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.[13, 19] 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.[20, 21]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 [17, 22] to eliminate the tuberculosis disease cannot be achieved, [22] where elimination is defined as an incidence rate of less than one TB case per 1 million persons per year.[23]

The therapeutic regimens currently recommended by the WHO have been found to be highly efficacious not only for treating, but also for preventing TB [24] 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.[25] 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.[9, 18, 26] Current American Thoracic Society guidelines recommend a 9-month regimen of INH taken daily as the regimen of choice.[26, 27] 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.[28] While this drug has been shown to be safe, cheap, easy to take and well tolerated, [29] its effectiveness has been shown to be dependent on adherence to treatment and adequate duration.[29, 30, 31] If taken properly, this regimen may reduce the risk of developing active disease by about 50% [30, 31] and has shown to be highly efficacious in preventing future active TB.[9, 32] 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.[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.[23, 33, 34, 35, 36] Treatment completion rates have been found to be overall between 50-60% [37], but it actually may be lower for the commonly recommended regimen with INH for 9 months. [16, 33]

Several studies have been conducted with the goal of identifying different strategies that may increase adherence and treatment completion for latent tuberculosis. [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. [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, [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. [47] Nevertheless, a strong rapport between the patient and the health-care worker is mandatory in order for this strategy be effective. [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. [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 condition [33] 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 health [17] 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. [71, 72] Of these infected individuals, between 8 and 9 million will develop TB disease each year, [8, 19, 73] 200 million will develop the disease during their lifetime, [8, 74] and 30 million will die from TB over the next decade. [8] 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. [75] 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. [68] Over the last 30 years, the epidemiology of tuberculosis infection and disease has changed dramatically in Canada. [9] The incidence of TB disease has declined steadily from the beginning of this century until the mid 1980's, when incidences levelled off. [68, 76] In 2000, Canada had one of the world's lowest reported rates of active TB, with five new active cases per 100 000 people, [9, 57, 77, 78, 79] but this low overall rate masks the much higher incidence in certain populations such as high-risk, disadvantaged and marginalized groups. [9, 61, 76, 80] Over two-thirds (>65%) of all active cases occur among foreign-born Canadians, [9, 57] with an incidence of TB twenty times higher than in the non-Aboriginal Canadian born population (16 vs. 0.8 cases/100 000 population). [57] 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. [81, 82]

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. [9] 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%. [83] 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. [57, 84]

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. [58, 87, 88] However, sometimes this latent state can develop into active disease referred to as reactivation which may be triggered at any time. [88] 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. [1, 9, 16, 17, 18, 47, 88]

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. [59]

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 [11, 89] and it was the only way to diagnose LTBI. [27, 90] 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. [27, 91] 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. [92] The site of injection is examined and the size of the reaction is measured (induration and not erythema). [26, 27] The size of the

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. [9, 18, 26] Because the last regimen has shown to have rates of liver injury, hospitalization, and death higher than the rates reported for isoniazid, [99] the CDC no longer recommends its use. [26, 99] Currently, the recommended regimen with acceptable safety is isoniazid alone for 9 months, [9, 18, 33, 42, 47, 100, 101] which in general results in a risk reduction of around 50%, even in individuals infected with HIV, [30, 31] and has 90% efficacy in preventing future active TB if more than 80% of the doses are taken for 9 months or more. [9, 32] Clinical trials have shown that, in those individuals who completed the prescribed treatment (≥80% of doses), [46] INH alone for 6 months results in a 69% reduction in TB, [9, 37] and 12 months of treatment in a 93% reduction. [37, 46] 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. [32] 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. [9]

The Canadian Tuberculosis Standards, published in 2007, recommended LTBI treatment for those individuals with a higher risk of developing active TB. [47] 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,

[115] 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), [57, 64, 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. [37]

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 [63, 143-146] and Horsburgh, in a study published in 2004, found lower rates for the nine-month regimen with INH. [16] In a systematic review of US and Canadian studies about the adherence to LTBI treatment, [37] 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%, [37] with some studies reporting lower rates for a particular population group such as Latino immigrants. [147] A study published in 2010, [35] 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. [35]

Another important factor related with the LTBI treatment is the occurrence of adverse events. [16] 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. [33, 84] 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. [100] All of the drugs used to treat LTBI can cause serious adverse events (SAEs). [100] This may lead to the discontinuation of the drug, to a change of the drug regimen and to significant morbidity and even mortality. [100] Some of the adverse events that a patient may encounter are: drug-induced hepatitis (most important adverse reaction associated with isoniazid), different dermatological reactions (hypersensitivity reactions, acne, alopecia, xerostomia, lupus erythematous-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. [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. [9] Along the same line, Dye et al. [10] stated that a patient-supportive approach should be adopted by the physician in order to encourage patients to complete their treatment. [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". [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. [159] It was suggested that treatment completion can be better predicted at the time of the first follow-up. [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. [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. [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. [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 [42] and may promote and encourage the patients to complete the treatment. [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. [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. [55] This same study suggested that the same physician should continue the follow-up until the patient successfully completes the treatment. [55]

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. [43] 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. [65, 159] 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. [42] However, according to Besch and other authors, the identification of such individuals by the health care provider may be difficult [162] and the prediction of non-adherence inaccurate. [163-165] Some studies suggested that demographic, social, clinical and other patient characteristics were not predictive or relate poorly with treatment completion. [43, 162]

Nevertheless, many studies [35, 41, 62, 65, 159] 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. [35, 65] 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. [41] The authors of this study, attributed the higher rates among Hispanics to the clinic staff's (where that study was taking place) cultural sensitivity, since it had bilingual and bicultural employees, which may have encouraged a greater sense of trust among the clinic's patients. [41] 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. [62] 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. [54, 17, 18, 26, 59]

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, [9, 18, 33, 47, 100, 101] 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. [9, 26, 49, 168-170] 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. [26, 168-170] New recommendations regarding the INH use for LTBI treatment were published in 2000, [47] 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, [26] hence for those aged between 1 and 19 years old, the completion was defined as medication dispensed for 241 days or more.

	INH dispensed between 1998 and 2000	INH dispensed between 2001 and 2005
Patients < 20 years old	INH dispensed for 241 days or more	INH dispensed for 241 days or more
Patients ≥ 20 years old	INH dispensed for 180 days or more	INH 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. [47] 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 "omnipratique/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. [171]

6.4.3. Potential Confounders

From review of the literature, patient characteristics such as age, [41, 43] sex, [84, 43] and type of major health conditions such as HIV+/AIDS, [118, 43, 119-122] cancer, [43, 107] diabetes, [43] renal failure, [43] Hepatitis B/ C, depression, [43, 108] alcoholism, [41] or other substance abuse [43, 172] 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. [47] 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. [173]

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 [174] 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).

Insert 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.

Insert 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.

