Impact of Diabetes on Montreal Tuberculosis Patients from 1995 to 2007

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ABSTRACT

The primary objective of this study was to examine the role of diabetes in the transmission dynamics of *Mycobacterium tuberculosis.* We conducted a molecular epidemiologic study of 1549 TB cases between January 1996 and November 2007 in Montreal. No significant association was found between diabetic status and cluster membership defined by shared strains. Diabetic TB patients did not generate more subsequent cases compared to non-diabetics (adj. relative transmission index 0.8, 95% CI 0.1-4.6). When tuberculin skin test (TST) positivity among contacts was analyzed using hierarchical logistic regression, TST positivity was weakly associated with diabetic status of source case (aOR 1.4, 95% CI 1.0-1.9). Contacts of diabetic TB patients were also more likely to receive isoniazid treatment for latent TB infection (OR 1.8, 95%CI 1.2-2.7).

The secondary objective of the study was to determine whether the combination of active TB and diabetes was associated with increased health care costs, as compared to active TB without diabetes. Univariate and multivariate linear regression analyses were performed to estimate the effect of diabetes on duration of hospitalization and TB therapy. Diabetes was not a significant predictor of hospitalization duration (adj. coefficient -0.7d, 95% CI -12.3d to11.0d), while concomitant kidney disease was the strongest predictor (adj. coefficient +14.3d, 95% CI 1.0d to 27.6d). Neither diabetes nor kidney disease was associated with longer TB therapy. However, diabetes and kidney disease each increased the risk of treatment failure, and were the strongest predictor of treatment failure when combined (aOR 13.6, 95%CI 1.6-119.4).

This study did not identify an association of diabetes with tuberculosis transmission as detected by linked secondary active cases, although index patients with active TB had a relatively higher proportion of contacts with positive tuberculin tests. Diabetes and renal disease were both associated with an increased risk of TB treatment failure.

Résumé

L'objectif principal de cette étude était d'examiner le rôle du diabète dans la dynamique de transmission de *Mycobacterium tuberculosis*. Nous avons mené une étude épidémiologique moléculaire de 1549 cas de tuberculose entre janvier 1996 et novembre 2007 à Montréal. Aucune association significative n'a été observée entre l'état diabétique et l'appartenance aux grappes de génotypes tuberculeux. Les patients diabétiques atteints de tuberculose ne généraient pas plus de cas ultérieurs comparés aux non-diabétiques. Lorsque les résultats du test de sensibilité à la tuberculine parmi les contacts ont été comparés par analyse de régression logistique hiérarchique, la positivité a été faiblement associé à l'état diabétique des cas-index (ORa 1,4; IC95% 1,0-1,9). Aussi, les contacts des patients diabétiques atteints de tuberculose ont été plus souvent traités à l'isoniazide pour l'infection tuberculeuse latente (ORa=1.8).

L'objectif secondaire de l'étude était de déterminer si la combinaison de la tuberculose active et le diabète est associée aux coûts augmentés des soins de santé, en comparaison avec la tuberculose active non diabétique. L’effet du diabète sur la durée de l'hospitalisation et sur le traitement de la tuberculose a été evalué par l’analyse de régression linéaire univariée et multivariée. Le diabète n'est pas un facteur indicatif significatif de la durée de l'hospitalisation, alors que la maladie rénale concomitante était le facteur indicateur le plus fort. Ni le diabète, ni la maladie rénale ont été associés à un traitement prolongé. Cependant, le diabète et les maladies rénales ont augmenté le risque d’échec thérapeutique.

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1. INTRODUCTION

1.1 RATIONALE

The number of diabetics with tuberculosis is rapidly growing as a result of the global pandemic of diabetes and the ongoing tuberculosis epidemic. Several recent systematic reviews have confirmed the significance of the interaction of tuberculosis and diabetes. The aim of the present study was to investigate the impact of diabetes on Montreal tuberculosis epidemiology.

1.2 OBJECTIVES

1.2.1 Primary Objective

The primary objective of the present study is to assess the effect of diabetes on the transmission dynamics of TB in Montreal. Specific questions addressed are:

1) Among active TB patients, do diabetics transmit TB to their contacts more frequently, compared to non-diabetics?

2) Among contacts of active TB patients, are diabetics more susceptible to TB disease, i.e. become more easily infected and develop disease, compared to non-diabetics?

1.2.2 Secondary Objective

The secondary objective aims to examine whether there is a significant additional financial burden imposed by diabetes and TB disease together. Specific questions addressed are:

1) In active TB patients, does diabetes as comorbidity extend TB-related hospitalization and TB therapy?

2) In TB patients in a high-income setting with complete public health care coverage, does diabetes still increase the risk of poorer clinical outcomes such as treatment failure and death?

1.2.3 Hypotheses

For the primary objective, the following hypotheses are tested in the study:

1) According to genotyping of *M. tuberculosis* isolates, the transmission index of diabetic active TB patients is higher than non-diabetic active TB patients.

2) Among contacts of active TB patients, contacts of diabetic patients have a higher proportion with positive tuberculin skin results compared to those of non-diabetic patients.

3) Among active TB patients, secondary active TB cases (as defined by genotyping) have a higher prevalence of diabetes as comorbidity compared to index cases.

For the secondary objective, the following hypotheses are tested:

1) Among TB patients, concomitant diabetes is associated with longer duration of TB-related hospital stay.

2) Among TB patients, diabetes is associated with longer duration of TB therapy.

3) Among TB patients, diabetics are more likely to have poorer clinical outcomes even in a high-income setting with complete public health care coverage.

