LTBI

The Purified protein derivative (PPD) tuberculin was first described by Koch in 1890, and in 1907 a French physician named Mantoux developed the tuberculin skin test (TST). Until 2001 it was the only practical and commercially available immunologic test for Mycobacterium tuberculosis approved in the United States and it was the only way to diagnose LTBI. The development of this test was based on the observation by Robert Koch who discovered that infection with the tuberculosis bacillus could cause a cutaneous reactivity (skin reaction) to tuberculin, a concentrated filtrates from cultures of the bacillus that had been heat-killed. The TB skin test is performed by injecting a small amount of a fluid (0.1 ml of PPD or 5 tuberculin units) into the skin on the lower part of the arm. The consequent reaction is read after 48-72 hours although a reading obtained up to one week later is still accurate. The site of injection is examined and the size of the reaction is measured (induration and not erythema).
reaction is used to classify individuals according to their likelihood of infection and to make a decision about the treatment. 59,26

Interferon-Gamma Release Assays (IGRAs) are whole-blood tests that have recently been approved for diagnosing Mycobacterium tuberculosis infection. 26, 59, 90, 93 The results of these tests can be available within 24 hours. It is not subject to reader bias and it is not affected by prior BCG (bacilli Calmette-Guérin) vaccination, all being important advantages to the traditional TST. 93 However, since a proper laboratory and specially trained laboratory technicians are required, the cost of these new tests is much higher. 59 In addition, there is limited data on the use of IGRAs for children under 5 years of age, for people recently exposed to M.tuberculosis, immunocompromised individuals, or serial testing. 93

A positive TB skin test or TB blood test only indicates that a person has been infected with TB bacteria but does not indicate whether or not the person has progressed to the active TB disease, it does not distinguish between latent or active TB. Clinical evaluation and additional tests, such as a chest x-ray, sputum smear and culture are needed to confirm the diagnosis of LTBI or TB disease. 18, 26, 59 In addition, the TST is not 100% sensitive for infection with M. tuberculosis, and even 10-20% of the individuals known to have TB will have a negative reaction. 94, 95 Nevertheless, the clinical usefulness of the TST has been well established as a reactive test that can predict the development of active disease, 96 and if these individuals are treated, the risk of incident TB can be reduced. 59, 97, 98

5.6. LTBI treatment

The Public Health Agency of Canada, through the sixth edition of the Canadian Tuberculosis Standards, recognized that TB prevention has been the cornerstone of TB control for almost 50 years and that with the treatment of LTBI the number of persons who develop active TB can be significantly diminished. 47 However, the levels of treatment completion were found to be consistently low in industrialized countries, such as the US and Canada, where LTBI is routinely treated. 37

In 1970 Ferebee et al. reported the effectiveness of INH alone to treat LTBI 97 and it has been the only available treatment for LTBI until recent years. The Canadian and American Thoracic Societies and the CDC have recently issued new treatment
recommendations. There are currently four different regimens available: INH for 9 months, INH for 6 months, Rifampin for 4 months and Rifampin plus Pyrazinamide for 2 months. Because the last regimen has shown to have rates of liver injury, hospitalization, and death higher than the rates reported for isoniazid, the CDC no longer recommends its use. Currently, the recommended regimen with acceptable safety is isoniazid alone for 9 months, which in general results in a risk reduction of around 50%, even in individuals infected with HIV, and has 90% efficacy in preventing future active TB if more than 80% of the doses are taken for 9 months or more. Clinical trials have shown that, in those individuals who completed the prescribed treatment (≥80% of doses), INH alone for 6 months results in a 69% reduction in TB, and 12 months of treatment in a 93% reduction. Though, more than a full year of INH treatment has not been shown to be more protective than the 9 months regimen since the maximum beneficial effect of INH has been shown to be achieved by 9 or 10 months of treatment. The effectiveness of a regimen is a function of the drug and duration prescribed, as well as the adherence of the patients, which tends to be lower with longer treatments.

The Canadian Tuberculosis Standards, published in 2007, recommended LTBI treatment for those individuals with a higher risk of developing active TB. The following Tuberculin Skin Test (TST) cut-offs were used to determine the LTBI treatment in that group. Thus, treatment was recommended with a TST result < 5mm in HIV infection and high risk of TB infection (contact with infectious TB, from high TB incidence country or abnormal chest x-ray), other severe immunosupression and high risk of TB infection and children less than 5 years of age and high risk of TB infection. In the case of a TST ≥ 5mm, treatment should be started in HIV infection, in those who had a recent contact with infectious TB, evidence of Fibronodular disease on chest radiograph (healed TB but not previously treated, or if treated, not adequately treated), organ transplantation (related to immune suppressant therapy) and other immunosuppressive drugs (e.g. corticosteroids equivalent of ≥ 15mg/day of prednisone for 1 month or more; risk of TB disease increases with higher dose and longer duration). Finally, in those individuals identified as converters within a period of 2 years and those with other immunosupression (silicosis, end-stage renal disease, carcinoma of head and neck),
treatment is indicated with a TST ≥ 10 mm. LTBI therapy should be considered in individuals who have resided or traveled in a high TB incidence country or Canadian Aboriginal community within the past 2 years, those HIV-seronegative injection drug users, workers or residents in a health care facility, correctional facility, or homeless shelter with a TST ≥ 10 mm as well. For any other individual not mentioned in the above criteria, the treating physician should judge each situation and decide the initiation of the treatment. 47

One of the main problems is that even though the LTBI treatment is prescribed, the treatment completion rate is very low, and this lack of completion has been considered the most important cause of failure of LTBI therapy. 33 In terms of TB control, adherence to treatment has been defined by Urquhart and colleagues as the extent to which the patient’s history of medication taking coincides with the prescribed treatment. 102 Low adherence to treatment for latent tuberculosis has been associated with different factors such as social aspects, economic barriers, cultural barriers, lower education level, idiosyncratic issues, and health beliefs among others. 103, 104, 105-107 However, patients with adherence issues with medical treatments is not unique to LTBI; and, over the last thirty years it has been the focus for those who were attempting to understand the limitations in the process of medical care delivery. 108

5.7. Issues in Treatment Completion

Treatment completion has been described as a multidimensional phenomenon determined by the interaction of five sets of factors or dimensions including health system/ health care team (HCT) factors, condition-related factors, social/economic factors, therapy related factors and patient-related factors. 43 In this model, in contrast to the common belief that patients are exclusively responsible for following their treatment, patient-related factors are just one of these five determinants. 43

Several studies have shown that across a variety of settings and conditions, almost half of all medical patients in the United States do not adhere to the recommendations of their physicians for prevention or treatment of acute or chronic conditions. 109-112 Moreover, a number of rigorous reviews have found that, in developed countries, treatment completion among patients suffering chronic diseases averages only 50%. 104, 113 Poor treatment completion is the primary reason for suboptimal clinical benefit. 114
This represents a very big challenge to public health efforts where success is determined primarily by accomplishment of long-term therapies.43

Besides LTBI/TB, there are many conditions associated with low rates of completion for the recommended treatment such as: depression,108, 116, 117 anxiety,108 psychiatric patients taking antipsychotic drugs,117 depression and end-stage renal disease or renal dialysis, 108 depression and renal transplant, 108 depression and rheumatoid arthritis, 108 depression and cancer, 108 asthma, 43, 105 hypertension, 43, 106 diabetes, 43 HIV/AIDS, 43, 107, 118-122 cancer related pain, 43, 123-125 epilepsy, 43, 126 patient prescribed with lipid-lowering drugs, 127-129 and cigarette smoking cessation therapy.43 The lack of adherence to medical treatment for any condition may lead to exacerbation of illness, incorrect diagnoses, patient and physician frustration,130-132 as well as increase the overall cost of health care.104 In summary, there is good evidence that poor adherence has an important negative effect on the individual treatment outcomes.37, 133-136

Given that patients with LTBI have no symptoms associated with TB, they are not contagious, may develop serious adverse drug events, and may have to change their lifestyle (such as decreased alcohol intake) for a long period of time; it may be difficult for them to complete the recommended treatment.17

Low rates of completion for the indicated LTBI treatment has been shown to be associated with many factors, such as patient satisfaction with the corresponding physician,44 relationship between patient and health care provider,45 pattern of health care delivery (professional availability and flexibility, organization of clinical services),43 treatment setting,45 linguistic barriers, patient characteristics,45 cultural taboos and stigmatization, low education level, perceived low risk progression from latent tuberculosis infection to active disease, belief that positive results from tuberculin skin tests are due to the Bacillus Calmette-Guérin (BCG) vaccine (a vaccine against TB that is used in 90% of countries),137 not wanting to have venipunctures, different economic factors (costs of commuting, insurance status, work absences),138-141 altered mental states caused by substance abuse, depression and psychological stress,43 smoking,142 and specific treatment regimens.45 Hirsch-Moverman and colleagues have found that in the United States and Canada, initiating LTBI treatment among foreign-born individuals who
come from TB-endemic regions and have a history of BCG vaccination has been a challenge for the treating physician.  

For the six-month course of self-administered therapy for LTBI, the completion rate ranges from 3 to 60%, with rates of 20 to 30% in most of the cases and Horsburgh, in a study published in 2004, found lower rates for the nine-month regimen with INH. In a systematic review of US and Canadian studies about the adherence to LTBI treatment, the completion rates were found to be consistently low across patient populations and treatment regimens. The majority of the studies found an overall rate between 50% and 60%, with some studies reporting lower rates for a particular population group such as Latino immigrants. A study published in 2010 found that the major risk factor for lack of treatment completion was being prescribed with the nine-month isoniazid regimen in comparison with INH for 6 months and RIF for 4 months. The authors of this study reported completion rates of 45%, 55% and 65% for the 9-months isoniazid, 6-months isoniazid and 4-months rifampin regimens respectively, suggesting an inverse relationship between the length of the LTBI regimen prescribed and the proportion treatment completion.