Insert Figure 4

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 fewer 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: 0.42-0.69). 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 [93]. In 2005 it was reported that there were 109 primary care physicians per 100 000 individuals [175] although 25.1% of the Quebec residents did not have a primary care physician. [175]

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. [47]

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. [9, 18, 26] 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, [161] Horsburgh, [35] and Menzies. [42] Parsyan et al., on a study conducted in 2 621 patients seen at the Boston Public Health Commission

tuberculosis clinic, [160] 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. [47] 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 in the case of a systematic review of US and Canadian studies (50%-60%). [37] 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 [35] 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. [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. [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) [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. [49, 179] Nonetheless, this proxy measure is relatively accurate despite the tendency to overestimate the actual completion rate and there is no "gold standard". [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, [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, [101, 118] but this is also problematic in large populations measured over ten years. [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. [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. [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, [184-188] or multiple conditions. [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

1. Ziv E, Daley CL, Blower SM. Early therapy for latent tuberculosis infection. American Journal of Epidemiology. 2001 Feb 15;153(4):381-5.
2. The World Health Report 2002: Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization2002.
3. Murray CJL, A.D. . The Global Burden of Disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020. Cambridge, MA: Harvard School of Public Health1996.
4. Fontela PS, Pant Pai N, Schiller I, Dendukuri N, Ramsay A, Pai M. Quality and reporting of diagnostic accuracy studies in TB, HIV and malaria: evaluation using QUADAS and STARD standards. PLoS One. 2009;4(11):e7753.
5. World malaria report 2008. Geneva: World Health Organization2008.
6. Global tuberculosis Control 2008: Surveillance, planning, financing. Geneva: World Health Organization2008.
7. Report on the global AIDS epidemic. Geneva: Joint United Nations Programme on HIV/AIDS2008.
8. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA. 1999 Aug 18;282(7):677-86.
9. Nguyen Dai DM, D. Diagnosis and Treatment of Tuberculosis Infection. The Canadian Journal of CME. 2001:9.
10. Dye C, Watt CJ, Bleed DM, Hosseini SM, Raviglione MC. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. JAMA. 2005 Jun 8;293(22):2767-75.
11. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. MMWR Recomm Rep. 2010 Jun 25;59(RR-5):1-25.
12. Global Tuberculosis Control 2010. Geneva: World Health Organization2010.
13. Ioachimescu OT, J.W. . Tuberculosis. Disease Mnagement Project [serial on the Internet]. 2010.

14. The Global Plan To Stop TB 2011-2015. Transforming the Fight. Towards Elimination of Tuberculosis. Geneva: World Health Organization2010.

15. Lung Disease Data: 2008: Amarican Lung Association2008.

16. Horsburgh CR, Jr. Priorities for the treatment of latent tuberculosis infection in the United States. New England Journal of Medicine. 2004 May 13;350(20):2060-7.

17. Kornfeld H. An ounce of tuberculosis prevention. Chest. 2008 Apr;133(4):835-6.

18. Hauck FR, Neese BH, Panchal AS, El-Amin W. Identification and management of latent tuberculosis infection. American Family Physician. 2009 May 15;79(10):879-86.

19. Dolin PJ, Raviglione MC, Kochi A. Global tuberculosis incidence and mortality during 1990-2000. Bull World Health Organ. 1994;72(2):213-20.

20. Chin DP, DeRiemer K, Small PM, de Leon AP, Steinhart R, Schecter GF, et al. Differences in contributing factors to tuberculosis incidence in U.S. -born and foreign-born persons. Am J Respir Crit Care Med. 1998 Dec;158(6):1797-803.

21. Schwartzman K. Latent tuberculosis infection: old problem, new priorities. CMAJ. 2002 Mar 19;166(6):759-61.

22. Tuberculosis elimination revisited: obstacles, opportunities, and a renewed commitment. Advisory Council for the Elimination of Tuberculosis (ACET). MMWR Recomm Rep. 1999 Aug 13;48(RR-9):1-13.

23. Geiter L. Ending Neglect: The Elimination of Tuberculosis in the United States. Washington DC: National Academy Press. Institute of Medicine2000.

24. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. Int J Tuberc Lung Dis. 1999 Oct;3(10 Suppl 2):S231-79.

25. Latent Tuberculosis Infection. 2011 [updated May 19, 2011; cited 2010 September 28]; Available from: http://en.wikipedia.org/wiki/Latent_tuberculosis.

26. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. Morbidity & Mortality Weekly Report Recommendations & Reports. 2000 Jun 9;49(RR-6):1-51.

27. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. N Engl J Med. 2002 Dec 5;347(23):1860-6.

28. Gantz NMB, R.B.; Berk, S.L. ; Esposito, A.L.; Gleckman, R.A. Manual of Clinical Problems in Infectious Diseases 5th ed: Lippincott Williams and Wilkins (LWW); 2005.
29. Tuberculosis. Information for Health Care Providers. Toronto, Ontario: The Lung Association. Ontario Thoracic Society. Ontario respiratory Care Society2009.
30. Wilkinson D. Drugs for preventing tuberculosis in HIV infected persons. Cochrane Database Syst Rev. 2000(4):CD000171.
31. Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev. 2004(1):CD000171.
32. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? International Journal of Tuberculosis & Lung Disease. 1999 Oct;3(10):847-50.
33. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America. (IDSA), September 1999, and the sections of this statement. American Journal of Respiratory & Critical Care Medicine. 2000 Apr;161(4 Pt 2):S221-47.
34. A strategic plan for the elimination of tuberculosis in the United States. MMWR Morb Mortal Wkly Rep. 1989 Apr 28;38(16):269-72.
35. Horsburgh CR, Jr., Goldberg S, Bethel J, Chen S, Colson PW, Hirsch-Moverman Y, et al. Latent TB infection treatment acceptance and completion in the United States and Canada. Chest. 2010 Feb;137(2):401-9.
36. Addington WW. Patient compliance: the most serious remaining problem in the control of tuberculosis in the United States. Chest. 1979 Dec;76(6 Suppl):741-3.
37. Hirsch-Moverman Y, Daftary A, Franks J, Colson PW. Adherence to treatment for latent tuberculosis infection: systematic review of studies in the US and Canada. Int J Tuberc Lung Dis. 2008 Nov;12(11):1235-54.
38. Kominski GF, Varon SF, Morisky DE, Malotte CK, Ebin VJ, Coly A, et al. Costs and cost-effectiveness of adolescent compliance with treatment for latent tuberculosis

infection: results from a randomized trial. Journal of Adolescent Health. 2007 Jan;40(1):61-8.

39. Nyamathi AM, Christiani A, Nahid P, Gregerson P, Leake B. A randomized controlled trial of two treatment programs for homeless adults with latent tuberculosis infection. International Journal of Tuberculosis & Lung Disease. 2006 Jul;10(7):775-82.

40. Tulsky JP, Hahn JA, Long HL, Chambers DB, Robertson MJ, Chesney MA, et al. Can the poor adhere? Incentives for adherence to TB prevention in homeless adults. International Journal of Tuberculosis & Lung Disease. 2004 Jan;8(1):83-91.

41. LoBue PA, Moser KS. Use of isoniazid for latent tuberculosis infection in a public health clinic. Am J Respir Crit Care Med. 2003 Aug 15;168(4):443-7.

42. Menzies D, Dion MJ, Francis D, Parisien I, Rocher I, Mannix S, et al. In closely monitored patients, adherence in the first month predicts completion of therapy for latent tuberculosis infection. Int J Tuberc Lung Dis. 2005 Dec;9(12):1343-8.

43. Sabate E. Adherence to Long-Term Therapies. Evidence for action. Geneva: World Health Organization2003.

44. Lewin SA, Skea ZC, Entwistle V, Zwarenstein M, Dick J. Interventions for providers to promote a patient-centred approach in clinical consultations. Cochrane Database Syst Rev. 2001(4):CD003267.

45. Sumartojo E. When tuberculosis treatment fails. A social behavioral account of patient adherence. Am Rev Respir Dis. 1993 May;147(5):1311-20.

46. Wobeser W, To T, Hoeppner VH. The outcome of chemoprophylaxis on tuberculosis prevention in the Canadian Plains Indian. Clin Invest Med. 1989 Jun;12(3):149-53.

47. Canadian Tuberculosis Standards- 5th Edition: Canadian Lung Association/Canadian Thoracic Society and Tuberculosis Prevention and Control, Centre for Infectious Diseases Prevention and Control, Health Canada2000

48. Guidelines for preventing the transmission of tuberculosis in Canadian Health Care Facilities and other institutional settings. Can Commun Dis Rep. 1996 Apr;22 Suppl 1:i-iv, 1-50, i-iv, 1-5.