1.3 BACKGROUND

1.3.1 Tuberculosis and Diabetes Mellitus

1.3.1.1 Diabetes Mellitus

Diabetes mellitus is a syndrome – a group of metabolic, vascular and neuropathic disorders – characterized by hyperglycemia resulting from impaired insulin secretion

and/or insulin resistance. Most diabetes can be classified into two categories based on etiology. Type 1 diabetes is characterized by the absence of insulin secretion, usually due to autoimmune destruction of the pancreatic β-cells responsible for insulin production. Insulin resistance in combination with insufficient insulin secretion characterizes type 2 diabetes. Many risk factors can be associated with this form of diabetes, such as age, obesity, lack of physical activity, and genetic predisposition. Other types of diabetes include genetic defects of β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas, other endocrinopathies, drug- or chemical-induced diabetes, infection and other less common forms of immune-mediated diabetes mellitus. For women, glucose intolerance and resulting hyperglycemia limited to pregnancy is called gestational diabetes, which may precede development of type 2 diabetes [1, 2]. Diabetes brings serious complications as it progresses at microvascular, macrovascular and neuropathic levels [2].

Of particular importance with respect to TB is the fact that infectious diseases are more frequent in diabetics than non-diabetics. For example, patients with diabetes mellitus type 1 and type 2 are at higher risk for lower respiratory tract infections, urinary tract infections, skin infections, and mucous membrane infections [3, 4]. A 12-month prospective cohort study that compared 7 417 diabetic patients with 18 911 control patients found that patients with type 1 and type 2 diabetes had a greater risk of lower respiratory infection (adjusted odds ratio of 1.42 and 1.32, respectively), urinary tract infection (aOR 1.96 and 1.24), bacterial skin and mucous membrane infection (aOR 1.34 and 1.44) [5]. Defects concerning cellular innate immunity have been studied in detail. Several studies showed that polymorphonuclear neutrophil (PMN) chemotaxis is impaired in patients with diabetes in addition to reduced superoxide production in parallel with increasing glycemic exposure, possibly due to an increase in polyol pathway activity as a consequence of raised intracellular glucose. Impaired adaptive immune function in diabetics have been suggested by *in vitro* studies, but it remains unclear whether these findings are relevant *in vivo* [3, 6].

1.3.1.2 Convergence of Diabetes Mellitus and Tuberculosis

The number of diabetic persons is estimated to be 350 million worldwide. This number is predicted to increase by 50% within two decades. Middle-East and African regions are expected to undergo the highest increase – an increase of 80-90% - while European and North American countries are expected to have the least – by 20-30% [7, 8]. While age-standardized death rates due to diabetes mellitus (DM) are expected to increase by over 1% each year for the period 2002-2020, about 80% of deaths from diabetes occur in low- and middle-income countries [9]. This is about 0.6% of all DM cases in these countries, where the prevalence is estimated to be around 4.5% [10]. Gaps in clinical management including limited access to suitable care may contribute to the higher death rates despite lower prevalence of DM, and this will be more problematic in near future, as the number of diabetics is expected to grow steeply in these countries.

The global expansion of diabetes and the unalleviated burden of TB in developing countries have resulted in the intersection and synergy of the two diseases. In the very poorest countries, type 2 diabetes mellitus is associated with relative affluence. But in many low- and middle-income countries, life-threatening food insecurity has been alleviated, with the result that diabetes then strikes the less affluent [11, 12]. While more affluent groups have access to nutrient-rich foods and better health care, the deprived groups can only afford energy-dense and nutrient poor foods and have limited resources for management of diabetes once it occurs [12, 13]. As TB is disproportionately more prevalent in the poor as well, this greatly increases the risk of TB-DM co-morbidity.

This association of tuberculosis and diabetes is of particular importance in large middle-income countries with emerging economies, such as Brazil, China, India, Peru and the Russian Federation where substantial TB burdens are coupled with an increasing prevalence of DM [14]. In areas where both TB and diabetes are common, the prevalence of diabetes is almost two-fold higher in TB patients compared to the general population: 39.3% versus 19.5% in South Texas and 36.0% versus 15.1% in

northeastern Mexico; the proportion of TB cases attributable to diabetes was estimated to be 25% [15].

In high income countries, the association may also reflect shared risk factors for the two diseases. In Canada, migrants from high TB incidence countries and Aboriginal peoples account for the majority of tuberculosis cases (See Section 1.4) [16, 17]. Aboriginal peoples have a 3 to 5 times greater age-adjusted prevalence of diabetes and a higher risk of ensuing complications and mortality due to diabetes [18]. Moreover, some of the immigrant groups at risk for TB, such as those of South Asian, Latin American and African origin, have a two to four times greater prevalence of type 2 diabetes than the Canadian-born [19-21]. In Quebec, where Aboriginals account for a substantial number of TB cases, the prevalence of type 2 diabetes is known to be 2-3 times higher in Aboriginal peoples compared to the general population in Quebec [22]. TB and diabetes in developed countries also share other social risk factors such as low socioeconomic status [14, 23], which is itself associated with other risk factors for TB such as tobacco and alcohol use, homelessness, as well as household overcrowding [24-27].