Another important factor related with the LTBI treatment is the occurrence of adverse events. In fact, in the majority of the cases, the decision to treat an individual with LTBI depends primarily on the balance between the likelihood of developing active disease and the risk of suffering therapy-related adverse events. For example, regardless of the proven INH effectiveness, the incidence of a serious event will cause the physician to choose between the long-term risk of developing disease and the immediate risk of drug toxicity. All of the drugs used to treat LTBI can cause serious adverse events (SAEs). This may lead to the discontinuation of the drug, to a change of the drug regimen and to significant morbidity and even mortality. Some of the adverse events that a patient may encounter are: drug-induced hepatitis (most important adverse reaction associated with isoniazid), different dermatological reactions (hypo- and hypersensitivity reactions, acne, alopecia, xerostomia, lupus erythematosus-like syndrome, etc), anaphylaxis, haematological reactions (anaemia, neutropenia, etc), neurological reactions (peripheral neurotoxicity, dysarthria, irritability, seizures, etc.), intoxication,
gastrointestinal symptoms (loss of appetite, nausea, etc), flu-like syndrome, rifampin-induced renal disease, drug interactions, among others. 9, 100, 148

The problem of development of drug-resistant TB strains is a key issue in the treatment of active TB. However, because LTBI is associated with a low organism burden there is little chance of development of resistance on monotherapy, this presents another argument for initiating treatment when the infection is still latent. 149

5.8. Potential role of primary care physician

Although the responsibility for tuberculosis control resides primarily within the public health sector, continuing progress toward elimination of tuberculosis requires the collaboration of a broad range of professionals and institutions including physicians, community health centers, community organizations, hospitals, academic medical centers, medical professional organizations, and long-term facilities. 54, 60 Sablan et al. 150 suggested that the current approach for TB control and prevention should be more through a community-driven public-private mix to actively address all the issues related to TB control. 150 In order to help ensure successful treatment of LTBI, physicians need to collaborate with public health agencies to educate patients and make the community aware of the important health implications that this infection carries. 54, 150 The treating physician prescribes the medical regimen, interprets it, follows the patient, monitors clinical outcomes, and provides information to patients. Variables related to how physicians interact and communicate with their patients are important determinants of adherence and patient health outcomes. 152-154

Studies in different populations undergoing LTBI treatment have shown that particular interventions may improve LTBI treatment adherence and completion rates. 38-42 Such approaches include: adherence counselling, social support, 39 intensive health education, 43, 155 enablers 43, 156 (free van transportation or bus tickets, reminder letters or phone calls, and other assistance that make it easier to keep appointments), financial or other incentives, 43, 157 staff motivation and supervision, 43 agreements, 43 peer assistance, 43 and in certain situations directly observed preventive therapy (DOPT). 47 These interventions have been found to be cost-effective and easily completed at clinic visits; 38-41 but it is even better to target these interventions to patients at higher risk of non-adherence. 42
Patient supervision by the prescribing physician and closer and more active follow-ups may improve the treatment completion.\textsuperscript{9, 10, 41, 55, 158} Menzies et al. stated that regular clinic visits and reinforcing the importance of treatment are crucial to enhancing completion of the prescribed therapy.\textsuperscript{9} Along the same line, Dye et al.\textsuperscript{10} stated that a patient-supportive approach should be adopted by the physician in order to encourage patients to complete their treatment.\textsuperscript{10} In 2003, the WHO stated that “Building on a patient’s intrinsic motivation by increasing the perceived importance of adherence, and strengthening confidence by building self-management skills, are behavioural treatment targets that must be addressed concurrently with biomedical ones if overall adherence is to be improved”.\textsuperscript{43}

Early stages of the treatment seem to be a critical time for the whole LTBI treatment regimen. Whether the patient returned to the first follow-up visit (first month) at the scheduled time and whether he/she took more than 80% of the doses during the first month, were found to be positively associated with treatment completion.\textsuperscript{159} It was suggested that treatment completion can be better predicted at the time of the first follow-up.\textsuperscript{159} In a study published in 2005, Menzies et al. showed an association between final completion of LTBI therapy and regularity of the medication intake during the first month of treatment, in those patients who were very closely monitored.\textsuperscript{42} In 2000, Parsyan et al. found that more than half of the patients who dropped the treatment did so within the first month of treatment.\textsuperscript{160} A recent study has shown that more than 20% of those initiating treatment stopped it within 1 month of starting and more than one-half of those who did not complete the treatment, stopped it within 2 months of starting.\textsuperscript{35} In both cases, the authors agreed that the physicians’ interventions should be concentrated in the early stages of treatment and a close follow-up of the patients during the first few months may help to improve treatment completion\textsuperscript{42} and may promote and encourage the patients to complete the treatment.\textsuperscript{35, 161}

Easier accessibility to the treating physician has been suggested to improve the LTBI treatment completion rates, and having flexible clinic hours may optimize patients’ adherence.\textsuperscript{9, 43} In a Spanish study, it was found that the fact that primary-care physicians see the patients for reasons other than LTBI treatment provides more opportunities for the primary care physician to reinforce and advise the patients about treatment completion.
than do other specialists. This same study suggested that the same physician should continue the follow-up until the patient successfully completes the treatment.

The identification of those patients who have a higher risk of dropping the treatment by the prescribing physician may be beneficial for the treatment outcomes. A physician may be able to recognize those patients that are unlikely to follow the recommended therapy and identify the barriers before or early in the treatment. This way, they could work with the patient using specific and targeted strategies in order to emphasize and improve the treatment completion, redirecting the available resources in a better way.

However, according to Besch and other authors, the identification of such individuals by the health care provider may be difficult and the prediction of non-adherence inaccurate. Some studies suggested that demographic, social, clinical and other patient characteristics were not predictive or relate poorly with treatment completion.

Nevertheless, many studies stated that the treating physician may be able to recognize certain patients who are more likely to not complete their treatment. For example, residents in congregate settings (nursing homes, homeless shelters, jails, and prisons), injection drug users, employees of hospitals and nursing homes, young individuals, pregnant and/or postpartum women, and uninsured people were found to be at higher risk of treatment withdrawal. A previous study done in 2003, found that lower completion rates were associated with self-reported alcohol intake, homelessness, and occurrence of at least one adverse effect other than hepatotoxicity. This same study also found the female sex, younger age groups (<34 y/o), white/Hispanic race/ethnicity, and non-US country of birth to be associated with higher completion rates. The authors of this study, attributed the higher rates among Hispanics to the clinic staff’s cultural sensitivity, since it had bilingual and bicultural employees, which may have encouraged a greater sense of trust among the clinic’s patients. Another study published in 2004, showed that the addition of specialized programs that are designed to be culturally sensitive in the management of LTBI in foreign-born individuals, improved the rates of treatment completion. This “culturally sensitive” approach means that case managers were matched to the ethnic and linguistic background of the patients. The authors of this study found that the LTBI treatment
completion rate improved from 37% to 82% with the implementation of the new case management model. 62 Similar findings have been found by Ailinger and colleagues where patients enrolled in a cultural intervention group (for example, a nurse speaking the patient’s language) vs. standard care, were found to have taken more doses of the prescribed INH. 166 Interestingly, in a recent study published in 2010, beliefs and attitudes have found to be more important than side effects for the prediction of the treatment adherence. 159

All the particular strategies, established relationships and innovative interventions, are vital to achieving the goal of eliminating tuberculosis. 54 However, until now, no studies have focused specifically on the role that primary care physicians play in treating patients with LTBI, or the characteristics of the patients they are treating, or the impact this may have on completion rates. Primary-care physicians may play a significant role in the treatment of latent tuberculosis in view of the fact that they may be the starting point in the health care chain for patients with LTBI and they may have an active and ongoing involvement with the patient. 18, 54 Once again, this type of physician sees the patients for reasons other than LTBI treatment, and therefore have increased opportunities to recognize patients that are unlikely to follow the recommended therapy, and thus can identify the barriers before or in the early stages of treatment 65, 159 and reinforce and advice the patients on the importance of the treatment completion. 55 At the same time, easier accessibility, 9, 43 closer patient supervision, more active and regular follow-ups with the treating physician may improve the treatment completion. 9, 10, 41, 55, 158 Moreover, as mentioned above, treatment completion has been defined as a multidimensional phenomenon 43 and all the factors influencing it need to be considered. Accordingly, primary care physicians, adopting a patient-supportive relationship 10 could provide a holistic approach. This meaningful and supportive bond between the patient and physician can help to overcome major barriers to complete the prescribed treatment. 167

In a recent population study of adverse events associated with latent tuberculosis infection, 30.8% of the initial treatment was prescribed by primary care physicians. 49 By detecting and successfully treating LTBI, primary care physicians not only reduce the individual’s risk for developing TB, but they also impart a public health benefit by reducing the pool of latently infected individuals. Since one of the most important
challenges to eradicate this disease is the persistence of a substantial number of people with latent tuberculosis who are at risk of reactivation and progression to active TB in the future.  

5.9. Summary

The importance of identifying and properly treating individuals with latent TB infection is at the moment well known. It is thought that primary care physicians may play a major role in improving adherence to treatment. However, this has not been systematically assessed. Given this scenario, I will be evaluating the role of the primary care physician in the treatment of tuberculosis infection. I expect that a significant proportion of the treatments for LTBI will be initiated by primary care physicians and that completion rates may be significantly different based on specialty of the initial prescribing physician after controlling for patient characteristics. It is also expected that those patients initially prescribed by a primary care physician may be healthier than patients who had treatment initiated by other specialists.

5.10. Study objective

To estimate whether or not the completion of the latent tuberculosis infection treatment with isoniazid is better or poorer when the treatment is initiated by a primary care physician in comparison with others medicine specialties after controlling for patients characteristics.
6. Methods

6.1. Study Design

In order to address the thesis objective, a cohort study with historical data was constructed. This historical cohort was assembled through population health databases from the province of Quebec in Canada (RAMQ: Régie de l’Assurance Maladie du Québec); with a coverage period that goes from January 1 1998 to December 31 2007. All data were collected 24 months prior to the index date and 12 month after the index date. The index date refers to the date when the LTBI medication was dispensed for the first time, which was assessed throughout the study period. The pre-and post-treatment period were used to assess the presence of comorbidities and completion of the LTBI treatment respectively. Individuals initially prescribed LTBI treatment by a primary care physician were compared to all other individuals prescribed LTBI treatment by different types of physicians, with treatment completion as the outcome.

6.2. Data Sources

The current study used the following databases to gather information about the patients, the treatment received and their treating physicians. (Refer to Table 1 for detailed RAMQ content):

I. The beneficiaries database base from RAMQ: This contains an encrypted health insurance number as a unique identifier for all patients, age, sex, first three digits of the postal code, region of residence, prescription drug insurance status and date of death if applicable.

II. The medical services database from RAMQ: This represents all medical acts and services billed by in-and out-of- province physicians on a fee-for-service basis (95% of all physician services provided in Quebec). Each record contains the treating physicians identification number (PID), class of treating physician, information on the referring physician, diagnosis code (ICD-9), institution code, role of the physician in the medical procedure, date and cost of the medical procedure.

III. The prescription claims database from RAMQ: This contains all prescriptions billed to RAMQ by any community based pharmacy in Quebec for persons covered by RAMQ for prescription drugs, and for all persons dispensed tuberculosis
medication since January 1 1997- regardless of other drug insurance coverage. It contains PID, prescribers’ professional class, encrypted information regarding prescribing physician and pharmacist, codes for prescription drugs, dosage, strength, generic name, quantity, duration of prescription, codes for substitution, renewal and type of prescription, cost, and the American Hospital Formulary service class (AHFS) of each drug dispensed. This was used to identify cases dispensed anti-TB drugs, ascertain completion of therapy, and identify co-morbidities in study subjects.