49. Smith BM, Schwartzman K, Bartlett G, Menzies D. Adverse events associated with treatment of latent tuberculosis in the general population. CMAJ. 2011 Feb 22;183(3):E173-9.
50. Donaldson MSY, K.D.; Lohr, K.N.; Vanselow, N.A. . Primary Care: America's Health in a New Era. Washington, DC: The National Academy press; 1996.
51. Stange KC, Jaen CR, Flocke SA, Miller WL, Crabtree BF, Zyzanski SJ. The value of a family physician. Journal of Family Practice. 1998 May;46(5):363-8.
52. Larson EB, Yao X. Clinical empathy as emotional labor in the patient-physician relationship. JAMA. 2005 Mar 2;293(9):1100-6.
53. Rothman AA, Wagner EH. Chronic illness management: what is the role of primary care? Annals of Internal Medicine. 2003 Feb 4;138(3):256-61.
54. Hauck FR, Panchal AS. Latent tuberculosis infection: the physician's role in tuberculosis control. Am Fam Physician. 2009 May 15;79(10):845-6.
55. Teruel F, Castilla J, Hueto J. [Dealing with tuberculosis in primary care. Contact tracing procedures]. An Sist Sanit Navar. 2007;30 Suppl 2:87-98.

56. Latent Tuberculosis Infection: A Guide For Primary Health Providers. Atlanta, Georgia: U.S. Department of Health and Human Services. Centers for Disease Control and Prevention. National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Division of Tuberculosis Elimination2010.
57. Greenaway C, Sandoe A, Vissandjee B, Kitai I, Gruner D, Wobeser W, et al. Tuberculosis: evidence review for newly arriving immigrants and refugees. CMAJ. 2010 Jul 15.
58. Young DB, Gideon HP, Wilkinson RJ. Eliminating latent tuberculosis. Trends in Microbiology. 2009 May;17(5):183-8.
59. Whalen CC. Diagnosis of latent tuberculosis infection: measure for measure. JAMA. 2005 Jun 8;293(22):2785-7.
60. Taylor Z, Nolan CM, Blumberg HM, American Thoracic S, Centers for Disease C, Prevention, et al. Controlling tuberculosis in the United States. Recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America.[Erratum appears in MMWR Morb Mortal Wkly Rep. 2005 Nov

18;54(45):1161]. Morbidity & Mortality Weekly Report Recommendations & Reports. 2005 Nov 4;54(RR-12):1-81.

61. Rivest P, Tannenbaum T, Bedard L. Epidemiology of tuberculosis in Montreal. CMAJ Canadian Medical Association Journal. 1998 Mar 10;158(5):605-9.

62. Goldberg SV, Wallace J, Jackson JC, Chaulk CP, Nolan CM. Cultural case management of latent tuberculosis infection. Int J Tuberc Lung Dis. 2004 Jan;8(1):76-82.

63. Bock NN, Metzger BS, Tapia JR, Blumberg HM. A tuberculin screening and isoniazid preventive therapy program in an inner-city population. American Journal of Respiratory & Critical Care Medicine. 1999 Jan;159(1):295-300.

64. Shieh FK, Snyder G, Horsburgh CR, Bernardo J, Murphy C, Saukkonen JJ. Predicting non-completion of treatment for latent tuberculous infection: a prospective survey. Am J Respir Crit Care Med. 2006 Sep 15;174(6):717-21.

65. Kwara A, Herold JS, Machan JT, Carter EJ. Factors associated with failure to complete isoniazid treatment for latent tuberculosis infection in Rhode Island. Chest. 2008 Apr;133(4):862-8.

66. Global Tuberculosis Control 2002: Surveillance, Planning, Financing. Geneva: World Health Organization2002.

67. Fox W. The problem of self-administration of drugs; with particular reference to pulmonary tuberculosis. Tubercle. 1958 Oct;39(5):269-74.

68. Respiratory Disease in Canada. Ottawa: Canadian Institute for Health Information, Canadian Lung Association, Health Canada, Statistics Canada2001.

69. Agrawal S, Thomas NS, Dhanikula AB, Kaul CL, Panchagnula R. Antituberculosis drugs and new drug development. Current Opinion in Pulmonary Medicine. 2001 May;7(3):142-7.

70. TB: A Global Emergency. WHO Report on the TB Epidemic. Geneva: World Health Organization1994.

71. Ziganshina LE, Garner P. Tuberculosis (HIV-negative people). Clin Evid (Online). 2009;2009.

72. Global Tuberculosis Control 2009: Epidemiology, Strategy, Financing. Geneva: World Health Organization2009.

73. Sudre P, ten Dam G, Kochi A. Tuberculosis: a global overview of the situation today. Bull World Health Organ. 1992;70(2):149-59.
74. Dye C. Tuberculosis 2000-2010: control, but not elimination. Int J Tuberc Lung Dis. 2000 Dec;4(12 Suppl 2):S146-52.
75. Grange JM, Zumla A. Paradox of the global emergency of tuberculosis. Lancet. 1999 Mar 20;353(9157):996.
76. Long R, Njoo H, Hershfield E. Tuberculosis: 3. Epidemiology of the disease in Canada. CMAJ Canadian Medical Association Journal. 1999 Apr 20;160(8):1185-90.
77. Tuberculosis in Canada 2006. Pre-Release. Ottawa: Tuberculosis Prevention and Control. Community Acquired Infections Division. Public Health Agency of Canada2007.
78. Tuberculosis in Canada 2004. Ottawa: Tuberculosis Prevention and Control. Community Acquired Infections Division. Centre for Communicable Diseases and Infection Control. Public Health Agency of Canada2007.
79. Tuberculosis in Canada 2000: executive summary. Can Commun Dis Rep. 2003 Jan 15;29(2):9-10.
80. Gaudette LA, Ellis E. Tuberculosis in Canada: a focal disease requiring distinct control strategies for different risk groups. Tuber Lung Dis. 1993 Aug;74(4):244-53.
81. Wagner EH, Austin BT, Davis C, Hindmarsh M, Schaefer J, Bonomi A. Improving chronic illness care: translating evidence into action. Health Aff (Millwood). 2001 Nov-Dec;20(6):64-78.
82. Schwartzman K, editor. Epidemiology of Tuberculosis: Global and Local. McGill Tuberculosis Course; 2010 November 26; Montreal. http://www.teachepi.org/documents/courses/mtltbcourse/2010/Schwartzman_Epidemiology.pdf
83. Cook VJ, Kuramoto L, Noertjojo K, Elwood RK, Fitzgerald JM. BCG vaccination and the prevalence of latent tuberculosis infection in an aboriginal population. Int J Tuberc Lung Dis. 2006 Dec;10(12):1347-53.
84. Canadian Tuberculosis Standards-6th Edition: Canadian Lung Association/Canadian Thoracic Society and Tuberculosis Prevention and Control, Centre for Infectious Diseases Prevention and Control, Health Canada2007.

85. Rivest P. Comite Quebecois de la Surveillance de la Tuberculose. Epidemiologie de la tuberculose au Québec de 2004 á 2007. Sante Public. Montreal: Direction de santé publique de l'Agence de la santé et des services sociaux de Montréal. Ministere de la Sante et de Services Sociaux Quebec2009.

86. Nguyen D, Proulx JF, Westley J, Thibert L, Dery S, Behr MA. Tuberculosis in the Inuit community of Quebec, Canada. Am J Respir Crit Care Med. 2003 Dec 1;168(11):1353-7.

87. Daniel TMB, W.H.; Ellner, J.J. Immunology of Tuberculosis. In: Reichman LBH, E.S., editor. Tuberculosis: a comprehensive international approach. 2nd ed. New York: Dekker; 2000. p. 27.