The convergence of the diabetes and tuberculosis epidemics has major implications for healthcare systems. First, the increasing prevalence of chronic diseases in low- and middle-income countries creates new demands on healthcare systems. Many developing countries lack the infrastructure to provide more complex and long-term care of chronic conditions [28]. Health systems in low- and middle-income countries typically focus on the management of maternal and neonatal mortality, and acute phases of infectious diseases such as malaria, respiratory tract infections ad diarrheal diseases. This implies a lack of longitudinal management of the patients, and of their ongoing medical conditions [29, 30]. Chronic conditions also generally require greater health expenditures that surpass the financial capacity of low-income countries; for example, the mean annual direct cost for diabetes care in the African region (US$876-1 220) exceeds the mean per capita expenditures on health care of that region (US$30-800) [31]. Microeconomic impact – out-of-pocket spending, productivity loss and other indirect costs – is also significant [28, 32, 33]. Secondly, chronic conditions such as

diabetes may contribute to the incidence and severity of infectious diseases that are already prevalent in the region, and escalate the financial burden; diabetic TB patients may require longer TB treatment and have higher relapse rates – reviewed in detail in the next section [34, 35]. New guidelines and programmes of care are required for co-management. The World Health Organization proposed a *Collaborative framework for care and control of tuberculosis and diabetes* in 2011 [36], but guidelines must be tailored to the needs and resources of each country.

1.3.1.3 Effect of Diabetes on TB Disease

Regardless of study design, background TB incidence or geographic region, most studies have shown that diabetes is a risk factor for active TB disease [37]. According to a meta-analysis of thirteen observational studies by *Jeon et al*. (2011), diabetes increases the risk of developing active TB by threefold (RR=3.11, 95% CI 2.27-4.26) [38], which is consistent with other systematic and narrative reviews [14, 31, 35]. The association was particularly strong in younger populations in areas with high TB incidence [35, 38]. Several studies have shown a higher prevalence of latent TB infection in diabetic patients, suggesting that DM increases the risk of TB infection. However, as most studies are small cross-sectional studies without appropriate controls [39-44], and a few studies found no relationship between DM and latent TB, it is still unclear whether the positive association is due to more frequent acquisition of the infection or progression to disease. In addition to its association with TB,

In addition to its association with TB, diabetes also aggravates disease severity and worsens clinical outcomes of tuberculosis. *Baker et al.*'s meta-analysis (2011) showed that TB patients who are diabetic (TB+DM+) have 1.69 (95% CI 1.36-2.12) times greater risk of facing the combined outcome of treatment failure and death, and 1.89 (95% CI 1.52-2.36) times greater risk of experiencing death during TB treatment, as compared to TB patients without known diabetes. The effect is larger after adjustment for age: 4.95 times greater mortality risk (95% CI 2.69-9.10). They also have 3.89 (95% CI 2.43-6.23) times greater risk of relapse after TB cure or treatment completion compared with those who are not diabetic [34]. In addition, diabetic TB patients

(TB+DM+) are more likely to present the most infectious smear-positive form, a greater bacterial concentration in sputum, increased lung cavitation, and infection in multiple lobes and in the lower parts of the lung [35]. Findings regarding risk of developing multi-drug resistant TB and that of remaining sputum culture positive (a marker of delayed treatment response and poorer cure rates) after 2-3 months of TB therapy have been inconsistent [34].

The exact mechanism behind the interaction between DM and TB remains uncertain. There are several possible explanations. First, similar to HIV infection, the weakened immune system secondary to diabetes may contribute to the higher risk of TB disease in diabetic patients. *In vitro* studies suggest that diabetic patients have compromised polymorphonuclear functions, including impaired transmigration (or chemotaxis), adherence, phagocytosis, and intracellular microbial killing. Reduced complement function (C4 in particular), weakened T-lymphocyte function and impaired cytokine function (TNF-α, IL-6 and IL-8; elevated resting concentration and attenuated response to stimulation) in diabetic patients are also proposed [3, 6, 45]. The weakened immune response therefore hampers host defense against the pathogen, failing to limit bacterial replication and increasing the probability of progression to disease.

Second, anti-diabetic and anti-tuberculosis drugs seem to interact. Rifampin, an important first-line drug in TB treatment, is a potent inducer of metabolizing enzymes in the liver including cytochrome P450 (CYP) enzymes, by which several anti-diabetic drugs are metabolized. Plasma levels of these anti-diabetic medications thus significantly decline when administered simultaneously with rifampin [31, 36, 46]. Moreover, insulin requirements may increase when the patient is treated with the latter, which causes transitory hyperglycemia with hyperinsulinemia [31]. Although any active infection including TB worsens DM control, the drug-drug interaction between anti-TB and anti-diabetic drugs may further complicate the disease.

1.3.1.4 TB, chronic renal failure and other Immunosuppressive Conditions

Patients with chronic renal failure on dialysis are reported to have anywhere from a 6.9 to 52.5-fold higher risk of active TB compared to the general population [47]. Renal failure can also involve other immunosuppressive conditions such as malnutrition, vitamin D deficiency, and hyperparathyroidism, resulting in higher rates of active TB and higher mortality after TB disease [47]. No study has yet investigated the effect of chronic renal failure on TB transmissibility as such, although there have been several reports of TB outbreaks involving dialysis units, possibly due to suppressed immunity and increased nosocomial exposure [48-50]. Chronic renal insufficiency can be a long-term consequence of diabetes mellitus, and it is possible that it may act as an intermediate between diabetes and TB in some cases. However, an expert meeting on TB and DM in 2009 concluded that an independent causal relationship between DM and TB is likely; increased TB risk with poorer glucose control is shown in some studies, although most studies on DM and TB did not always stratify the subjects as to the presence or absence of concomitant renal failure, and similarly in studies on renal failure as a risk for TB [51].