IV. The hospital services database (MED-ECHO) from the Ministère de la Santé et des Services Sociaux (Quebec Ministry of Health and Social Services), consists of the PID, type of institute, dates of admission and discharge, total numbers of days of stay, death, death 48 hours before or after admission, date and code of accident, type of physician, primary and all secondary diagnoses, and procedures (coded using ICD-9 codes by trained archivists).

All the information extracted from the four databases was de-identified. Each individual receiving treatment for LTBI who was included in this study has a file with a unique identification number linking all the information coming from the different databases.

**Insert Table 1**

6.3. Study Population

The study population for this thesis consists of all Quebec province residents of different ages who have been dispensed medication for latent tuberculosis infection. These individuals were considered to have LTBI if they were dispensed either INH alone or RIF alone for at least 30 days between January 1, 1998 and December 31, 2005. A 7-day lag period was allowed for defining the initial regimens (any prescription filled in the first 7 days of the index date was considered to be prescribed as part of the initial regimen).

The original database goes until December 31, 2007, but for this study those individuals who were initially dispensed the LTBI medication between January 1, 2006
and December 31, 2007 were excluded because there would not be enough follow-up time for them. In addition, the identification of comorbidities for those last two years would have been possible problematic since in 2006 the International Classification of Diseases-9 (ICD-9) code was replaced by the ICD-10 for the billing services in Quebec with mixed codes being used during the transition period.

Originally five categories were identified from the database for the first regimen dispensed for LTBI treatment: Isoniazid (INH) alone, Rifampin (RIF) alone, Pyrazinamide plus Rifampin (RIF+PZA), Isoniazid switch to Rifampin, Rifampin switch to Isoniazid and Rifampin plus Isoniazid. Since INH for 9 months is the currently recommended regimen with acceptable safety, the study population was then restricted to only those individuals initiated with the regimen consisting of INH alone. Those who were initiated with INH and then switched to RIF were still considered for the analysis but only the INH part of the treatment was considered for the completion calculation.

6.4. Measures

6.4.1. Outcome: LTBI Treatment completion

Therapy was considered complete if the number of days the medication was dispensed corresponded to the shortest recommended duration. For the purpose of this study treatment duration corresponded to number of days INH was dispensed and treatment completion was defined as dispensed 180 days (6 months) or 241 days (> 8 months) of INH during the 12 months period after the index date which was the date the LTBI drug was first dispensed. New recommendations regarding the INH use for LTBI treatment were published in 2000, which recommended INH for nine months (270 days), whereas the recommendation prior to that was INH for six months (180 days). If the treatment was initiated between January 1 1998 and December 31 2000, completion was defined as 180 days or more of INH dispensed. If the first prescription was dispensed between January 1 2001 and December 31 2005, completion was defined as 241 or more days dispensed. In the case of LTBI treatment in the paediatric population, INH for nine months has always been the recommended duration, hence for those aged between 1 and 19 years old, the completion was defined as medication dispensed for 241 days or more.
A cut-off of 241 days was used in the case of the 9 months (270 days) regimen, because it represents 89% of the total treatment duration, and completion of at least 80% a standard goal. Given that the 6 months regimen is a shorter period, 180 days was used.

6.4.2. Main Predictor - Specialty of the initial prescribing physician for the treatment for LTBI

Specialty of the initial prescribing physician was ascertained from the medical services and the prescription claims databases. Each prescribing physician was identified from the database with a code that represents the different specialties. Codes 00 “omnipraticque/general practitioner” or 39 “médecine familiale/family physician” were used to identify “primary care physicians”. The rest of the codes were grouped as “other specialties”. We felt this was appropriate as the majority of primary care is provided by family physicians in Canada.

6.4.3. Potential Confounders

From review of the literature, patient characteristics such as age, sex, and type of major health conditions such as HIV+/AIDS, cancer, diabetes, renal failure, Hepatitis B/ C, depression, alcoholism, or other substance abuse were identified as factors potentially influencing the treatment completion and, thus, were included as potential confounders. The period to determine any of these comorbidities for each patient was 24 months prior treatment initiation for LTBI. The comorbid conditions were identified from ICD-9 diagnostic codes listed in the Med-Echo discharge database and medical billing services databases, using two or more medical records or one or more hospital discharge diagnoses. For HIV, antiretroviral medication dispensed for 30 days or more were used as well. In the case of cancer only malignant neoplasms diagnoses were included. For substance abuse, alcohol and other drugs were
included. Under viral hepatitis, any diagnosis of hepatitis A, B or C was included (See Appendix 1 for a complete list of ICD-9 codes used to define comorbidities).

The beneficiaries database was used to get information about the age, sex, income status, and education level of the patients to account for confounding when evaluating treatment completion. Those individuals under the age of 20 were grouped together given that treatment recommendations were specific for the paediatric population. Canadian tuberculosis guidelines defined paediatric population as those aged 15 years old or younger. \(^4\) However, since the age of the patients was provided in the database as a 5-year range, we decided to extend this category up to 19 years old instead of cutting it off at 14 years old. The education level was defined as the percentage of individuals that have a University degree residing in the same residential area as the study patient. The income status was defined as the median average household income for the residential area of the patient as defined by 2001 Statistics Canada census data for 6 digit postal codes. Both variables were included in the logistic model as continuous variables. For descriptive purposes they were re-coded as low and high education level or income status where low was defined as any value equal or lower than the lowest quartile, i.e. \(\leq 14\%\) of residents with a university degree and \(\leq $30 439\) average household income.

The volume of patients that an individual physician prescribed was identified as another potential confounder. This was defined based on the number of prescriptions initiated by the individual prescribing physician, where “more frequent prescribers” corresponded to those physicians who initially prescribed LTBI treatment for more than 5 patients over the 8 year period of the study, and “less frequent prescribers” having 5 or fewer patients over the same period of time.

Other potential confounders were years of practice for the prescribing physician and number of medical visits the patient made during the 12 month period after the index date.

6.5. Statistical Analysis

Basic descriptive statistics were done using frequency distributions for categorical variables and means with standard deviations for continuous variables. The following variables were treated as categorical variables: age, gender, associated conditions such as HIV/AIDS, diabetes, renal failure, viral hepatitis A/B/C, liver diseases, cancer,
depression, and substance abuse (alcohol or drugs), specialty of prescriber physician, hospitalizations within 30 days prior and 12 months after the index date, medical visits within the 12 months after the index date, low level of education, and low income status. The number of hospitalizations within 30 days prior and 12 months after the index date, length of those hospitalizations, number of medical visits within the year after treatment initiation, proportion of university degrees in the residential area, average neighbourhood income and treatment duration of each individual prescription were treated as continuous variables.

Basic descriptive statistics were also used to describe the annual proportion of LTBI treatment that had been initiated by a primary care physician. Ninety-five percent confidence intervals were calculated around these proportions.

Treatment duration was divided into 9 month mutually exclusive categories and the proportion of patients completing each of these categories was calculated. A Chi-square test was done to compare the distribution of each of these groups between the two groups of prescribing physicians. A p-value ≤ 0.05 was accepted as statistically significant.

In addition, student’s t-tests and Chi-square tests were used to compare the distribution of continuous and categorical variables respectively, between patients prescribed by primary care physicians and other specialists. A Structured Query Language (SQL) procedure was done in order to obtain the number of unique prescribers or individual physicians included in the databases. Basic descriptive statistics and a Chi-square test were done to describe the specialty and number of prescriptions initiated by each of the unique prescribers.

A clustered analysis in the logistic regression model was done to assess the prescribing physician’s specialty as a predictor for LTBI treatment completion, adjusting for patient characteristics such as age, sex, comorbidities, average household income and education level, and whether the prescribing physician is a more or less frequent prescriber. The clustering was on prescribing physician to control for the fact that physicians may have prescribed for more than one patient thereby reducing the variation between those patients. The logistic regression was ordered by date where date corresponded to the year when the initial LTBI prescription was done. The parameters estimates and odds ratios (OR) with 95% confidence intervals were reported for the main
predictor and for all the covariates used in the analysis. All the data from the different databases was analyzed using the SAS Systems 9.2.

6.6. Ethical Considerations

This project was part of a larger already funded study, which received ethical approval from McGill IRB and no major ethical risks were anticipated. The current study has received a certification of ethical acceptability from the McGill Faculty of Medicine Institutional Review Board on September 2010.
7. Results

7.1. Study population

From the original cohort of 23,379 individuals, 2,873 were excluded as they were dispensed treatment for active TB. This left a study population of 20,506 individuals corresponding to those dispensed with any of the regimens used for LTBI. Individuals who had the initial LTBI prescription dispensed between January 1, 2006 and December 31, 2007 were excluded (n=4,141). After assessing the different LTBI types of treatments, 366 individuals who were dispensed two drugs regimens (INH + RIF or PZA + RIF) were excluded. In a subsequent step, 1,246 individuals dispensed treatments other than INH were excluded. The final study cohort was 14,753 individuals.

Insert Figure-1: Study Cohort

Details of the baseline characteristics of this study population are presented in Tables 2A and 2B. Approximately one third of the population (29%) was between 35 and 49 years old at the time of the initial prescription and women represented more than half of all the patients. 12,416 (84.2%) individuals receiving INH had no comorbidities; among those individuals who had at least one, the three most common were diabetes, cancer and depression. There were 931 (6.3%) individuals who did not have a medical visit during the 12 months after the initial LTBI prescription. More than half of these patients were males and 63% were dispensed INH initiated by physicians other than a primary care doctor; their mean treatment duration was 152.9 days (SD= 95.3). From the total cohort of 14,753 individuals who were dispensed at least 30 days of INH alone, in 3,863 (26.2%) patients the initial prescription was from a primary care physician. In regards to treatment duration, 93.1% of the prescriptions were captured within the 12 months period after the index date. In other words, 13,854 individuals filled their LTBI prescriptions within the first year after the initial prescription was dispensed. The average years of practice for the prescribing physicians was 24.8 years (SD=11.7).

Insert Table 2A and 2B
7.2. Primary care physician initiating LTBI treatment

The proportion of dispensed LTBI treatments initiated by primary care physicians each year of the study period is shown in Table 3. The total number of LTBI prescriptions increased throughout the study period. However, the proportion of prescriptions initiated by primary care physicians dropped almost 8% (95% CI 0.05, 0.10) between 1998 and 2005, with the only transitory increase in the year 2000.