88. Piessens WFN, E.A. Pathogenesis of Tuberculosis. In: Reichman LBH, E.S., editor. Tuberculosis: a comprehensive international approach
2nd ed. New York: Dekker; 2000. p. 19.

89. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. American Journal of Respiratory & Critical Care Medicine. 2000 Apr;161(4 Pt 1):1376-95.

90. Huebner RE, Schein MF, Bass JB, Jr. The tuberculin skin test. Clin Infect Dis. 1993 Dec;17(6):968-75.

91. Menzies RI. Tuberculin skin testing. In: Reichman LBH, E.S., editor. Tuberculosis: a comprehensive international approach. 2nd ed. New York: Dekker; 2000. p. 43.

92. Slutkin G, Perez-Stable EJ, Hopewell PC. Time course and boosting of tuberculin reactions in nursing home residents. Am Rev Respir Dis. 1986 Nov;134(5):1048-51.

93. Health Personnel Trends in Canada 1995-2004- Health Personnel Database. Ottawa: Canadian Institute for Health Information2006.

94. Holden M, Dubin MR, Diamond PH. Frequency of negative intermediate-strength tuberculin sensitivity in patients with active tuberculosis. N Engl J Med. 1971 Dec 30;285(27):1506-9.
95. Nash DR, Douglass JE. Anergy in active pulmonary tuberculosis. A comparison between positive and negative reactors and an evaluation of 5 TU and 250 TU skin test doses. Chest. 1980 Jan;77(1):32-7.
96. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. Am J Epidemiol. 1974 Feb;99(2):131-8.
97. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. Bibl Tuberc. 1970;26:28-106.
98. Whalen CC, Johnson JL, Okwera A, Hom DL, Huebner R, Mugyenyi P, et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. Uganda-Case Western Reserve University Research Collaboration. New England Journal of Medicine. 1997 Sep 18;337(12):801-8.
99. McElroy PD, Ijaz K, Lambert LA, Jereb JA, Iademarco MF, Castro KG, et al. National survey to measure rates of liver injury, hospitalization, and death associated with rifampin and pyrazinamide for latent tuberculosis infection. Clin Infect Dis. 2005 Oct 15;41(8):1125-33.
100. Forget EJ, Menzies D. Adverse reactions to first-line antituberculosis drugs. Expert Opinion on Drug Safety. 2006 Mar;5(2):231-49.
101. Eidlitz-Markus T, Zeharia A, Baum G, Mimouni M, Amir J. Use of the urine color test to monitor compliance with isoniazid treatment of latent tuberculosis infection. Chest. 2003 Mar;123(3):736-9.
102. Urquhart J. Patient non-compliance with drug regimens: measurement, clinical correlates, economic impact. Eur Heart J. 1996 Mar;17 Suppl A:8-15.
103. Farmer KC. Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clin Ther. 1999 Jun;21(6):1074-90; discussion 3.
104. Sackett DL, Haynes RB, Gibson ES, Taylor DW, Roberts RS, Johnson AL. Patient compliance with antihypertensive regimens. Patient Couns Health Educ. 1978 1st

Quart;1(1):18-21.
105. Reid D, Abramson M, Raven J, Walters HE. Management and treatment perceptions among young adults with asthma in Melbourne: the Australian experience from the European Community Respiratory Health Survey. Respirology. 2000 Sep;5(3):281-7.
106. Critical overview of antihypertensive therapies: what is preventing us from getting there? Based on a presentation by Mark A. Munger, PharmD. Am J Manag Care. 2000 Mar;6(4 Suppl):S211-21.
107. Markowitz AJ, Winawer SJ. Screening and surveillance for colorectal cancer. Semin Oncol. 1999 Oct;26(5):485-98.
108. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000 Jul 24;160(14):2101-7.
109. DiMatteo MR. Enhancing patient adherence to medical recommendations. JAMA. 1994 Jan 5;271(1):79, 83.
110. DiMatteo MRD, D.D. Achieving patient compliance. Elmsford, New York: Press Inc; 1982.
111. Epstein LH, Cluss PA. A behavioral medicine perspective on adherence to long-term medical regimens. J Consult Clin Psychol. 1982 Dec;50(6):950-71.
112. Lin EH, Von Korff M, Katon W, Bush T, Simon GE, Walker E, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. Med Care. 1995 Jan;33(1):67-74.
113. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev. 2002(2):CD000011.
114. Rybacki JJ. Improving cardiovascular health in postmenopausal women by addressing medication adherence issues. J Am Pharm Assoc (Wash). 2002 Jan-Feb;42(1):63-71; quiz 2-3.
115. Dunbar-Jacob J, Erlen JA, Schlenk EA, Ryan CM, Sereika SM, Doswell WM. Adherence in chronic disease. Annu Rev Nurs Res. 2000;18:48-90.
116. Demyttenaere K. Noncompliance with antidepressants: who's to blame? Int Clin

Psychopharmacol. 1998 Feb;13 Suppl 2:S19-25.
117. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatr Serv. 1998 Feb;49(2):196-201.
118. Stephenson BJ, Rowe BH, Haynes RB, Macharia WM, Leon G. The rational clinical examination. Is this patient taking the treatment as prescribed? JAMA. 1993 Jun 2;269(21):2779-81.
119. Stein MD, Rich JD, Maksad J, Chen MH, Hu P, Sobota M, et al. Adherence to antiretroviral therapy among HIV-infected methadone patients: effect of ongoing illicit drug use. Am J Drug Alcohol Abuse. 2000 May;26(2):195-205.
120. Laine C, Newschaffer CJ, Zhang D, Cosler L, Hauck WW, Turner BJ. Adherence to antiretroviral therapy by pregnant women infected with human immunodeficiency virus: a pharmacy claims-based analysis. Obstet Gynecol. 2000 Feb;95(2):167-73.
121. Bedell SE, Jabbour S, Goldberg R, Glaser H, Gobble S, Young-Xu Y, et al. Discrepancies in the use of medications: their extent and predictors in an outpatient practice. Arch Intern Med. 2000 Jul 24;160(14):2129-34.
122. Lerner BH, Gulick RM, Dubler NN. Rethinking nonadherence: historical perspectives on triple-drug therapy for HIV disease. Ann Intern Med. 1998 Oct 1;129(7):573-8.
123. Miaskowski C, Dodd MJ, West C, Paul SM, Tripathy D, Koo P, et al. Lack of adherence with the analgesic regimen: a significant barrier to effective cancer pain management. J Clin Oncol. 2001 Dec 1;19(23):4275-9.
124. Du Pen SL, Du Pen AR, Polissar N, Hansberry J, Kraybill BM, Stillman M, et al. Implementing guidelines for cancer pain management: results of a randomized controlled clinical trial. J Clin Oncol. 1999 Jan;17(1):361-70.
125. Ward SE, Goldberg N, Miller-McCauley V, Mueller C, Nolan A, Pawlik-Plank D, et al. Patient-related barriers to management of cancer pain. Pain. 1993 Mar;52(3):319-24.
126. Hargrave R, Remler MP. Noncompliance. J Natl Med Assoc. 1996 Jan;88(1):7, 11.
127. Kiortsis DN, Giral P, Bruckert E, Turpin G. Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients. J Clin Pharm Ther.