Diabetes is most often compared with the human immunodeficiency virus (HIV) infection for its immunosuppressive effect and interaction with TB. HIV infection causes acquired immunodeficiency syndrome (AIDS), where the infected person's immunity progressively fails, particularly the cell-mediated immune system with decline of CD4+ T helper cells. HIV-infected persons therefore are more likely to fail to contain TB infection, increasing the risk of TB disease. HIV is the strongest risk factor known for the development of TB disease: the risk of disease following infection with *Mycobacterium tuberculosis* (MTB) increases from 10% per lifetime in immunocompetent hosts to 10% per year in persons with AIDS. However, HIV-positive TB patients seem to be less contagious than HIV-negative TB patients, on average [48].

Examples of other conditions that suppress systemic and/or local lung immune function and are known risk factors for TB disease include organ transplantation with immunosuppressant therapy (RR=20-74), silicosis (RR=30), treatment of autoimmune

conditions such as TNF-α blocking agents (RR=1.5-5.8), and glucocorticoids (RR=4.9) [48, 52]. Although impaired immunity increases the risk of TB disease in all these conditions, the pathophysiological mechanisms, clinical characteristics and the effect on TB transmission dynamics appear to differ in each disease. For example, patients with advanced HIV disease tend to have lower sputum bacillary burden, decreased duration of smear positivity, and more frequent disseminated TB, but not cavitary TB; while TB disease in diabetics is associated with the most infectious smear-positive form, with a greater bacterial concentration in sputum and increased lung cavitation.

1.3.2 Background on Tuberculosis

1.3.2.1 Pathogenesis

Members of the *Mycobacterium tuberculosis* complex are the causative agents of human and animal tuberculosis (TB). Species in the complex include *M. tuberculosis* – the major cause of human tuberculosis – *M. africanum*, *M. canetti*, *M. caprae*, *M. microti*, *M. pinnipedii* and *M. bovis*, but the term *M. tuberculosis* (MTB) is used throughout this section to describe any member of the complex [52].

Humans are the main reservoir for *M. tuberculosis*. MTB is almost exclusively transmitted through the airborne route in the form of droplet nuclei, particles 1-5 μm in diameter that are the dried residues from the evaporation of droplets coughed or sneezed into the atmosphere. During an exposure to an active TB patient, once a susceptible individual inhales small infectious droplet nuclei that contain about 1-10 bacteria, MTB reaches the vulnerable outer reaches of the lungs and triggers a non-specific innate immune response in the host. Successful elimination of the mycobacteria by alveolar macrophages prevents the individual from developing tuberculosis. However, macrophages engulf, but may fail to destroy the bacilli, allowing them to multiply and initiate infection. Infected macrophages aggregate to form granulomas and constrain the spread of the pathogen [48, 52].

Within two to four weeks after the primary infection, macrophages and dendritic cells activate T-lymphocytes in the peripheral lymph nodes and the adaptive immune

response develops. Cell-mediated immunity and delayed-type hypersensitivity are initiated. Cell-mediated immunity involves CD4+ T-cells that secrete cytokines to enhance macrophages' capacity to ingest and kill bacteria. Delayed type hypersensitivity involves CD8+ cytotoxic cells that destroy infected macrophages along with some surrounding tissue. The Ghon focus, the initial site of infection in the lungs, and hilar lymph nodes where bacilli have been drained together constitute the primary complex [48].

Progression to disease depends on the balance between the host immunity and bacterial multiplication. Most immunocompetent persons are able to stop the bacterial replication but the initial lesion may still contain viable dormant bacilli, in which case the host is said to have latent TB. Active immune surveillance, particularly the production of interferon-gamma (IFN-γ) by CD4+ T-cells that activates macrophages, is required to maintain latency. About 5% of newly infected immunocompetent persons fail to limit bacillary replication and the infection develops into primary or progressive primary disease within a few months. Another 5% develop post-primary TB disease later on in their lives through reactivation of the dormant MTB after a variable period of latency, or re-infection from a different source case. Hence in general, 90% of persons with latent TB infection never develop active disease. However, the balance between host and bacterium is shifted in immunocompromised individuals; not only are the host immune responses to mycobacteria lowered, but immune surveillance is also weakened. Immunosuppressive conditions therefore increase the susceptibility to TB infection, the risk of rapid progression to active disease, and the risk of reactivation of latent TB. The most compelling example is HIV infection. The risk of progression to disease increases from 10% per lifetime to 10% per year in TB+HIV+ co-infected patients; the risk of TB reactivation is 79-fold greater in HIV-infected compared to HIV-noninfected persons [48]. Diabetes mellitus appears to be associated with a milder form of immunosuppression, increasing the risk of active TB by 3-fold [38].

Although less common, TB disease can involve structures other than the respiratory organs when *M. tuberculosis* spreads to other organs through mucosa, blood, or

lymphatics. Extrapulmonary TB is more common with reactivation disease and in individuals with weaker immunity, such as HIV-infected persons or young children (<5); they fail to contain MTB and allow lymphohematogenous spread of the bacilli. Symptoms of active pulmonary TB may include chronic cough, sputum production (sometimes with blood), fever, night sweats and weight loss. Symptoms of extrapulmonary TB are varied and depend on the body site involved. Active disease is defined by the presence of clinical symptoms, and/or positive bacteriologic, radiographic and/or biopsy findings. Globally, of all new cases of TB in 2012, about a third of all new cases of TB had extrapulmonary TB only [53]. In Canada, extrapulmonary TB represented 36% of all reported TB cases [21].

In more severe or advanced cases of active pulmonary TB, progressive lung destruction through necrotizing granulomatous inflammation results in liquid-filled cavities. Cavities can harbor a large number of bacteria and make patients highly infectious. They can also erode into the adjacent blood vessels or airway to cause further dissemination of bacilli within the host, and potentially life-threatening bleeding.