Insert Table 3

7.3. Physician specialty and patient characteristics

The baseline characteristics of the patients prescribed INH by the two groups of physicians is shown in Tables 4A and 4B. The distribution of patients’ age is comparable with approximately a third of each physicians’ population being represented by those individuals between 35 and 49 years old and the difference is not significant (p=0.068). The proportion of patients with a low level of education was higher for those prescribed LTBI treatment by primary care physicians. Individuals who were dispensed medication initiated by primary care physicians had higher rates of hospitalizations but lower rates of medical visits. The median number of medical visits was 6 and 7 for primary care and others specialists’ patients respectively. Five percent of individuals prescribed by either type of physician did not have any medical visit within the 12 months after the index date. 648 (16.8%) and 1 689 (15.5%) individuals dispensed INH initiated by primary care physician and by other type of physicians respectively, had at least one comorbidity. Those comorbidities for which a statistical significant association with the specialty of the prescriber was found were renal failure, liver disease and substance abuse. While the percentage of individuals with renal failure was higher for other specialists, the percentage of patients with liver disease and substance abuse was higher for primary care physicians. Although significant (p<0.0001), there was no meaningful difference between the average years of practice of primary care physicians (23.8 SD=11.3) and the rest of the specialties (25.1 SD=11.8).

Insert Table 4A and 4B
7.4. Specialty of prescribing physician and treatment duration

A statistically significant association was found between the treatment length and the specialty of the prescriber, with a longer duration for the dispensed treatment that was prescribed by a non-primary care physician ($p < 0.0001$) (Table 4B).

Table 5 shows the proportion of patients in each of the nine month categories of the LTBI treatment. For both groups of physicians, most of the people had treatment duration greater than 241 days, and 81.7% of those prescriptions were initiated by a physician other than a primary care physician. Around 15% of patients for both groups had a treatment length between 151 and 180 days with details provided in Table 5.

**Insert Table 5**

Figures 3A and 3B show amount of days of LTBI treatment completed by patients who were initially prescribed medication dispensed before and after December 31 2000 respectively. There were more people with treatment durations between 151 and 180 days during the first three years of the study. Among these individuals the LTBI treatment was more frequently initiated by non-primary care physicians. For those individuals who got their prescriptions after 2000, almost 40% had a treatment length greater than 241 days, with non-primary care physicians being the most frequent prescriber. While the proportion of prescriptions with duration greater than 241 days increased 23% after December 31 2000 compared to before that date, those with durations between 151-180 days decreased by almost 14 percent.

**Insert Figure 3A and 3B**

7.5. LTBI treatment completion

Between a third and half of the population completed the INH regimen for LTBI. The completion rate is 6% higher for those initially prescribed by physicians other than a primary care doctor. A statistically significant association ($p < 0.0001$) was shown between treatment completion and the specialty of the prescriber physician (Table 6).
For those individuals who completed the LTBI treatment, a significant association was shown for young age (p<0.002), substance abuse, depression, low levels of education, hospitalizations within 30 days before index, and medical visits within the year after index after stratifying by type of prescriber. Patients that completed the LTBI therapy and were prescribed by a primary care physician had higher percentages of substance abuse, depression, low levels of education, and hospitalizations within 30 days before index. Whereas patients that completed the treatment prescribed by other specialist were found to have more medical visits within the year after the index date. Young patients were more likely to be prescribed by other specialists as shown by Table 7.

The proportion of LTBI treatment completed at six and nine months by the adult population (> 19 years old) along the study period is shown in Figure 4. Since the beginning and through the whole study period, there was an increase of the proportion of patients completing a 9 month regimen, whereas, a decrease was shown for the 6 month INH regimen.

Among the entire cohort of 14 753 individuals prescribed with INH, 2 637 (17.9%) individual physicians were identified who initiated all of the INH prescriptions included in this study. Sixty-five percent (1 714) of the individual physicians corresponded to primary care doctors and the other 35% (923) belonged to other specialties.

Table 8 shows the number of INH prescriptions (or number of patients) initiated by each individual prescriber. Almost two thirds of the prescribers initiated LTBI treatment in only one patient and 90% of the physicians initiated fewer than 10 LTBI treatments. Ninety-five percent of the primary care physicians initiated fewer than 10 prescriptions
and 90% fewer than 4, whereas 95% of the physicians with a different specialty initiated few less than 40 prescriptions and 90% fewer than 17. The median number of INH treatment initiated by primary care physicians and other specialists was one and two respectively. In Table 8, chi-square tests were performed for each line and the p-value was reported in the last column.

**Insert Table 8**

More than 50% of the individuals that completed the LTBI treatment were patients prescribed by physicians who had initiated more than 50 LTBI treatments. Almost 44% of the individuals prescribed by physicians that initiated an LTBI treatment in more than 50 patients completed their treatment; while the rate of completion for those individuals prescribed by physicians who initiated INH therapy in only one patient was 36.5% (Table 9). A significant association (p < 0.001) was shown between the type of prescribing physician, based on number of LTBI treatments initiated, and treatment completion, where 42% of the individuals prescribed by a more frequent prescriber completed the INH treatment. We found that 77.2% (4676) of the individuals who completed the treatment have been initially prescribed by a more frequent prescriber.

**Insert Table 9**

The logistic regression model with cluster analysis, to assess the prescriber specialty as a predictor for treatment completion, was done by adjusting for patient age, sex, comorbidities, level of education, and income status.

In this analysis, patients dispensed medication initiated by primary care physicians were less likely to complete LTBI treatment (OR: 0.80, 95% CI: 0.67-0.95). Men were more likely to complete the treatment than women (OR: 1.14, 95% CI: 1.04-1.23). Those individuals between 50 and 64 years old were more likely to complete the treatment than those between 35 and 49 years old (OR: 1.34, 95% CI: 1.18-1.50). Patients with HIV/AIDS were more likely to complete the treatment (OR: 1.80, 95% CI: 1.21-2.66), whereas cancer patients were less likely to complete the LTBI treatment (OR: 0.54, 95% CI: 0.37-0.78).
CI: 0.42-0.69). The rest of the covariates were not significantly associated with treatment completion (Table 10).

**Insert Table 10**
8. Discussion

In this study, the final results showed poor completion rates for the LTBI treatment for individuals who were dispensed INH; this was even lower when the treatment was initially prescribed by a primary care physician. The average time of treatment completion for those initially prescribed by primary care physicians was 11 days shorter than for those initially prescribed by other specialists, representing almost two weeks out of nine months. Just under a third of all LTBI prescriptions were initiated by a primary care physician although this proportion seems to be reducing over time despite the fact that Canadian data from the last 15 years has shown that the actual number of primary care physicians in the province of Quebec has increased from 7 679 in 1998 to 8 165 in 2004. In 2005 it was reported that there were 109 primary care physicians per 100 000 individuals although 25.1% of the Quebec residents did not have a primary care physician.

Contrary to what was hypothesized, the patients prescribed treatment by primary care physicians were found to have more comorbidities and illnesses. But regardless of the specialty, none of the listed comorbidities had a high prevalence among the study population. This may be because one third of the population were 35 and 45 years old, and may represent a “healthy” study cohort. In addition the rates for HIV/AIDS were lower than expected since the TB-HIV coinfection has become more important in Canada.

For treatment length, the current study found higher proportions of individuals having treatment duration equal to one, six and nine months. After an initial drop of 12% in the first 30 days, the decline in completion for each month was between 6 - 9% for both types of prescribing physician. Completion at month 6 was 14% and month 9 was 30.1%. The observation regarding the higher percentage of treatment with 6 and 9 months duration may be explained by the fact that those are the current recommended regimens for LTBI treatment with INH. The drop in the completion rate after one month of treatment, except for the 6 and 9 month as noted, could mean that the first months of the LTBI treatment may be crucial for reinforcing the importance of regimen completion, as was found in studies by Rennie, Horsburgh, and Menzies. Parsyan et al., on a study conducted in 2 621 patients seen at the Boston Public Health Commission
tuberculosis clinic, showed that more than half of the patients who dropped the treatment did it within the first month. However, data from this current study showed that 50% of the population had a treatment duration equal or lesser than 180 days and 75% of the individuals equal or lesser than 270 days. Those 1,677 (11.4%) individuals who were found to have durations greater than 270 days may have been prescribed with a 12 month INH regimen or had interruptions in the treatment.

In 2000, the treatment recommendations for INH therapy changed from 6 to 9 months for the adult population, although the paediatric recommendation has always been for 9 months. Our population level data demonstrated that physicians changed their prescribing practices as we observed that the percentage of people having treatment duration equal to 6 months was higher before 2000 and the proportion of individuals with treatment greater than 8 months was higher after 2000. However, there was a gradual transition between guidelines as it took more than a year for the new recommendations to be seen in dispensing durations. Interestingly, we also found that for both periods the treatment duration with the highest proportion of individuals corresponded to treatments initiated by other specialists and not by primary care doctors.

This study found that less than half (41.1%) of the patients that have been dispensed INH for LTBI completed the recommended treatment duration. Also this data showed that LTBI completion rates were statistically significantly higher for those individuals dispensed medication prescribed by other specialists and by frequent prescribers. In the literature, the overall completion rates were found to be higher than ours, such as in the case of a systematic review of US and Canadian studies (50%-60%). However, Horsburgh in 2010 conducted a study in 720 individuals in 32 different clinical sites across Canada and US; he reported completion rates lower than 45% and lower than 55% for the 9-month and 6-month INH regimen respectively which are similar to those reported by this current study. In fact, when completion rates were calculated at 6 and 9 months separately (Figure 4), the values were identical to those found by Horsburgh.

Even though a third of the prescriptions were initiated by a primary care physician, there were many more primary care physicians (almost two times) initiating a small number of LTBI prescriptions. There were fewer numbers of specialists but this small number actually initiated the majority of treatments. Around half of the individual
physicians initiated the LTBI treatment in only one patient over the 10 year period. We did not examine whether or not these physicians continued to prescribe the treatments or whether they referred their patients for follow-up. 9, 10, 41, 55, 158

In addition to the specialty of the prescribing physician, sex and age were also found to increase the chance of completing treatment, with middle age men (>49 and < 65 y/o) being the most likely to complete the prescribed treatment. This is in contrast with findings of a study conducted in 3 788 individuals in San Diego, California, published in 2003, 41 where younger women (<34 y/o) where associated with higher completion rates. At the same time our study found that, although not significant, older individuals (80 +) had the lowest completion rates and that younger patients (<20 y/o) where more likely to complete the treatment. This may be explained by the existence of more clear guidelines for paediatric patients and frail health in the elderly. The finding that patients with a cancer diagnosis were significantly less likely to complete the treatment may be due in part to the fact that very often these patients are already receiving complex treatment regimens, and this has been found to negatively affect treatment completion rates. 176 Whether the prescribing physician is a more or less frequent prescriber was not found to be a predictor. This has important implications for which patients to target for improving compliance and that all primary care physicians, regardless of experience, may require additional support to improve the completion rates in their patients.