2000 Dec;25(6):445-51.
128. Andrade SE, Walker AM, Gottlieb LK, Hollenberg NK, Testa MA, Saperia GM, et al. Discontinuation of antihyperlipidemic drugs--do rates reported in clinical trials reflect rates in primary care settings? N Engl J Med. 1995 Apr 27;332(17):1125-31.
129. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995 Nov 16;333(20):1301-7.
130. Joshi N, Milfred D. The use and misuse of new antibiotics. A perspective. Arch Intern Med. 1995 Mar 27;155(6):569-77.
131. Sanson-Fisher R, Bowman J, Armstrong S. Factors affecting nonadherence with antibiotics. Diagn Microbiol Infect Dis. 1992 May-Jun;15(4 Suppl):103S-9S.
132. Haynes RBW, D.T.; Sackett, D.L. Compliance in health care. Baltimore: Johns Hopkins University Press; 1979.
133. Murphy LM, Thompson RJ, Jr., Morris MA. Adherence behavior among adolescents with type I insulin-dependent diabetes mellitus: the role of cognitive appraisal processes. J Pediatr Psychol. 1997 Dec;22(6):811-25.
134. Schectman G, Hiatt J, Hartz A. Evaluation of the effectiveness of lipid-lowering therapy (bile acid sequestrants, niacin, psyllium and lovastatin) for treating hypercholesterolemia in veterans. Am J Cardiol. 1993 Apr 1;71(10):759-65.
135. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986 Jan;24(1):67-74.
136. Rovelli M, Palmeri D, Vossler E, Bartus S, Hull D, Schweizer R. Noncompliance in organ transplant recipients. Transplant Proc. 1989 Feb;21(1 Pt 1):833-4.
137. Langley J, Ellis E, Deeks S. Statement on Bacille Calmette Guerin (BCG) vaccine. Can Commun Dis Rep. 2004 Dec 1;30:1-11.
138. Wyss LLA, Alderman MK. Using Theory to Interpret Beliefs in Migrants Diagnosed with Latent TB. The Online Journal of Issues in Nursing. 2006 January 07;12.
139. Coreil J, Lauzardo M, Heurtelou M. Cultural feasibility assessment of tuberculosis prevention among persons of Haitian origin in South Florida. J Immigr Health. 2004 Apr;6(2):63-9.

140. Ailinger RL, Dear MR. Adherence to tuberculosis preventive therapy among Latino immigrants. Public Health Nurs. 1998 Feb;15(1):19-24.
141. Pang SC, Harrison RH, Brearley J, Jegathesan V, Clayton AS. Preventive therapy for tuberculosis in Western Australia. Int J Tuberc Lung Dis. 1998 Dec;2(12):984-8.
142. Lavigne M, Rocher I, Steensma C, Brassard P. The impact of smoking on adherence to treatment for latent tuberculosis infection. BMC Public Health. 2006;6:66.
143. Tulsky JP, Hahn JA, Long HL, Chambers DB, Robertson MJ, Chesney MA, et al. Can the poor adhere? Incentives for adherence to TB prevention in homeless adults. International Journal of Tuberculosis & Lung Disease. 2004 Jan;8(1):83-91.
144. Gilroy SA, Rogers MA, Blair DC. Treatment of latent tuberculosis infection in patients aged > or =35 years. Clinical Infectious Diseases. 2000 Sep;31(3):826-9.
145. Nolan CM, Roll L, Goldberg SV, Elarth AM. Directly observed isoniazid preventive therapy for released jail inmates. American Journal of Respiratory & Critical Care Medicine. 1997 Feb;155(2):583-6.
146. Kohn MR, Arden MR, Vasilakis J, Shenker IR. Directly observed preventive therapy. Turning the tide against tuberculosis. Arch Pediatr Adolesc Med. 1996 Jul;150(7):727-9.
147. Ailinger RL, Black P, Nguyen N, Lasus H. Predictors of adherence to latent tuberculosis infection therapy in Latino immigrants. J Community Health Nurs. 2007 Fall;24(3):191-8.
148. Young H, Wessolossky M, Ellis J, Kaminski M, Daly JS. A retrospective evaluation of completion rates, total cost, and adverse effects for treatment of latent tuberculosis infection in a public health clinic in central massachusetts. Clin Infect Dis. 2009 Aug 1;49(3):424-7.
149. Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI). Practice Guidance from the Washington TB Advisory Council. [Power Point Presentation]. In press.
150. Sablan B. An update on primary care management for tuberculosis in children. Curr Opin Pediatr. 2009 Dec;21(6):801-4.
151. Interventions to improve adherence to medical regimens in the elderly. Washington, DC: Center for the Advancement of Health, National Institute on

Aging1999.
152. Caron HS, Roth HP. Patients' cooperation with a medical regimen. Difficulties in identifying the noncooperator. JAMA. 1968 Mar 11;203(11):922-6.
153. Brown VJ. The association of concordance between physician and patient medical concepts and patient satisfaction, compliance and medical outcomes. Humanities and Social Sciences. 1994;54.
154. Horne R. Patients' beliefs about treatment: the hidden determinant of treatment outcome? J Psychosom Res. 1999 Dec;47(6):491-5.
155. Morisky DE, Malotte CK, Choi P, Davidson P, Rigler S, Sugland B, et al. A patient education program to improve adherence rates with antituberculosis drug regimens. Health Educ Q. 1990 Fall;17(3):253-67.
156. Cuneo WD, Snider DE, Jr. Enhancing patient compliance with tuberculosis therapy. Clin Chest Med. 1989 Sep;10(3):375-80.
157. Malotte CK, Hollingshead JR, Larro M. Incentives vs outreach workers for latent tuberculosis treatment in drug users. Am J Prev Med. 2001 Feb;20(2):103-7.
158. Chan ED, Iseman MD. Current medical treatment for tuberculosis. BMJ. 2002 Nov 30;325(7375):1282-6.
159. Trajman A, Long R, Zylberberg D, Dion MJ, Al-Otaibi B, Menzies D. Factors associated with treatment adherence in a randomised trial of latent tuberculosis infection treatment. Int J Tuberc Lung Dis. 2010 May;14(5):551-9.
160. Parsyan AE, Saukkonen J, Barry MA, Sharnprapai S, Horsburgh CR, Jr. Predictors of failure to complete treatment for latent tuberculosis infection. J Infect. 2007 Mar;54(3):262-6.
161. Rennie TW, Bothamley GH, Engova D, Bates IP. Patient choice promotes adherence in preventive treatment for latent tuberculosis. Eur Respir J. 2007 Oct;30(4):728-35.
162. Besch CL. Compliance in clinical trials. AIDS. 1995 Jan;9(1):1-10.
163. Mushlin AI, Appel FA. Diagnosing potential noncompliance. Physicians' ability in a behavioral dimension of medical care. Arch Intern Med. 1977 Mar;137(3):318-21.
164. Caron HS, Roth HP. Patients' cooperation with a medical regimen. Difficulties in identifying the noncooperator. JAMA. 1968 Mar 11;203(11):922-6.

165. Davis MS. Predicting non-compliant behavior. J Health Soc Behav. 1967 Dec;8(4):265-71.
166. Ailinger RL, Martyn D, Lasus H, Lima Garcia N. The effect of a cultural intervention on adherence to latent tuberculosis infection therapy in latino immigrants. Public Health Nurs. 2010 Mar;27(2):115-20.
167. Sbarbaro JA. The patient-physician relationship: compliance revisited. Ann Allergy. 1990 Apr;64(4):325-31.
168. A double-blind placebo-controlled clinical trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. Am Rev Respir Dis. 1992 Jan;145(1):36-41.
169. Gordin F, Chaisson RE, Matts JP, Miller C, de Lourdes Garcia M, Hafner R, et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons: an international randomized trial. Terry Beirn Community Programs for Clinical Research on AIDS, the Adult AIDS Clinical Trials Group, the Pan American Health Organization, and the Centers for Disease Control and Prevention Study Group. JAMA. 2000 Mar 15;283(11):1445-50.
170. Control CfD. Core Curriculum on Tuberculosis. In: Washington Uo, editor. Treatment of Latent TB Infection (LTBI). Washington: University of Washington; 2000.
171. Rosser WEM, R; . Canadian Family Medicine Submission to the Canadian Institutes of Health Research Initiative from the Chairs of the Departments of Family Medicine of Canada and the College OF Family Physicians of Canada (CFPC)2005 April 22.
172. Cayla JA, Rodrigo T, Ruiz-Manzano J, Caminero JA, Vidal R, Garcia JM, et al. Tuberculosis treatment adherence and fatality in Spain. Respir Res. 2009;10:121.
173. Wilson EB. Probable Inference, the Law of Succession, and Statistical Inference. Journal of the American Statistical Association, 22, 209-212 (1927). 1927(22):4.
174. Liang KYZ, S.L. Longitudinal data analysis using generalized linear models. Biometrika 1986;73(1):10.
175. Gladu FP. Perceived shortage of family doctors in Quebec: can we do something about it? Can Fam Physician. 2007 Nov;53(11):1858-60, 71-3.