The understanding of MTB transmission is therefore crucial for TB control. A person with active TB who has transmitted infection to others is called a *source*. In an ideal situation where active TB is diagnosed and reported in a timely manner, the source case is also the *index case*, the first case of active TB identified in a series of individuals linked through putative transmission events. *Contacts* are the persons who have been in contact with a potentially infectious TB patient. They can be household contacts (people living in the same household as the source case), casual contacts (e.g. classmates or co-workers) or community contacts (those living in the same community, and/or attending the same school or work). Transmission occurs from a source case to contacts, and the index case is a surrogate for the source case, as the true source case may not always be known with certainty [54].

1.3.2.2 Epidemiology of Tuberculosis

It is estimated that one in three people in the world is infected with *Mycobacterium tuberculosis*. TB was declared a global public health emergency by the World Health Organization (WHO) in 1993, and remains a leading cause of morbidity and mortality globally. According to the *WHO Global Tuberculosis Report 2013*, there were 8.6 million estimated cases of active TB worldwide (equivalent to 122 cases per 100 000 population) and 1.3 million associated deaths in 2012. Most incident cases occurred in Asia (58%) and the African Region (27%), and the five countries with the largest number of TB patients were India (2.0-2.4 million), China (0.9-1.1 million), South Africa (0.4-0.6 million), Indonesia (0.4-0.5 million) and Pakistan (0.3-0.5 million).

Global incidence was relatively stable from 1990 to 2001, and then started to decline slowly. The rate of decline was 2% between 2011 and 2012 [53]. HIV-endemic countries in Africa had the highest incidence of TB. There were an estimated 450 000 new cases of multi-drug resistant TB (MDR-TB) worldwide in 2012 [53]; MDR-TB is defined as TB that is resistant to the two most important first-line drugs (isoniazid and rifampin). Patients can acquire drug resistance following inadequate therapy, or after infection from a source patient with a drug-resistant strain. Drug resistance challenges TB treatment in patients and TB control within a community, as the resistant strains require longer and more expensive treatment regimens, and are associated with poorer outcomes [48, 52, 55, 56]. Today, the HIV epidemic, undernutrition, diabetes, alcohol misuse, smoking, and indoor air pollution are highlighted as direct TB risk factors, in addition to underlying social determinants (e.g., poverty, and poor living and working conditions) [48, 53, 57].

In high-income countries such as the United States, Canada, and Australia, migrants from high TB incidence countries and Aboriginal peoples account for the majority of tuberculosis cases. In Canada, the overall incidence of active TB was 4.8 cases per 100 000 population in 2012. Most cases occurred in foreign-born individuals (64%) and Canadian-born Aboriginal people (23%), but there was a wide variation in disease rates among regions and communities. The overall incidence rate of active TB among

Aboriginal people in Canada was estimated to be 29.4 per 100 000 and that among the foreign-born to be 13.6 per 100 000. Individuals between the ages of 25 and 34 years accounted for the largest number of reported cases, accounting for 15% of the total, although the incidence rate was highest in those aged 74 years and older at 9.1 per 100 000 population [21].

Quebec accounted for 15.8% of newly reported cases in 2012; 51.9% of these cases in Quebec were in foreign born persons. The incidence rates for Aboriginals and the foreign born in Quebec were 69.2 and 11.9 per 100 000 respectively. While the increasing incidence in Nunavik in northern Quebec has been noted for over ten years, an outbreak in 2012 contributed to a noticeable increase in the incidence rate among Inuit people in Canada relative to previous years [21]. With regards to latent TB infection in the population, a tuberculin skin test (TST) screening survey in Montreal estimated a point prevalence of positive TST of 17.7% among a sample of urban Aboriginal people, in contrast to a prevalence of 4.3% among the general population in 2006 [16, 17]. Among foreign-born individuals in Montreal, tuberculin skin tests were given to students and clinic visitors. Newly arrived immigrant children in elementary and secondary schools of age 4-18, during the years 1998-2003, had a prevalence of TST positivity of 21%, while 25% of refugee claimants who attended a primary care clinic had TST positivity in 1999 [58].

1.3.3 Studying TB Transmission

1.3.3.1 Factors Influencing Transmission

According to a traditional model of infectious disease causation, known as the epidemiological triad, characteristics of the infectious agent, of the host and of the environment in which host and agent interact cause the disease to occur. In TB transmission, *Mycobacterium tuberculosis* is the agent, potential transmitter and potential transmittees are the hosts, and environment is where the transmittees encounter the transmitter.

Host factors can be classified as those associated with the transmitter, i.e. the source case, and those with the transmittee, i.e. the contact. The degree of infectiousness is an important characteristic of the potential transmitter that influences TB transmission. Factors associated with infectiousness include sputum smear-positive pulmonary TB (6-10 times more contagious than smear-negative pulmonary disease), laryngeal TB (4-5 times more contagious than pulmonary TB), and a source case of adolescent or adult age. Other characteristics of the transmitter such as the bacillary load in sputum, physical and chemical properties of sputum, the mechanism of the coughing maneuver, as well as the shape of the upper airway during coughing are hypothesized to affect transmission. State of immunity is a characteristic of the transmittee, which acts as a major determinant in TB transmission. Although the lifetime cumulative risk of developing active TB in immunocompetent persons is estimated to be 10% once infected (primary and post-primary disease), weakened local or systemic immune function can significantly increase the risk of progression into active disease. Also, immunocompetent persons with prior exposure to MTB have a lower risk of becoming infected when re-exposed, compared to those with no prior exposure. Other characteristics that increases the susceptibility of contact include age, gender, substance abuse, nutritional status and other systemic diseases [59]

Among social and environmental factors, migration is one of the key epidemiological TB determinants in low-burden countries (see Section 1.3.2.2). Migrants who reactivate latent TB infection acquired abroad now account for the majority of active TB in Canada and other low-burden countries. Indoor exposure, poor air circulation, and proximity increase the concentration of viable bacilli, and the risk of transmission. Indirect environmental factors such as the use of biomass fuel and indoor cooking are also suggested in the literature [21, 60]

As agent factor, recent studies have suggested that several biological characteristics of the infecting MTB strain may also affect TB transmissibility as well as progression to active TB disease [52].