There were several advantages to using these population-based provincial databases for this study. The almost universal level of coverage provided high external validity and increased levels of statistical power. 177 These databases allowed access to information on demographics, diagnosis, treating physician and dispensed medication, for more than 99% of the population. Given that since January 1997 the RAMQ has provided all TB medications free of charge to all legal Quebec residents regardless of drug insurance status, we were able to study a large population with a great deal of information on potential confounders. The prescription claims database contains all prescriptions billed to the RAMQ by any community based pharmacy in Quebec for persons covered by RAMQ for prescription drugs, and for all persons dispensed tuberculosis medication - regardless of other drug insurance coverage. Tamblyn et al. found that in comparison with
clinical data, the prescription claims database in Quebec may be one of the most accurate methods of determining drugs dispensed to individuals.\textsuperscript{178}

One of the main limitations of this database study is that LTBI was defined by prescription of LTBI medication and not by medical diagnosis. However, after 30 days of treatment with any of the regimens used to treat latent tuberculosis the diagnosis is almost certain; and the three regimens currently prescribed for LTBI are normally not used as initial therapy for active TB.\textsuperscript{26} Whether the LTBI treatment with INH was prescribed for 6 or 9 months was not directly ascertained from the databases. However, by using the index year in the completion calculation and dividing it pre and post guidelines change (year 2000)\textsuperscript{47} the shift in duration of dispensed treatment was apparent with a gradual transition.

Another important limitation is that using a pharmacy database to check when prescriptions are initially filled and refilled over time may have the inherent problem that obtaining the medicine does not ensure its use. Because it was not possible to verify actual INH consumption, dispensed medication was used as a proxy measure for treatment completion.\textsuperscript{49,179} Nonetheless, this proxy measure is relatively accurate despite the tendency to overestimate the actual completion rate and there is no “gold standard”.\textsuperscript{49,179,43,103,180} A variety of strategies has been reported in the literature and direct methods such as directly observed treatment, drug-level measurement and clinic attendance, were found to be generally more objective than the indirect methods (prescription refill rate, pill count, patient self-report, provider assessment and electronic monitoring device), yielding more reliable assessments of treatment adherence,\textsuperscript{181} however these would not have been possible in such a large study population. Also the use of an objective urine test in conjunction with patient-reported compliance and clinic attendance has been very useful in guiding physicians in assessing LTBI treatment completion,\textsuperscript{101,118} but this is also problematic in large populations measured over ten years.\textsuperscript{181} Any overestimation of completion rates would have been similar between prescriber groups and would not significantly change our conclusions.

Since diagnostic information is not needed for reimbursement, these types of databases are not audited to ensure accuracy for clinical veracity, and so this type of information may be less accurate than other administrative data.\textsuperscript{182} Nevertheless, to
ensure maximum sensitivity, the method of using two or more medical records or one or more hospital discharge diagnoses, which has been validated in administrative data, were used in order to indicate the presence of co-morbid condition.\textsuperscript{183} A body of literature has been developed that has found that administrative databases may be used and still show reasonable accuracy for diagnosis of co-morbidities,\textsuperscript{184-188} or multiple conditions.\textsuperscript{177, 189} Even though in the literature it was found that smoking may affect treatment completion, it was not possible to assess smoking status with this study databases. The potential bias would result in non-differential misclassification leading to an underestimation of the association between completion rates between specialties of prescribing physicians.

For the study population, non-Quebec residents residing in this province and First Nations people were not included as they are funded for healthcare by the federal government, and therefore, RAMQ would have no information for them. Individuals with LTBI living in Northern Quebec province are seen more often by primary care physicians than by other specialty physicians. However, since the LTBI medication is prescribed by a nurse and not by the physician, the RAMQ also has no records for them. Also, for those immigrants who have received TB drugs in their country of origin and have developed multidrug resistance, the RAMQ would not have the information for the period of time before the individual appears in the system. Illegal immigrants and refugee claimants would not have been in the databases. Many of these populations are at higher risk for HIV infection and this may account for the low HIV rates found in our study.

It would have been interesting to make a distinction between primary care physicians working in a specialized hospital and those working at primary care settings. Some isolated primary care physicians work in remote areas whereas others work with the support of a team and specialist and others work in specialized clinics. However, information on the name or type of institution where the prescription took place was not possible to retrieve due to privacy concerns. It may be that the location of practice is more relevant to completion rates than the actual speciality of the prescriber.
9. Conclusion and Summary

Despite the advances in medical technology, in 2011 we are still struggling with one of the most ancient of infections. Treating latent TB infection is possible and feasible; nevertheless, treatment completion is a keystone for its success. Between a third and a quarter of the LTBI prescriptions dispensed in Quebec are initiated by a primary care physician. More than half of patients treated for LTBI in this province are still not completing the recommended regimen; and the average time of treatment completion for those initially prescribed by primary care physicians was 11 days shorter than for those initially prescribed by other specialists. The reasons why completion is less likely for those initiated by primary care physicians need to be investigated. Factors such as the occurrence of adverse events, death of the patient or available support for the clinician and patient may be affecting the treatment completion and need to be explored. Most of the treating physicians are prescribing the LTBI therapy in only one patient with the exception of a very small number of professionals that do this for hundreds of individuals. Within this study, treatment completion did not appear to be affected by this fact, however it is an important aspect to take into account since the development and redirection of guidelines should be targeting the correct audience and the correct areas in order to be the most efficient.

Given that TB is a reportable infectious disease, public health departments are ultimately responsible for the control of the disease, but this cannot be accomplished without the collaboration of the physicians who deal everyday with the patients. With a better understanding of the situation through further research, clearer recommendations could be accomplished. The treating physicians will be able to use their positive influence on the patient and enhance the LTBI treatment completion, and through this make a significant contribution to the public health.
10. References


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11. Tables and Figures

Figure 1 - Study cohort conformation

Dispensed any TB drug for 30 days or more  
\( n = 23\,379 \)

\[ \text{Excluded } n = 2\,873 \]
\- Active TB cases

Dispensed a regimen used for LTBI only  
\( n = 20\,506 \)

\[ \text{Excluded } n = 4\,141 \]
\- Index prescription between 01/01/2006-12/31/2007

Index prescription between 01/01/1999-12/31/2005  
\( n = 16\,365 \)

\[ \text{Excluded two drugs regimens } n = 366 \]
\- Initial LTBI regimen dispensed INH + RIF  
\( n = 305 \)
\- Initial LTBI regimen dispensed PZA + RIF  
\( n = 61 \)

Dispensed only one TB drug (at a time)  
\( n = 15\,999 \)

\[ \text{Excluded } n = 1246 \]
\- Initial LTBI regimen dispensed RIF  
\( n = 1\,213 \)
\- Initial LTBI regimen dispensed RIF switched to INH  
\( n = 33 \)

INH as initial treatment regimen  
\( n = 14\,753 \)
(Includes initially INH and switched to RIF  
\( n = 511 \)
<table>
<thead>
<tr>
<th>Type of database</th>
<th>Primary Use</th>
<th>Data Variables</th>
</tr>
</thead>
</table>
| Beneficiaries    | Registration and Identification of beneficiaries | Age of Patient (5 years brackets)  
|                  |             | Month and year of death (if applicable)  
|                  |             | Gender  
|                  |             | Postal Code (first three digits)  
|                  |             | Income/Education indicators for postal code area  
|                  |             | Prescription drug insurance status  
|                  |             | Dates of change of status  
| Hospital Services (Med-Echo) | Hospital Administration and Social service records | In-hospital procedures (e.g. Surgery)  
|                  |             | Dates of admission and discharge  
|                  |             | Admission diagnosis (coded using ICD-9)  
|                  |             | Primary and secondary discharge diagnosis (coded using ICD-9)  
| Medical Services | Reimbursements to physicians | Physician claims (in hospital and outpatient services)  
|                  |             | ICD-9 diagnostic code for each service/unit  
|                  |             | Diagnosis  
|                  |             | Dates and cost of services  
|                  |             | Location of service (Clinic, ER, Private office, Hospital)  
|                  |             | Specialty of Physician (treating and referring)  
|                  |             | Physician’s unique identifier (encrypted)  
| Prescription claims | Reimbursement to pharmacists | Specific drug filled by pharmacist  
|                  |             | Classification of drug (AHFS)  
|                  |             | Date of prescription filled  
|                  |             | Dosage of drug treatment  
|                  |             | Quantity of drug  
|                  |             | Duration of treatment  
|                  |             | Route of absorption  
|                  |             | Pharmacist’s unique identifier  
|                  |             | Prescribing physician  

AHFS: American Hospital Formulary service class
**Table 2A - Baseline characteristics**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-19</td>
<td>2502</td>
<td>17.0%</td>
</tr>
<tr>
<td>20-34</td>
<td>3447</td>
<td>23.4%</td>
</tr>
<tr>
<td>35-49</td>
<td>4273</td>
<td>29.0%</td>
</tr>
<tr>
<td>50-64</td>
<td>2868</td>
<td>19.4%</td>
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<tr>
<td>65-79</td>
<td>1613</td>
<td>10.9%</td>
</tr>
<tr>
<td>80+</td>
<td>50</td>
<td>0.3%</td>
</tr>
<tr>
<td><strong>Sex (Male)</strong></td>
<td>6512</td>
<td>44.1%</td>
</tr>
<tr>
<td><strong>Comorbidities identified 2 years before index date</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>513</td>
<td>3.5%</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>139</td>
<td>0.9%</td>
</tr>
<tr>
<td>Cancer (Malignant neoplasms)</td>
<td>468</td>
<td>3.2%</td>
</tr>
<tr>
<td>Viral Hepatitis (A, B, or C)</td>
<td>92</td>
<td>0.6%</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>292</td>
<td>2.0%</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>218</td>
<td>1.5%</td>
</tr>
<tr>
<td>Substance Abuse (Alcohol or drugs)</td>
<td>170</td>
<td>1.2%</td>
</tr>
<tr>
<td>Depression</td>
<td>445</td>
<td>3.0%</td>
</tr>
<tr>
<td><strong>Individuals living in census area with low level of education</strong></td>
<td>4094</td>
<td>27.8%</td>
</tr>
<tr>
<td><strong>Individuals as above with low income status</strong></td>
<td>3822</td>
<td>25.9%</td>
</tr>
<tr>
<td><strong>Individuals hospitalized within 1 year after index date</strong></td>
<td>1191</td>
<td>8.1%</td>
</tr>
<tr>
<td><strong>Individuals hospitalized within 30 days before index date</strong></td>
<td>411</td>
<td>2.8%</td>
</tr>
<tr>
<td><strong>Individuals with a medical visit within 1 year after index date</strong></td>
<td>13822</td>
<td>93.7%</td>
</tr>
<tr>
<td><strong>Specialty of prescribing physician initiating LTBI treatment (Primary care physician)</strong></td>
<td>3863</td>
<td>26.2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>14753</td>
<td></td>
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</table>
Table 2A - Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mean</th>
<th>SD</th>
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<tr>
<td>Number of hospitalizations within 1 year after index</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>Number of hospitalizations within 30 days before index</td>
<td>0.03</td>
<td>0.2</td>
</tr>
<tr>
<td>Length of hospitalizations within 1 year after index</td>
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<td>10.3</td>
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<td>Length of hospitalizations within 30 days before index</td>
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<td>1.9</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>178.5</td>
<td>98.8</td>
</tr>
<tr>
<td>Number of medical visits within 1 year after index</td>
<td>14.5</td>
<td>30.8</td>
</tr>
<tr>
<td>Level of education</td>
<td>32.1</td>
<td>24.9</td>
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Table 3 - Proportion of LTBI Treatments Initiated by a Primary Care Physician (PC) by year