176. Zeppetella G. How do terminally ill patients at home take their medication? Palliat Med. 1999 Nov;13(6):469-75.
177. Miller E, Blatman B, Einarson TR. A survey of population-based drug databases in Canada. CMAJ. 1996 Jun 15;154(12):1855-64.
178. Tamblyn R, Lavoie G, Petrella L, Monette J. The use of prescription claims databases in pharmacoepidemiological research: the accuracy and comprehensiveness of the prescription claims database in Quebec. J Clin Epidemiol. 1995 Aug;48(8):999-1009.
179. Bartlett G, Abrahamowicz M, Tamblyn R, Grad R, Capek R, du Berger R. Longitudinal patterns of new Benzodiazepine use in the elderly. Pharmacoepidemiol Drug Saf. 2004 Oct;13(10):669-82.
180. Timmreck TC, Randolph JF. Smoking cessation: clinical steps to improve compliance. Geriatrics. 1993 Apr;48(4):63-6, 9-70.
181. Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. Am J Hosp Pharm. 1991 Sep;48(9):1978-88.
182. Ayanian JZ. Using administrative data to assess health care outcomes. Eur Heart J. 1999 Dec;20(23):1689-91.
183. Tu K, Campbell NR, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. Open Med. 2007;1(1):e18-26.
184. Newschaffer CJ, Bush TL, Penberthy LT. Comorbidity measurement in elderly female breast cancer patients with administrative and medical records data. J Clin Epidemiol. 1997 Jun;50(6):725-33.
185. Cleves MA, Sanchez N, Draheim M. Evaluation of two competing methods for calculating Charlson's comorbidity index when analyzing short-term mortality using administrative data. J Clin Epidemiol. 1997 Aug;50(8):903-8.
186. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol. 1993 Oct;46(10):1075-9; discussion 81-90.
187. Humphries KH, Rankin JM, Carere RG, Buller CE, Kiely FM, Spinelli JJ. Co-morbidity data in outcomes research: are clinical data derived from administrative databases a reliable alternative to chart review? Journal of Clinical Epidemiology. 2000

Apr;53(4):343-9.

188. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992 Jun;45(6):613-9.

189. Levy AR, Tamblyn RM, Fitchett D, McLeod PJ, Hanley JA. Coding accuracy of hospital discharge data for elderly survivors of myocardial infarction. Can J Cardiol. 1999 Nov;15(11):1277-82.

11. Tables and Figures

Figure 1 - Study cohort conformation

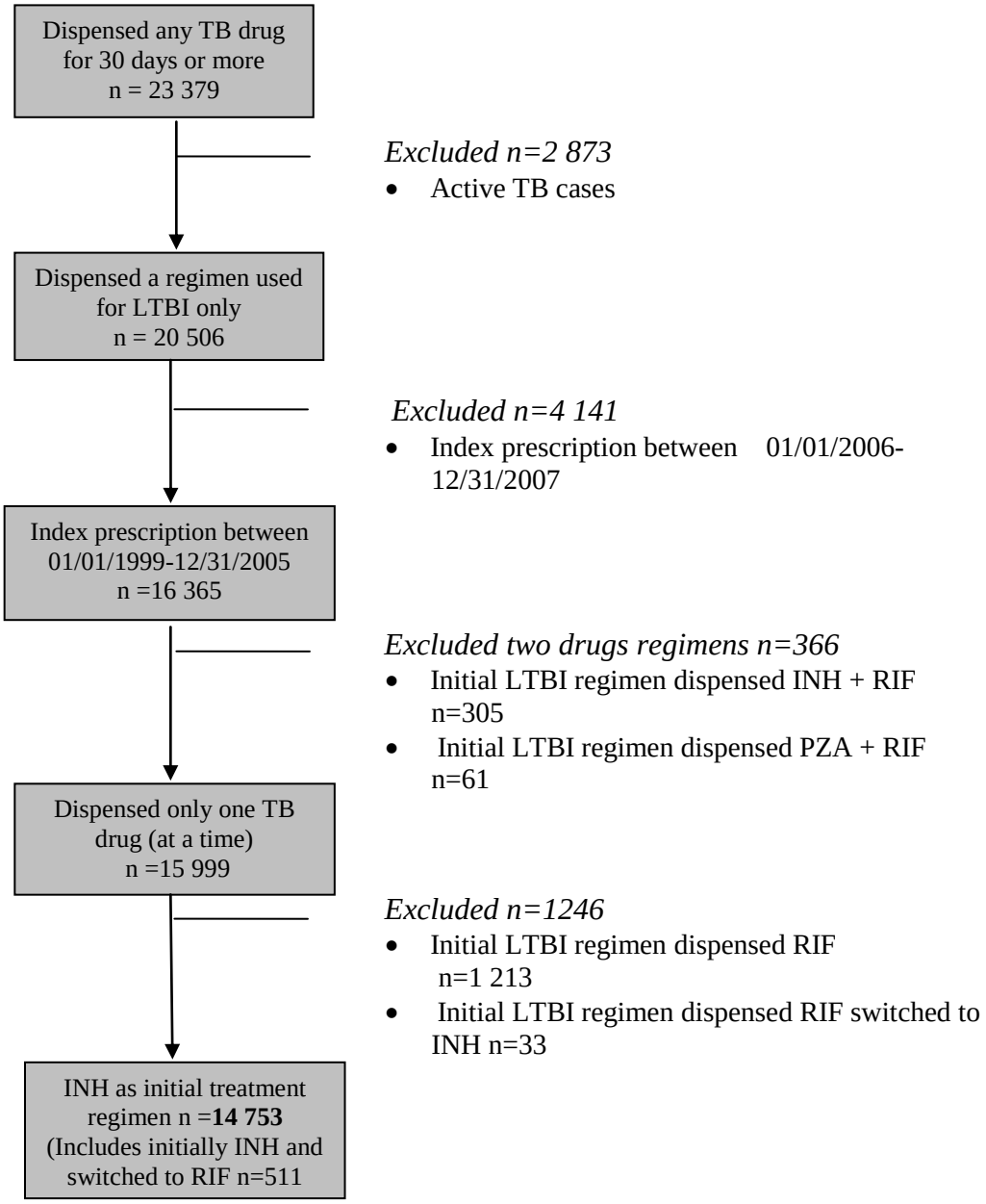


Table 1 - RAMQ Databases and Type of Information Included

Type of database	Primary Use	Data Variables
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

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

Table 2A - Baseline characteristics

	mean	SD
Number of hospitalizations within 1 year after index	0.1	0.3
Number of hospitalizations within 30 days before index	0.03	0.2
Length of hospitalizations within 1 year after index	1.5	10.3
Length of hospitalizations within 30 days before index	0.3	1.9
Treatment duration	178.5	98.8
Number of medical visits within 1 year after index	14.5	30.8
Level of education	32.1	24.9