The potential contribution of diabetes to transmission mostly involves host factors. First, studies have reported that TB disease may be more severe in diabetics, with a higher frequency of smear-positive disease, greater sputum bacterial concentrations, and a longer interval until culture conversion [34, 35]. Diabetic TB patients may therefore be more contagious then non-diabetics. Second, diabetes increases the risk of both TB infection and its progression to active disease (see Section **1.3.1.3**). Also, in many settings, type 2 diabetes is associated with low socio-economic position [23], a risk factor for TB in its own right [14, 57]. A review of studies on the effect of diabetes mellitus on the transmission dynamics of tuberculosis is in Section *2.1*. Whether diabetes is a risk factor specifically for being a transmitter, a transmittee, or both, is not yet clear.

1.3.3.2 Methods for detecting transmission

a) Contact tracing

One key approach to the study of MTB transmission is to conduct contact tracing: an epidemiological investigation of a TB patient to identify and screen his/her contacts for latent TB infection and TB disease. When contacts of a source case who has a specific characteristic have a higher prevalence of TB infection and/or TB disease, it is suggested that the characteristic is associated with TB transmissibility; when contacts who have a specific characteristic have a higher prevalence of TB infection and/or disease, it is suggested that the characteristic is associated with TB susceptibility. Depending on the epidemiological situation and the resources available, contact screening includes a medical evaluation complemented by appropriate diagnostic measures such as tuberculin skin tests (TST), an interferon-gamma release assay (IGRA), sputum microbiologic testing, and/or chest X-ray (CXR) [48].

In low-incidence, high-income countries such as Canada, the standard diagnostic test for latent TB infection in contacts is the tuberculin skin test (TST), which detects latent infection by evoking a cell-mediated immune reaction through injection of a small amount of purified protein originally derived from *M. tuberculosis*. In a person who has

been previously sensitized to these proteins – either because of acquired TB infection or sometimes because of prior Bacille Calmette-Guérin (BCG) vaccination – a delayed hypersensitivity reaction develops within 48 to 72 hours of the injection. Positive results from these tests in contacts, whether or not they have TB symptoms, suggest they have contracted TB infection. Similarly, the interferon-γ release assays (IGRAs), such as the Quantiferon Gold In-Tube® assay (QFT) and T-SPOT.TB assay, quantify IFN-γ released by T-lymphocytes in response to TB antigens, in order to detect prior sensitization due to TB infection. The antigens used do not cross-react with BCG; hence the specificity is improved in BCG-vaccinated populations compared to TST. IGRAs also appear to be unaffected by most infections with nontuberculous mycobacteria that may cause false-positive TSTs. Although its sensitivity is impaired by immunosuppression, T-SPOT.TB may perform somewhat better than QFT and TST [52].

The use of contact tracing for epidemiologic studies of TB transmission has critical limitations. First, contact investigation relies on the identification of the contacts by the index case and their being found, recruited and tested, which brings selection bias. In addition, the extent of contact investigation varies with the perceived infectiousness of the index case. Extrapulmonary or smear-negative pulmonary TB is rarely followed by extensive contact investigation compared to pulmonary smear-positive pulmonary TB. Symptomatic contacts and those already followed for other health conditions are also more likely to undergo testing than those without symptoms, resulting in potential overestimation of transmission to such individuals [61]. Evaluation is almost always incomplete as casual and brief contacts are often missed [62]. Also, contact tracing studies often use the closeness of “contact” as a surrogate for extent of exposure to MTB, which is problematic for source cases with unstable housing, employment or education status.

Secondly, using the crude prevalence of latent infection among contacts as an indicator of transmission can be misleading, as the prevalence is also affected by likelihood of prior exposure, independently of any recent contact. In order to minimize this inaccuracy, the proportion of positive TST results caused by recent transmission is sometimes

estimated by subtracting the estimated likelihood of a previous positive TST within the demographic group to which each contact belongs, from the observed proportion of positive TST using the following formulas [63, 64]:

$$\begin{aligned}&(\text{Est. prop. of recent transmission})\\&=(\text{Observed prop. with positive TST})\text{-}(\text{Prob. of prev. infection in the group})\end{aligned}$$

$$\begin{aligned}&(\text{Probability of previous TB infection})\\&=\frac{\sum\left[1-(1-\text{average estimated annual risk of TB infection in each country of origin})^{\text{age at immigration}}\right]}{(\text{Number of contacts in the group})}\end{aligned}$$

b) Genotyping MTB Isolates

A second key approach to the detection and study of transmission relies on genotyping *M. tuberculosis* isolates from persons with active TB disease, and comparing the resulting genotype [52]. The standard method is restriction-fragment-length polymorphism (RFLP) analysis using insertion sequence IS*6110*, which is supplemented by secondary typing methods for isolates with few copies of this insertion sequence. Identical RFLP pattern – in number and chromosomal location of insertion sequence *IS6110* - shared by different isolates suggest an epidemiological link. A genotyping modality that is often used as secondary typing method is spoligotyping, which examines the variable presence of spacers in the direct repeat locus. This method complements RFLP analysis as it is PCR-based and requires minimal amounts of DNA. However, spoligotyping alone has lower molecular resolution than IS*6110*-based RFLP [48]. A more recent molecular typing method is genotyping based on variable number of tandem repeats (VNTR) of different classes of genetic elements called mycobacterial interspersed repetitive units (MIRUs). MIRU-VNTR typing is technically flexible and considerably faster than IS*6110*-RFLP typing and is therefore increasingly used to save time and labor required for culturing the isolates and purifying the DNA in RFLP typing. In particular, the use of containing MIRU-VNTR using 24 loci has enhanced the predictive value for evaluating *M. tuberculosis* transmission [65].