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<th>Year of Initial prescription</th>
<th>PC proportion</th>
<th>95% CI</th>
<th>Total</th>
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<tr>
<td>1998</td>
<td>0.29</td>
<td>(0.26, 0.31)</td>
<td>1731</td>
</tr>
<tr>
<td>1999</td>
<td>0.28</td>
<td>(0.25, 0.29)</td>
<td>1722</td>
</tr>
<tr>
<td>2000</td>
<td>0.32</td>
<td>(0.29, 0.33)</td>
<td>1781</td>
</tr>
<tr>
<td>2001</td>
<td>0.27</td>
<td>(0.25, 0.29)</td>
<td>1562</td>
</tr>
<tr>
<td>2002</td>
<td>0.28</td>
<td>(0.25, 0.29)</td>
<td>1914</td>
</tr>
<tr>
<td>2003</td>
<td>0.26</td>
<td>(0.24, 0.27)</td>
<td>2091</td>
</tr>
<tr>
<td>2004</td>
<td>0.21</td>
<td>(0.19, 0.22)</td>
<td>1977</td>
</tr>
<tr>
<td>2005</td>
<td>0.21</td>
<td>(0.19, 0.22)</td>
<td>1975</td>
</tr>
<tr>
<td>Total</td>
<td>0.26</td>
<td>(0.25, 0.27)</td>
<td>14753</td>
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### Table 4A - Baseline characteristics by prescribing physician specialty

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<th></th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>%</th>
<th>p-value</th>
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<td><strong>Age</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-19</td>
<td>569 (14.7%)</td>
<td>1933 (17.8%)</td>
<td>2502 (17.0%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>20-34</td>
<td>961 (24.9%)</td>
<td>2486 (22.8%)</td>
<td>3447 (23.4%)</td>
<td>0.009</td>
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<tr>
<td>35-49</td>
<td>1163 (30.1%)</td>
<td>3110 (28.6%)</td>
<td>4273 (29.0%)</td>
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<tr>
<td>50-64</td>
<td>767 (19.9%)</td>
<td>2101 (19.3%)</td>
<td>2868 (19.4%)</td>
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<tr>
<td>65-79</td>
<td>387 (10.0%)</td>
<td>1226 (11.3%)</td>
<td>1613 (10.9%)</td>
<td>0.333</td>
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<tr>
<td>80+</td>
<td>16 (0.4%)</td>
<td>34 (0.3%)</td>
<td>50 (0.3%)</td>
<td>0.348</td>
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</tr>
<tr>
<td><strong>Sex (Male)</strong></td>
<td>1620 (41.9%)</td>
<td>4892 (44.9%)</td>
<td>6512 (44.1%)</td>
<td>0.001</td>
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</tr>
<tr>
<td><strong>Comorbidities identified 2 years before index date</strong></td>
<td></td>
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</tr>
<tr>
<td>Diabetes</td>
<td>136 (3.5%)</td>
<td>377 (3.5%)</td>
<td>513 (3.5%)</td>
<td>0.864</td>
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<tr>
<td>HIV/AIDS</td>
<td>41 (1.1%)</td>
<td>98 (0.9%)</td>
<td>139 (0.9%)</td>
<td>0.372</td>
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<td>Cancer (Malignant neoplasms)</td>
<td>115 (3.0%)</td>
<td>353 (3.2%)</td>
<td>468 (3.2%)</td>
<td>0.420</td>
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<tr>
<td>Viral Hepatitis (A/B/C)</td>
<td>31 (0.8%)</td>
<td>61 (0.6%)</td>
<td>92 (0.6%)</td>
<td>0.100</td>
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<tr>
<td>Renal Failure</td>
<td>48 (1.2%)</td>
<td>244 (2.2%)</td>
<td>292 (2.0%)</td>
<td>0.0001</td>
<td></td>
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<tr>
<td>Liver Disease</td>
<td>74 (1.9%)</td>
<td>144 (1.3%)</td>
<td>218 (1.5%)</td>
<td>0.008</td>
<td></td>
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<td>Substance Abuse (Alcohol/ drugs)</td>
<td>73 (1.9%)</td>
<td>97 (0.9%)</td>
<td>170 (1.2%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>130 (3.4%)</td>
<td>315 (2.9%)</td>
<td>445 (3.0%)</td>
<td>0.14</td>
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<td><strong>Individuals living in census area w/ low level of education</strong></td>
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<tr>
<td></td>
<td>1443 (37.4%)</td>
<td>2651 (24.3%)</td>
<td>4094 (27.8%)</td>
<td>&lt;0.0001</td>
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<td><strong>Individuals as above with low income status</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1033 (26.7%)</td>
<td>2789 (25.6%)</td>
<td>3822 (25.9%)</td>
<td>0.287</td>
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<td><strong>Individuals hospitalized within 1 year after index date</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>324 (8.4%)</td>
<td>867 (8.0%)</td>
<td>1191 (8.1%)</td>
<td>0.404</td>
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<td><strong>Individuals hospitalized within 30 days before index date</strong></td>
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<tr>
<td></td>
<td>153 (4.0%)</td>
<td>258 (2.4%)</td>
<td>411 (2.8%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Individuals w/ a medical visit within 1 year after index date</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3515 (91.0%)</td>
<td>10307 (94.6%)</td>
<td>13822 (93.7%)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3863 (26.2%)</td>
<td>10890 (73.8%)</td>
<td>14753</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 4B - Baseline characteristics by prescribing physician specialty

<table>
<thead>
<tr>
<th></th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
<td>mean</td>
</tr>
<tr>
<td>Number of hospitalizations within 1 year after index</td>
<td>0.08</td>
<td>0.3</td>
<td>0.08</td>
</tr>
<tr>
<td>Number of hospitalizations within 30 days before index</td>
<td>0.04</td>
<td>0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Length of (a)</td>
<td>1.5</td>
<td>9.8</td>
<td>1.5</td>
</tr>
<tr>
<td>Length of (b)</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>170.9</td>
<td>101.4</td>
<td>181.3</td>
</tr>
<tr>
<td>Number of medical visits within 1 year after index</td>
<td>13.1</td>
<td>28.4</td>
<td>15.3</td>
</tr>
<tr>
<td>Level of education</td>
<td>27.2</td>
<td>23.3</td>
<td>33.7</td>
</tr>
</tbody>
</table>

For Tables 2A and 2B- (a) p-values correspond to comparison of patient’s baseline characteristics between specialties of prescribing physician. (b) Missing values: 178 for income status and education level
Table 5 - Days of Treatment dispensed by Prescribing Physician Specialty

<table>
<thead>
<tr>
<th>Days</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>0-30</td>
<td>527</td>
<td>13.6%</td>
<td>1235</td>
<td>11.3%</td>
</tr>
<tr>
<td>31-60</td>
<td>310</td>
<td>8.0%</td>
<td>878</td>
<td>8.1%</td>
</tr>
<tr>
<td>61-90</td>
<td>341</td>
<td>8.8%</td>
<td>843</td>
<td>7.7%</td>
</tr>
<tr>
<td>91-120</td>
<td>296</td>
<td>7.7%</td>
<td>611</td>
<td>5.6%</td>
</tr>
<tr>
<td>121-150</td>
<td>251</td>
<td>6.5%</td>
<td>671</td>
<td>6.2%</td>
</tr>
<tr>
<td>151-180</td>
<td>622</td>
<td>16.1%</td>
<td>1467</td>
<td>13.5%</td>
</tr>
<tr>
<td>181-210</td>
<td>307</td>
<td>7.9%</td>
<td>891</td>
<td>8.2%</td>
</tr>
<tr>
<td>211-240</td>
<td>226</td>
<td>5.9%</td>
<td>830</td>
<td>7.6%</td>
</tr>
<tr>
<td>241+</td>
<td>983</td>
<td>25.4%</td>
<td>3464</td>
<td>31.8%</td>
</tr>
<tr>
<td>Total</td>
<td>3863</td>
<td>26.2%</td>
<td>10890</td>
<td>73.8%</td>
</tr>
</tbody>
</table>

(a) Corresponds to comparison of days of LTBI treatment dispensed between specialty of prescribing physician
Insert for Figure 3A

**Fig-3A Days of Treatment Completed by Specialty of Prescribing Physician for index year 1998, 1999, 2000**

Days of treatment completed

Days of treatment completed

Proportion of Patients

- Primary Care
- Others

Insert for Figure 3B


Days of treatment completed

Days of treatment completed

Proportion of Patients

- Primary Care
- Others
Table 6 - Treatment Completion and Specialty of Prescribing Physician

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>p-value a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Complete</td>
<td>1412</td>
<td>36.6%</td>
<td>4647</td>
<td>42.7%</td>
</tr>
<tr>
<td>Did not complete</td>
<td>2451</td>
<td>63.4%</td>
<td>6243</td>
<td>57.3%</td>
</tr>
<tr>
<td>Total</td>
<td>3863</td>
<td>26.2%</td>
<td>10890</td>
<td>73.8%</td>
</tr>
</tbody>
</table>

(a) Corresponds to comparison of treatment completion rates between specialty of prescribing physician
Table 7-Baseline Characteristics of Individuals who completed the LTBI Treatment by Prescribing Specialty