Table 3 - Proportion of LTBI Treatments Initiated by a Primary Care Physician (PC) by year

Year of Initial prescription	PC proportion	95%CI	Total
1998	0.29	(0.26, 0.31)	**1731**
1999	0.28	(0.25, 0.29)	**1722**
2000	0.32	(0.29, 0.33)	**1781**
2001	0.27	(0.25, 0.29)	**1562**
2002	0.28	(0.25, 0.29)	**1914**
2003	0.26	(0.24, 0.27)	**2091**
2004	0.21	(0.19, 0.22)	**1977**
2005	0.21	(0.19, 0.22)	**1975**
Total	**0.26**	**(0.25, 0.27)**	**14753**

Table 4A - Baseline characteristics by prescribing physician specialty

	Primary Care		Others		Total		
	3863	**26.2%**	**10890**	**73.8%**	**14753**	**%**	**p-value**
Age							
1-19	569	14.7%	1933	17.8%	2502	17.0%	<0.0001
20-34	961	24.9%	2486	22.8%	3447	23.4%	0.009
35-49	1163	30.1%	3110	28.6%	4273	29.0%	0.068
50-64	767	19.9%	2101	19.3%	2868	19.4%	0.448
65-79	387	10.0%	1226	11.3%	1613	10.9%	0.033
80+	16	0.4%	34	0.3%	50	0.3%	0.348
Sex (Male)	1620	41.9%	4892	44.9%	6512	44.1%	0.001
Comorbidities identified 2 years before index date							
Diabetes	136	3.5%	377	3.5%	513	3.5%	0.864
HIV/AIDS	41	1.1%	98	0.9%	139	0.9%	0.372
Cancer (Malignant neoplasms)	115	3.0%	353	3.2%	468	3.2%	0.420
Viral Hepatitis (A/B/C)	31	0.8%	61	0.6%	92	0.6%	0.100
Renal Failure	48	1.2%	244	2.2%	292	2.0%	0.0001
Liver Disease	74	1.9%	144	1.3%	218	1.5%	0.008
Substance Abuse (Alcohol/ drugs)	73	1.9%	97	0.9%	170	1.2%	<0.0001
Depression	130	3.4%	315	2.9%	445	3.0%	0.14
Individuals living in census area w/ low level of education	1443	37.4%	2651	24.3%	4094	27.8%	<0.0001
Individuals as above with low income status	1033	26.7%	2789	25.6%	3822	25.9%	0.287
Individuals hospitalized within 1year after index date	324	8.4%	867	8.0%	1191	8.1%	0.404
Individuals hospitalized within 30 days before index date	153	4.0%	258	2.4%	411	2.8%	<0.0001
Individuals w/ a medical visit within 1 year after index date	3515	91.0%	10307	94.6%	13822	93.7%	<0.0001
Total	**3863**	**26.2%**	**10890**	**73.8%**	**14753**		

Table 4B - Baseline characteristics by prescribing physician specialty

	Primary Care		Others		Total		
	mean	SD	mean	SD	mean	SD	p-value
Number of hospitalizations within 1 year after index	0.08	0.3	0.08	0.3	0.1	0.3	0.403
Number of hospitalizations within 30 days before index	0.04	0.2	0.02	0.1	0.03	0.2	<0.0001
Length of (a)	1.5	9.8	1.5	10.5	1.5	10.3	0.84
Length of (b)	0.4	0.4	0.2	0.2	0.3	1.9	<0.0001
Treatment duration	170.9	101.4	181.3	97.8	178.5	98.8	<0.0001
Number of medical visits within 1 year after index	13.1	28.4	15.3	32.4	14.5	30.8	0.0002
Level of education	27.2	23.3	33.7	25.2	32.1	24.9	<0.0001

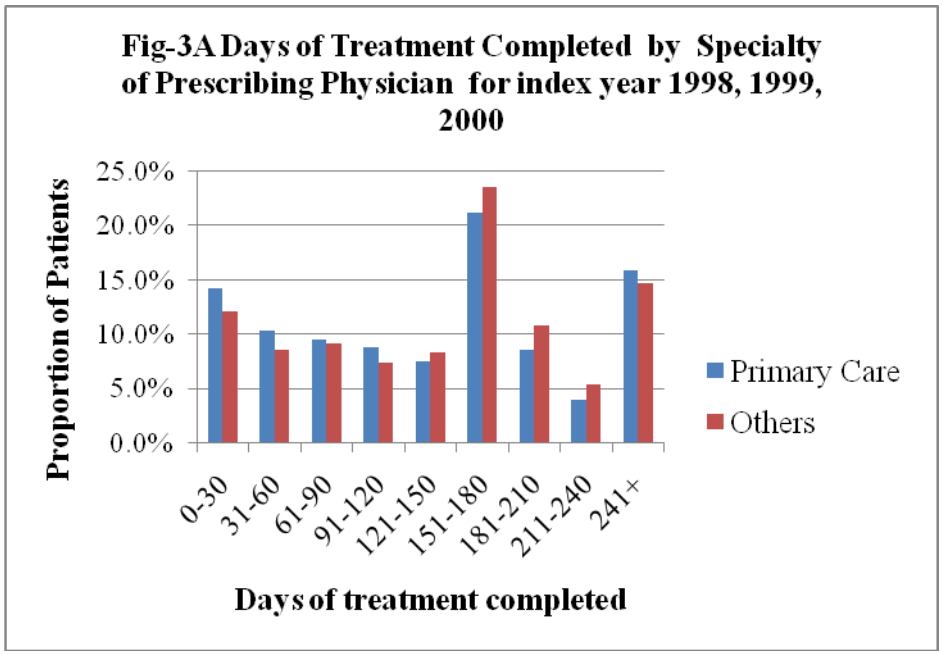
For Tables 2A and 2B- (a) p-values correspond to comparison of patient's baseline characteristics between specialties of prescribing physician. (b) Missing values: 178 for income status and education level

Table 5-Days of Treatment dispensed by Prescribing Physician Specialty

Days	Primary Care		Others		Total		
	n	%	n	%	n	%	p-value[a]
0-30	527	13.6%	1235	11.3%	**1762**	11.9%	0.002
31-60	310	8.0%	878	8.1%	**1188**	8.1%	0.914
61-90	341	8.8%	843	7.7%	**1184**	8.0%	0.032
91-120	296	7.7%	611	5.6%	**907**	6.1%	<0.0001
121-150	251	6.5%	671	6.2%	**922**	6.2%	0.458
151-180	622	16.1%	1467	13.5%	**2089**	14.2%	<0.0001
181-210	307	7.9%	891	8.2%	**1198**	8.1%	0.646
211-240	226	5.9%	830	7.6%	**1056**	7.2%	0.0002
241+	983	25.4%	3464	31.8%	**4447**	30.1%	<0.0001
Total	**3863**	**26.2%**	**10890**	**73.8%**	**14753**		

(a) Corresponds to comparison of days of LTBI treatment dispensed between specialty of prescribing physician