Identical *M. tuberculosis* genotypes in isolates from different patients, suggest that the individuals are linked by transmission events. Patients infected with the same bacterial strain (sometimes called a “cluster” of linked cases) may have been infected by a common source, or there could have been sequential transmission events. It is essential to integrate the genotyping data with epidemiologic data, as shared strains from individuals living in a closed community can simply represent reactivation of a common strain that had been circulating in the community in the past, rather than recent transmission [52, 66].

Several parameters may be used to summarize the extent of transmission in a particular community or group. Most molecular epidemiological studies report the proportion of clustered cases (i.e. cases where the *M. tuberculosis* genotype is shared with at least one other individual) among genotyped isolates, and assume that cases within each cluster are epidemiologically related [48]:

$$\frac{(\text{Number of clustered isolates})}{(\text{Total number of isolates genotyped})}$$

When subjects with a given characteristic are found to have a significantly higher probability of being cluster members, the study will conclude that the characteristic in question is associated with transmission. However, this approach does not provide insight into whether a given feature is associated with infectiousness, susceptibility to acquire infection, to develop disease once infected, or all three.

Another method is to report the proportion of TB patients within the community who have developed active TB attributable to transmission during the time period of interest (N-1 method). It assumes that one case within each cluster was the result of reactivation, and has transmitted TB to the others in the cluster – either directly, or via intermediaries. As one cluster member is subtracted from each cluster of *n* members, the remainder of the numerator consists of secondary cases, which are active TB arisen due to transmission [48]:

$$\frac{(\text{Number of clustered isolates}) - (\text{Number of clusters})}{(\text{Total number of isolates genotyped})}$$

The method does not require identification of the specific source case for each cluster, but simply assumes that a single unspecified cluster member is ultimately responsible for other cases in the cluster.

A more refined analytic method is the calculation of the transmission index, which is the average number of subsequent cases infected from potential index cases [67]. A putative source case – an index case – is designated by identifying the first TB case diagnosed within a cluster, whose MTB genotype is unique to the population on the date of diagnosis. Other cases in the cluster are assumed to be subsequent cases that result from transmission [68]. The transmission index is calculated by dividing the number of secondary TB cases by the total number of potential index cases (sum of clustered index cases, plus cases with unique genotypes with pulmonary TB i.e. who could but did not transmit):

$$\text{Transmission index} = \frac{(\text{Number of secondary cases})}{(\text{Number of index cases} + \text{Number of nonclustered cases})}$$

By identifying index cases and examining their capacity to generate subsequent cases, it is possible to distinguish characteristics associated with higher risk of transmitting the disease to others. An inherent limitation is that a source case cannot be always identified with certainty. The index case may be attributed based on timing and type of TB (pulmonary TB), assuming a unique *M. tuberculosis* genotype in the sample at the time of diagnosis to have arisen from endogenous reactivation or through in-migration. An alternative is to use a probabilistic approach, where all individuals in clusters can be considered to be partially source cases (P^s_i) and partially the result of recent transmission from other partial source cases in the cluster ($1-P^s_i$); the probability of having been a source case is estimated based on ethnicity, country of birth, date of diagnosis, etc [62]. However, a true source can be misclassified as secondary, if his/her diagnosis has been substantially delayed. The assumption that a single source is

responsible for all other cases within its cluster can also be less valid if a cluster extends over a long time period [67, 68].

Genotyping yields “near-identical” as well as “identical” matches between isolates, since even closely matched isolates may differ because of mutations that accrue over time. Hence, the use of, and inference from, genotyping techniques vary with context and setting. The interpretation of genotyping results will be different when used to investigate specific individuals who are suspected to be part of an outbreak as opposed to broader population-based studies. The criterion for genotypic matching is therefore not always fixed, but may vary according to the context and the question. For example, it is reasonable to apply a stricter matching criterion when comparing isolates from two persons without any known epidemiologic link in a population-based study, than would be used when comparing serial isolates from the same patient over time, to determine whether a second episode of active TB reflected relapse or re-infection with a new organism [48].

The greatest limitation to the use of RFLP and other genotyping techniques is that these tests only apply to persons with active TB disease. As only 5-10% of newly infected individuals ever develop active TB, this captures only a small minority of transmission events. In addition, even fewer infected contacts will develop active TB within the time frame of any given epidemiologic study of transmission; this magnifies the apparent effect of factors that accelerate progression to active disease (e.g. HIV infection), regardless of how they affect susceptibility to transmission. DNA fingerprinting studies also miss transmission events that involve cases outside the geographic and/or temporal limits of the cohorts involved. In fact, cluster analysis is strongly influenced by the study duration: the contribution of recent transmission to TB occurrence may be underestimated in shorter studies, and inference is severely hampered by incomplete *M. tuberculosis* genotyping data for the population and/or time frame of interest. Another technical difficulty in addition to defining matching criteria is the time delays in analysis, as genotyping is only possible once the isolated bacteria have grown in culture, which can take weeks [48]. This means that genotyping is usually not useful for immediate

public health decisions involving individual patients, but can be used to investigate larger outbreaks.