<table>
<thead>
<tr>
<th>Age</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-19</td>
<td>13.8%</td>
<td>17.3%</td>
<td>16.5%</td>
<td>0.002</td>
</tr>
<tr>
<td>20-34</td>
<td>24.2%</td>
<td>22.7%</td>
<td>23.1%</td>
<td>0.242</td>
</tr>
<tr>
<td>35-49</td>
<td>28.6%</td>
<td>27.7%</td>
<td>27.9%</td>
<td>0.481</td>
</tr>
<tr>
<td>50-64</td>
<td>23.6%</td>
<td>21.7%</td>
<td>22.1%</td>
<td>0.138</td>
</tr>
<tr>
<td>65-79</td>
<td>9.5%</td>
<td>10.4%</td>
<td>10.2%</td>
<td>0.325</td>
</tr>
<tr>
<td>80+</td>
<td>0.3%</td>
<td>0.2%</td>
<td>0.2%</td>
<td>0.095</td>
</tr>
</tbody>
</table>

| Sex (Male) | 43.9% | 46.4% | 45.8% | 0.977 |

<table>
<thead>
<tr>
<th>Comorbidities identified 2 years before index date</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>3.8%</td>
<td>3.3%</td>
<td>3.4%</td>
<td>0.449</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1.6%</td>
<td>1.1%</td>
<td>1.2%</td>
<td>0.111</td>
</tr>
<tr>
<td>Cancer (Malignant neoplasms)</td>
<td>2.1%</td>
<td>2.0%</td>
<td>2.0%</td>
<td>0.942</td>
</tr>
<tr>
<td>Viral Hepatitis (A/B/C)</td>
<td>0.8%</td>
<td>0.4%</td>
<td>0.5%</td>
<td>0.057</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>1.2%</td>
<td>2.2%</td>
<td>1.9%</td>
<td>0.023</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>1.5%</td>
<td>1.2%</td>
<td>1.3%</td>
<td>0.369</td>
</tr>
<tr>
<td>Substance Abuse (Alcohol/drugs)</td>
<td>1.8%</td>
<td>0.9%</td>
<td>1.1%</td>
<td>0.002</td>
</tr>
<tr>
<td>Depression</td>
<td>3.5%</td>
<td>2.6%</td>
<td>2.9%</td>
<td>0.007</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals living in census area with low level of education</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>485 34.3% 1084 23.3% 1569 25.9% &lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals as above with low income status</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>397 28.1% 1189 25.6% 1586 26.2% 0.058</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals hospitalized within 1 year after index date</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 6.4% 275 5.9% 365 6.0% 0.528</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals hospitalized within 30 days before index date</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>49 3.5% 92 2.0% 141 2.3% 0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals w/ a medical visit within 1 year after index date</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1294 91.6% 4461 96.0% 5755 95.0% &lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1412 23.3% 4647 76.7% 6059 &lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) Corresponds to comparison of baseline characteristics of patients who completed the treatment between specialty of prescribing physician
(b) 25% of the cells have expected counts less than 5. Chi-Square may not be a valid test
Fig-4 Completion of 6 and 9 months Treatment Annually by Adult Population (>19 yo)
Table 8 - Number of Patients initiated on LTBI treatment during the entire study period by Individual Prescribing Physician

<table>
<thead>
<tr>
<th>Number of patients started on treatment</th>
<th>Primary Care</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>1113</td>
<td>64.9%</td>
<td>438</td>
</tr>
<tr>
<td>2-5</td>
<td>514</td>
<td>30.0%</td>
<td>260</td>
</tr>
<tr>
<td>6-15</td>
<td>69</td>
<td>4.0%</td>
<td>122</td>
</tr>
<tr>
<td>16-50</td>
<td>13</td>
<td>0.8%</td>
<td>62</td>
</tr>
<tr>
<td>50+</td>
<td>5</td>
<td>0.3%</td>
<td>41</td>
</tr>
<tr>
<td>Total</td>
<td>1714</td>
<td>65.0%</td>
<td>923</td>
</tr>
</tbody>
</table>

(a) Corresponds to comparison of number of patients started on treatment between primary care physicians vs. other specialists

Table 9 - Treatment Completion by Type of Prescribing Physician (based on number of treatments initiated)

<table>
<thead>
<tr>
<th>Number of patients started on LTBI treatment by the Physician</th>
<th>Treatment complete</th>
<th>Treatment not complete</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>1</td>
<td>566</td>
<td>9.3%</td>
<td>985</td>
</tr>
<tr>
<td>2-5</td>
<td>817</td>
<td>13.5%</td>
<td>1313</td>
</tr>
<tr>
<td>6-15</td>
<td>609</td>
<td>10.1%</td>
<td>1047</td>
</tr>
<tr>
<td>16-50</td>
<td>768</td>
<td>12.7%</td>
<td>1077</td>
</tr>
<tr>
<td>50+</td>
<td>3299</td>
<td>54.4%</td>
<td>4272</td>
</tr>
<tr>
<td>Total</td>
<td>6059</td>
<td>41.1%</td>
<td>8694</td>
</tr>
</tbody>
</table>

(a) Corresponds to comparison of type of prescribing physician (based on number of patients treatment initiated) between individuals that completed or not the LTBI treatment
Table 10- Odds ratios with 95% Confidence Intervals (95% CI) for factors impacting completion of LTBI treatment in a clustered regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Adjusted Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Care Physician vs. Other Specialties</strong></td>
<td>0.80</td>
<td>(0.67, 0.95)</td>
</tr>
<tr>
<td><strong>More Experienced vs. Less Experienced Prescriber</strong></td>
<td>0.98</td>
<td>(0.84, 1.14)</td>
</tr>
<tr>
<td><strong>Patient Characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male vs. Female</td>
<td>1.14</td>
<td>(1.04, 1.23)</td>
</tr>
<tr>
<td><strong>Age (years vs. 35-49 years old)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-19</td>
<td>1.02</td>
<td>(0.85, 1.23)</td>
</tr>
<tr>
<td>20-34</td>
<td>1.05</td>
<td>(0.95, 1.16)</td>
</tr>
<tr>
<td>35-49 (reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-64</td>
<td>1.34</td>
<td>(1.18, 1.50)</td>
</tr>
<tr>
<td>65-79</td>
<td>0.94</td>
<td>(0.80, 1.09)</td>
</tr>
<tr>
<td>80+</td>
<td>0.88</td>
<td>(0.48, 1.60)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.06</td>
<td>(0.85, 1.31)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>1.80</td>
<td><strong>(1.21, 2.66)</strong></td>
</tr>
<tr>
<td>Cancer (Malignant neoplasms)</td>
<td>0.54</td>
<td><strong>(0.42, 0.69)</strong></td>
</tr>
<tr>
<td>Viral Hepatitis (A, B, or C)</td>
<td>0.86</td>
<td>(0.51, 1.44)</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>1.04</td>
<td>(0.79, 1.36)</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>0.80</td>
<td>(0.59, 1.08)</td>
</tr>
<tr>
<td>Substance Abuse (Alcohol or drugs)</td>
<td>1.01</td>
<td>(0.73, 1.39)</td>
</tr>
<tr>
<td>Depression</td>
<td>0.97</td>
<td>(0.79, 1.18)</td>
</tr>
<tr>
<td>Level of Education</td>
<td>1.00</td>
<td>(1.00, 1.00)</td>
</tr>
<tr>
<td>Income status</td>
<td>1.00</td>
<td>(1.00, 1.00)</td>
</tr>
</tbody>
</table>
Appendix 1

Specific ICD-9 Codes: For Comorbid Conditions

Neoplasms:
140 Malignant neoplasm of lip
141 Malignant neoplasm of tongue
142 Malignant neoplasm of major salivary glands
143 Malignant neoplasm of gum
144 Malignant neoplasm of floor of mouth
145 Malignant neoplasm of other and unspecified parts of mouth
146 Malignant neoplasm of oropharynx
147 Malignant neoplasm of nasopharynx
148 Malignant neoplasm of hypopharynx
149 Malignant neoplasm of other and ill-defined sites within the lip oral cavity and pharynx
150 Malignant neoplasm of esophagus
151 Malignant neoplasm of stomach
152 Malignant neoplasm of small intestine including duodenum
153 Malignant neoplasm of colon
154 Malignant neoplasm of rectum rectosigmoid junction and anus
155 Malignant neoplasm of liver and intrahepatic bile ducts
156 Malignant neoplasm of gallbladder and extrahepatic bile ducts
157 Malignant neoplasm of pancreas
158 Malignant neoplasm of retroperitoneum and peritoneum
159 Malignant neoplasm of other and ill-defined sites within the digestive organs and peritoneum
160 Malignant neoplasm of nasal cavities middle ear and accessory sinuses
161 Malignant neoplasm of larynx
162 Malignant neoplasm of trachea bronchus and lung
163 Malignant neoplasm of pleura
164 Malignant neoplasm of thymus heart and mediastinum
165 Malignant neoplasm of other and ill-defined sites within the respiratory system and intrathoracic organs
170 Malignant neoplasm of bone and articular cartilage
171 Malignant neoplasm of connective and other soft tissue
172 Malignant melanoma of skin
173 Other malignant neoplasm of skin
174 Malignant neoplasm of female breast
175 Malignant neoplasm of male breast
176 Kaposi's sarcoma
179 Malignant neoplasm of uterus-part unspecified
180 Malignant neoplasm of cervix uteri
181 Malignant neoplasm of placenta
182 Malignant neoplasm of body of uterus
183 Malignant neoplasm of ovary and other uterine adnexa
184 Malignant neoplasm of other and unspecified female genital organs
185 Malignant neoplasm of prostate
186 Malignant neoplasm of testis
187 Malignant neoplasm of penis and other male genital organs
188 Malignant neoplasm of bladder
189 Malignant neoplasm of kidney and other and unspecified urinary organs
190 Malignant neoplasm of eye
191 Malignant neoplasm of brain
192 Malignant neoplasm of other and unspecified parts of nervous system
193 Malignant neoplasm of thyroid gland
194 Malignant neoplasm of other endocrine glands and related structures
195 Malignant neoplasm of other and ill-defined sites
196 Secondary and unspecified malignant neoplasm of lymph nodes
197 Secondary malignant neoplasm of respiratory and digestive systems
198 Secondary malignant neoplasm of other specified sites
199 Malignant neoplasm without specification of site
200 Lymphosarcoma and reticulosarcoma
201 Hodgkin’s disease
202 Other malignant neoplasms of lymphoid and histiocytic tissue
203 Multiple myeloma and immunoproliferative neoplasms
204 Lymphoid leukemia
205 Myeloid leukemia
206 Monocytic leukemia
207 Other specified leukemia
208 Leukemia of unspecified cell type
209.0 Malignant carcinoid tumors of the small intestine
209.1 Malignant carcinoid tumors of the appendix, large intestine and rectum
209.2 Malignant carcinoid tumors of other and unspecified
209.3 Malignant poorly differentiated neuroendocrine tumors