Insert for Figure 3A



Insert for Figure 3B

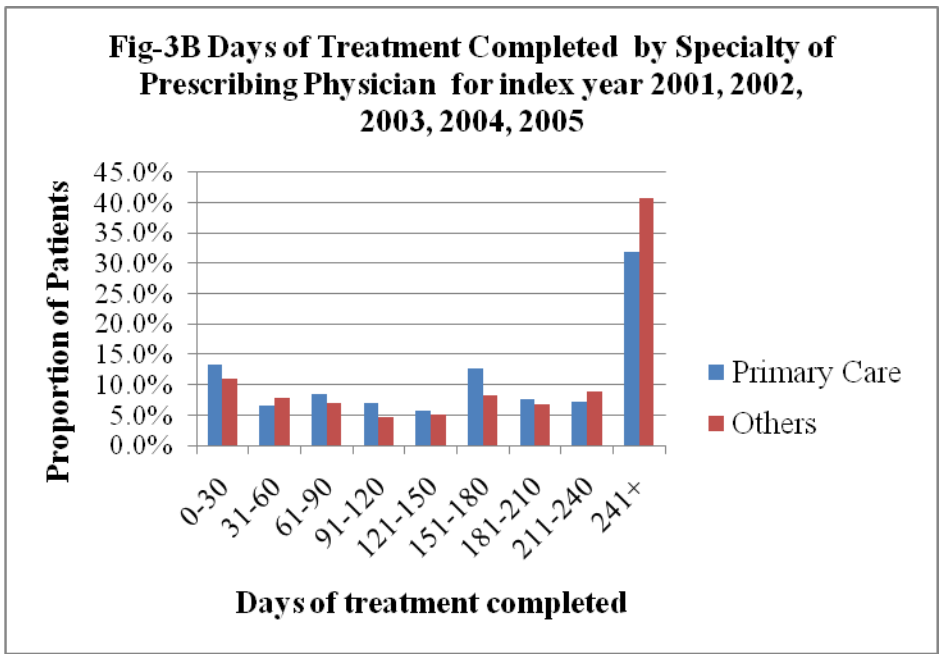


Table 6-Treatment Completion and Specialty of Prescribing Physician

Treatment	Primary Care		Others		Total		
	n	%	n	%	n	%	p-value [a]
Complete	1412	36.6%	4647	42.7%	**6059**	**41.1%**	<0.0001
Did not complete	2451	63.4%	6243	57.3%	**8694**	**58.9%**	
Total	**3863**	**26.2%**	**10890**	**73.8%**	**14753**	**%**	**p-value**

(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

	Primary Care		Others		Total		
	n	%	n	%	n		p-value
Age							
1-19	195	13.8%	803	17.3%	998	16.5%	**0.002**
20-34	342	24.2%	1056	22.7%	1398	23.1%	0.242
35-49	404	28.6%	1285	27.7%	1689	27.9%	0.481
50-64	333	23.6%	1009	21.7%	1342	22.1%	0.138
65-79	134	9.5%	483	10.4%	617	10.2%	0.325
80+	4	0.3%	11	0.2%	15	0.2%	0.095
Sex (Male)	620	43.9%	2157	46.4%	2777	45.8%	0.977
Comorbidities identified 2 years before index date							
Diabetes	53	3.8%	155	3.3%	208	3.4%	0.449
HIV/AIDS	23	1.6%	51	1.1%	74	1.2%	0.111
Cancer (Malignant neoplasms)	29	2.1%	94	2.0%	123	2.0%	0.942
Viral Hepatitis (A/ B/C)	12	0.8%	20	0.4%	32	0.5%	0.057
Renal Failure	17	1.2%	100	2.2%	117	1.9%	0.023
Liver Disease	21	1.5%	55	1.2%	76	1.3%	0.369
Substance Abuse (Alcohol/ drugs)	26	1.8%	40	0.9%	66	1.1%	**0.002**
Depression	50	3.5%	123	2.6%	173	2.9%	**0.007**
Individuals living in census area with low level of education	485	34.3%	1084	23.3%	1569	25.9%	**<0.0001**
Individuals as above with low income status	397	28.1%	1189	25.6%	1586	26.2%	0.058
Individuals hospitalized within 1year after index date	90	6.4%	275	5.9%	365	6.0%	0.528
Individuals hospitalized within 30 days before index date	49	3.5%	92	2.0%	141	2.3%	**0.001**
Individuals w/ a medical visit within 1 year after index date	1294	91.6%	4461	96.0%	5755	95.0%	**<0.0001**
Total	**1412**	**23.3%**	**4647**	**76.7%**	**6059**		

(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

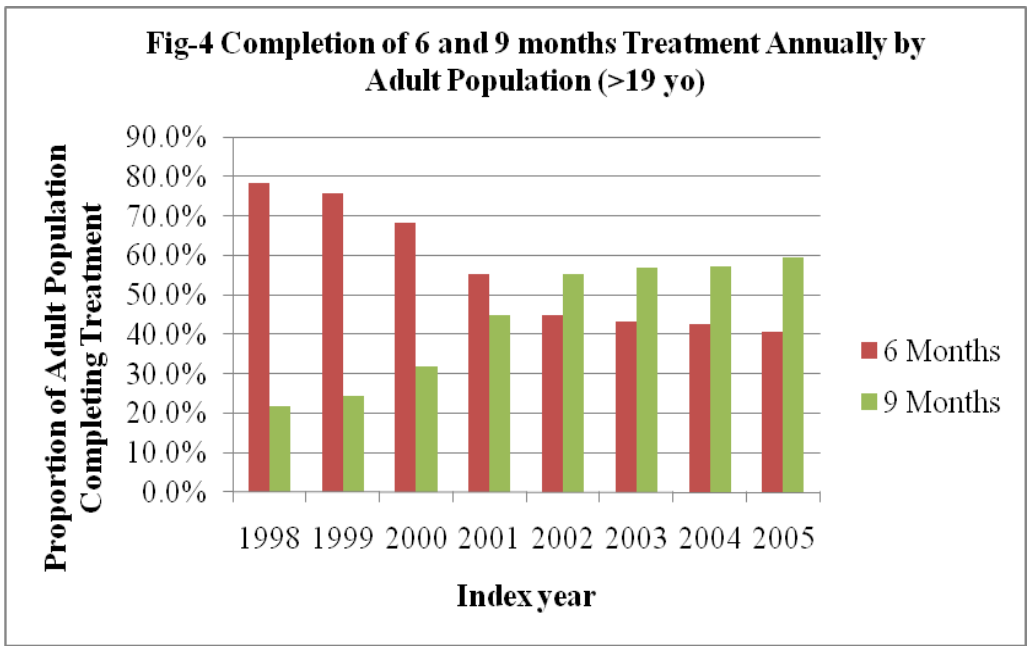


Fig-4 Completion of 6 and 9 months Treatment Annually by Adult Population (>19 yo)
Proportion of Adult Population Completing Treatment
90.0%
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
1998 1999 2000 2001 2002 2003 2004 2005
Index year
6 Months
9 Months

Table 8-Number of Patients initiated on LTBI treatment during the entire study period by Individual Prescribing Physician

Number of patients started on treatment	Primary Care		Others		Total		
	n	%	N	%	N	%	p-value
1	1113	64.9%	438	47.5%	**1551**	58.8%	<0.0001
2-5	514	30.0%	260	28.2%	**774**	29.4%	0.328
6-15	69	4.0%	122	13.2%	**191**	7.2%	<0.0001
16-50	13	0.8%	62	6.7%	**75**	2.8%	<0.0001
50+	5	0.3%	41	4.4%	**46**	1.7%	<0.0001
Total	**1714**	**65.0%**	**923**	**35.0%**	**2637**		

(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)

Number of patients started on LTBI treatment by the Physician	Treatment complete		Treatment not complete		Total		
	n	%	n	%	n	%	p-value [a]
1	566	9.3%	985	11.3%	1551	10.5%	0.0001
2-5	817	13.5%	1313	15.1%	2130	14.4%	0.006
6-15	609	10.1%	1047	12.0%	1656	11.2%	0.0002
16-50	768	12.7%	1077	12.4%	1845	12.5%	0.603
50+	3299	54.4%	4272	49.1%	7571	51.3%	<0.0001
Total	**6059**	**41.1%**	**8694**	**58.9%**	**14753**		

(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

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

12. 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

249.81Secondary 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