**Diabetes:**

249 Secondary diabetes mellitus
249.0 Secondary diabetes mellitus without mention of complication
249.00 Secondary diabetes mellitus without mention of complication, not stated as uncontrolled, or unspecified
249.01 Secondary diabetes mellitus without mention of complication, uncontrolled
249.1 Secondary diabetes mellitus with ketoacidosis
249.10 Secondary diabetes mellitus with ketoacidosis, not stated as uncontrolled, or unspecified
249.11 Secondary diabetes mellitus with ketoacidosis, uncontrolled
249.2 Secondary diabetes mellitus with hyperosmolarity
249.20 Secondary diabetes mellitus with hyperosmolarity, not stated as uncontrolled, or unspecified
249.21 Secondary diabetes mellitus with hyperosmolarity, uncontrolled
249.3 Secondary diabetes mellitus with other coma
249.30 Secondary diabetes mellitus with other coma, not stated as uncontrolled, or unspecified
249.31 Secondary diabetes mellitus with other coma, uncontrolled
249.4 Secondary diabetes mellitus with renal manifestations
249.40 Secondary diabetes mellitus with renal manifestations, not stated as uncontrolled, or unspecified
249.41 Secondary diabetes mellitus with renal manifestations, uncontrolled
249.5 Secondary diabetes mellitus with ophthalmic manifestations
249.50 Secondary diabetes mellitus with ophthalmic manifestations, not stated as uncontrolled, or unspecified
249.51 Secondary diabetes mellitus with ophthalmic manifestations, uncontrolled
249.6 Secondary diabetes mellitus with neurological manifestations
249.60 Secondary diabetes mellitus with neurological manifestations, not stated as uncontrolled, or unspecified
249.61 Secondary diabetes mellitus with neurological manifestations, uncontrolled
249.7 Secondary diabetes mellitus with peripheral circulatory disorders
249.70 Secondary diabetes mellitus with peripheral circulatory disorders, not stated as uncontrolled, or unspecified
249.71 Secondary diabetes mellitus with peripheral circulatory disorders, uncontrolled
249.8 Secondary diabetes mellitus with other specified manifestations
249.80 Secondary diabetes mellitus with other specified manifestations, not stated as uncontrolled, or unspecified
249.81 Secondary diabetes mellitus with other specified manifestations, uncontrolled
249.9 Secondary diabetes mellitus with unspecified complications
249.90 Secondary diabetes mellitus with unspecified complication, not stated as uncontrolled, or unspecified
249.91 Secondary diabetes mellitus with unspecified complication, uncontrolled
250 Diabetes mellitus
250.0 Diabetes mellitus without mention of complication
250.00 Diabetes mellitus without complication type ii or unspecified type not stated as uncontrolled
250.01 Diabetes mellitus without complication type i not stated as uncontrolled
250.02 Diabetes mellitus without complication type ii or unspecified type uncontrolled
250.03 Diabetes mellitus without complication type i uncontrolled
250.1 Diabetes with ketoacidosis
250.10 Diabetes mellitus with ketoacidosis type ii or unspecified type not stated as uncontrolled
250.11 Diabetes mellitus with ketoacidosis type i not stated as uncontrolled
250.12 Diabetes mellitus with ketoacidosis type ii or unspecified type uncontrolled
250.13 Diabetes mellitus with ketoacidosis type i uncontrolled
250.2 Diabetes with hyperosmolarity
250.20 Diabetes mellitus with hyperosmolarity type ii or unspecified type not stated as uncontrolled
250.21 Diabetes mellitus with hyperosmolarity type i not stated as uncontrolled
250.22 Diabetes mellitus with hyperosmolarity type ii or unspecified type uncontrolled
250.23 Diabetes mellitus with hyperosmolarity type i uncontrolled
250.3 Diabetes with other coma
250.30 Diabetes mellitus with other coma type ii or unspecified type not stated as uncontrolled
250.31 Diabetes mellitus with other coma type i not stated as uncontrolled
250.32 Diabetes mellitus with other coma type ii or unspecified type uncontrolled
250.33 Diabetes mellitus with other coma type i uncontrolled
250.4 Diabetes with renal manifestations
250.40 Diabetes mellitus with renal manifestations type ii or unspecified type not stated as uncontrolled
250.41 Diabetes mellitus with renal manifestations type i not stated as uncontrolled
250.42 Diabetes mellitus with renal manifestations type ii or unspecified type uncontrolled
250.43 Diabetes mellitus with renal manifestations type i uncontrolled
250.5 Diabetes with ophthalmic manifestations
250.50 Diabetes mellitus with ophthalmic manifestations type ii or unspecified type not stated as uncontrolled
250.51 Diabetes mellitus with ophthalmic manifestations type i not stated as uncontrolled
250.52 Diabetes mellitus with ophthalmic manifestations type ii or unspecified type uncontrolled
250.53 Diabetes mellitus with ophthalmic manifestations type i uncontrolled
250.6 Diabetes with neurological manifestations
250.60 Diabetes mellitus with neurological manifestations type ii or unspecified type not stated as uncontrolled
250.61 Diabetes mellitus with neurological manifestations type i not stated as uncontrolled
250.62 Diabetes mellitus with neurological manifestations type ii or unspecified type uncontrolled
250.63 Diabetes mellitus with neurological manifestations type i uncontrolled
250.7 Diabetes with peripheral circulatory disorders
250.70 Diabetes mellitus with peripheral circulatory disorders type ii or unspecified type not stated as uncontrolled
250.71 Diabetes mellitus with peripheral circulatory disorders type i not stated as uncontrolled
250.72 Diabetes mellitus with peripheral circulatory disorders type ii or unspecified type uncontrolled
250.73 Diabetes mellitus with peripheral circulatory disorders type i uncontrolled
250.8 Diabetes with other specified manifestations
250.80 Diabetes mellitus with other specified manifestations type ii or unspecified type not stated as uncontrolled
250.81 Diabetes mellitus with other specified manifestations type i not stated as uncontrolled
250.82 Diabetes mellitus with other specified manifestations type ii or unspecified type uncontrolled
250.83 Diabetes mellitus with other specified manifestations type i uncontrolled
250.9 Diabetes with unspecified complication
250.90 Diabetes mellitus with unspecified complication type ii or unspecified type not stated as uncontrolled
250.91 Diabetes mellitus with unspecified complication type i not stated as uncontrolled
250.92 Diabetes mellitus with unspecified complication type ii or unspecified type uncontrolled
250.93 Diabetes mellitus with unspecified complication type i uncontrolled

**Viral Hepatitis (A, B, or C)**

070    Viral hepatitis
070.2  Viral hepatitis b with hepatic coma
070.20 Viral hepatitis b with hepatic coma acute or unspecified without hepatitis delta
070.21 Viral hepatitis b with hepatic coma acute or unspecified with hepatitis delta
070.22 Chronic viral hepatitis b with hepatic coma without hepatitis delta
070.23 Chronic viral hepatitis b with hepatic coma with hepatitis delta
070.3  Chronic viral hepatitis b without mention of hepatic coma
070.30 Viral hepatitis b without hepatic coma acute or unspecified without hepatitis delta
070.31 Viral hepatitis b without hepatic coma acute or unspecified with hepatitis delta
070.32 Chronic viral hepatitis b without hepatic coma without hepatitis delta
070.33 Chronic viral hepatitis b without hepatic coma with hepatitis delta

V02.6  Asymptomatic hepatitis B carriers

**HIV/ AIDS**

V08    Asymptomatic HIV infection
042    Human immunodeficiency virus (HIV) disease with specified conditions
042.0  HIV infection with certain specified infections
042.1  HIV infection causing other specified infections
042.2  HIV infection with specified malignant neoplasm
042.9  Acquired immunodeficiency syndrome with or without other conditions
043    HIV infection causing other specified conditions
043.0  HIV infection causing lymphadenopathy (785.6)
043.1  HIV infection causing specified diseases of the central nervous system
043.2  HIV infection causing other disorders involving the immune mechanism
043.3  HIV infection causing other specified conditions
043.9  Acquired immunodeficiency syndrome-related complex with or without other conditions

044   Other human immunodeficiency virus (hiv) infection

044.0 HIV infection causing specified acute infections

044.9 HIV infection not otherwise specified (with or without other conditions not classifiable to 042, 043, 044.0)

AHF   81808 for anti-retroviral medications

Liver disease

456.0 Esophageal varices with bleeding

456.1 Esophageal varices without mention of bleeding

456.2 Esophageal varices in diseases classified elsewhere

456.20 Esophageal varices in diseases classified elsewhere with bleeding

456.21 Esophageal varices in diseases classified elsewhere without bleeding

571 Chronic liver disease and cirrhosis

571.0 Alcoholic fatty liver

571.1 Acute alcoholic hepatitis

571.2 Alcoholic cirrhosis of liver

571.3 Alcoholic liver damage unspecified

571.4 Chronic hepatitis

571.40 Chronic hepatitis unspecified

571.41 Chronic persistent hepatitis

571.42 Autoimmune hepatitis

571.49 Other chronic hepatitis

571.5 Cirrhosis of liver without alcohol

571.6 Biliary cirrhosis

571.8 Other chronic non-alcoholic liver disease

571.9 Unspecified chronic liver disease without alcohol

572 Liver abscess and sequelae of chronic liver disease

572.0 Abscess of liver

572.1 Portal pyema
572.2 Hepatic encephalopathy (Hepatic coma)
572.3 Portal hypertension
572.4 Hepatorenal syndrome
572.8 Other sequelae of chronic liver disease
573 Other disorders of liver
573.0 Chronic passive congestion of liver
573.1 Hepatitis in viral diseases classified elsewhere
573.2 Hepatitis in other infectious diseases classified elsewhere
573.3 Hepatitis unspecified
573.4 Hepatic infarction
573.8 Other specified disorders of liver
573.9 Unspecified disorder of liver

**Renal Failure**
584 Acute kidney failure
585 Chronic kidney disease (ckd)
586 Renal failure unspecified

**Substance Abuse (Alcohol or drugs, excluding tobacco)**
291 Alcoholic psychoses
291.0 Delirium tremens
291.1 Korsakov’s alcoholic psychosis
291.2 Other alcoholic dementia
291.3 Other alcoholic hallucinosis
291.4 Pathological drunkenness
291.5 Alcoholic jealousy
291.8 Other (includes alcohol withdrawal syndrome)
291.9 Unspecified alcoholic psychosis
292 Drug psychoses □
292.0 Drug withdrawal syndrome
292.1 Paranoid and/or hallucinatory states induced by drugs
292.2 Pathological drug intoxication
292.8 Other
292.9 Unspecified
303 Alcohol dependence (and all sub-categories)
304 Drug Dependence □
304.0 Morphine type
304.1 Barbiturate dependence
304.2 Cocaine dependence
304.4 Amphetamine type and other psychostimulants
304.5 Hallucinogens
304.6 Other drugs
304.7 Combinations of morphine type drug with any other
304.8 Combinations excluding morphine
304.9 Unspecified drug addiction
305.2 Cannabis abuse
305.3 Hallucinogens
305.4 Barbiturates and tranquillizers
305.5 Morphine type
305.6 Cocaine type
305.7 Amphetamine type
305.8 Antidepressants
305.9 Other, mixed or unspecified
357.5 Alcoholic polyneuropathy

**Depression**
296.2 Major depressive disorder, single episode
296.3 Major depressive disorder, recurrent episode
300.4 Dysthymic disorder
309.0 Adjustment disorder with depression
309.1 Prolonged depressive reaction
311 Depressive disorder not elsewhere classified