1.3.4 TB Health Care Costs

1.3.4.1 Economic Impact of TB at International, National, and Household Levels

Tuberculosis remains a major global health problem, and considerable resources are required for its care and control. In addition to the monetary resources spent on public health programs, clinical management, and research, its economic impact encompasses loss of productivity due to time lost from work during illness, and from premature mortality. In fact, 75% of TB cases worldwide arise during people's most productive years (between the ages of 15 and 54). TB is the eighth leading cause of death in the world, giving rise to 34.2 million disability-adjusted life years (DALYs). US$614 million from international agencies – such as the United States National Institutes of Health, the Bill & Melinda Gates Foundation, the European Union, and the European and Developing Countries Clinical Trial Partnership – were spent on research and development of new TB drugs, diagnostics and vaccines in 2009.

For TB care and control, the *Global Plan to Stop TB* projected about US$37 billion to be needed during the years from 2011 to 2015 [53]. At the national level, data on TB-related health service costs are often restricted to those financed through the public sector. The costs also vary significantly among different countries, depending on their health policies and budget [48]. In Canada, about CAD$70 million were spent for TB care in 2004, which included the costs of drugs, hospitalization, public health salaries, laboratory, and out-patient care [69]. In high-burden countries, TB expenditures relate to national TB control programmes (NTP) (usually more than half of the total expenditures) and to general health-care services. The latter, mostly hospitalization and outpatient visits, depends on the extent of TB care covered by NTP and the national TB management standards. The NTP budget ranges from US$73 million to US$475 million in the five countries with the largest number of TB cases (Pakistan, Indonesia, India, China and South Africa in increasing order of budget amount), and the cost of general

health-care services provided to TB patients from less than US$1 million to US$341 million (China, Pakistan, Indonesia, India and South Africa in increasing order) [53].

At the household level, the economic impact of TB is greatest for low-income families, especially in countries where the social support and healthcare infrastructure cannot offset financial losses to patients. This includes loss of employment income, costs borne by patients prior to and during TB treatment – i.e. out-of-pocket expenditures for administrative fees, therapy, transport, hospitalization and food – and costs incurred by care givers or family members during a patient's illness, e.g. for child care [48, 70].

1.3.4.2 Costs for TB in Canada

In the US and Canada, the cost of treating TB has increased in the last decades due to the increasing incidence of multidrug-resistant TB, longer courses of treatment for HIV-infected patients, an increasing frequency of cases in difficult-to-reach populations (the homeless, substance users, immigrants) and increasing need for hospitalization [71]. Canada has a publicly funded health care system; all medical visits and prescription drugs are covered by the provincial insurance plan. According to a survey by the Public Health Agency of Canada on TB-related expenditures by governments and other third parties, Canada spent $74 million for TB in total in 2004, including spending on research and development. Treatment for active TB accounted for the largest portion of provincial/territorial TB spending: more than $47 000 per active TB case, of which about $20 000 was attributed to direct patient care and the remainder to public health intervention, e.g. contact investigation [69]. Information on indirect costs and patients' out-of-pocket spending is limited.

Hospitalization accounted for almost half of the active TB related costs and the other half was comprised of public health salaries, laboratory costs and drug treatment. In Canada, TB patients are hospitalized when they are considered very contagious, have severe symptoms (fever, life-threatening hemoptysis, malaise, or cachexia), respond poorly to drug treatment (significant side effects from drugs or known/suspected drug resistance), are homeless, have comorbidities complicating TB diagnosis (e.g. HIV

infection), develop resistance to antituberculous drugs, or if home isolation arrangements are not reliable [52]. The average length of hospital stay of TB patients during the period between 1996 and 2000 was estimated to be 20.6 days and the average cost per day was $929.96 in 2004 [69]. Extended drug therapy and resistance (or intolerance) to TB drugs has a significant impact on the costs of TB treatment. Over the last decade, an average of 9.3% of the active TB isolates tested in Canada were resistant to at least one of the four first-line drugs (INH, RMP, EMB and PZA) [72].

2. PREVIOUS STUDIES

2.1 EFFECT OF DIABETES MELLITUS ON TB TRANSMISSION

Literature reviews were performed separately for genotyping studies and for contact investigation based on tuberculin skin testing, which are two fundamentally different methods that are used to assess the effect of diabetes on the transmission dynamics of *M. tuberculosis*.

2.1.1 Genotyping Studies

Genotyping studies assume that TB cases with isolates of identical RFLP patterns are epidemiologically related through recent transmission (See Section **1.3.3.2**). There was no study that directly addressed the relationship between diabetes and TB transmission in a quantitative manner using genotyping methods.

Hernandez-Garduno et al. (2004) compared clustering proportions according to sputum smear results (smear positive patients had two-fold higher odds of being in a cluster (95% CI 1.1-3.6)); the proportion of diabetics was compared between smear-negative and smear-positive patients, but not according to RFLP results: smear positive patients had 2.8 times greater odds of having diabetes mellitus (95% CI 1.1-7.0) compared to smear negative patients [73]. Hence their results indirectly suggested a link between diabetes and transmission, related to an increased prevalence of diabetes in smear-positive patients, but did not directly address this relationship.

In another study, a population-based study in Mexico based on the national health survey and community-level TB screening conducted from 1995 to 2003, *Ponce-de-Leon et al.* (2004) reported risk factors associated with clustered active TB (assumed to have resulted from recent transmission) and non-clustered active TB (assumed to have reactivated). The effect of diabetes on clustering itself, conditional on having TB, was not directly calculated. The incidence rate of clustered TB was 6.9 times greater (95% CI 4.7-9.9) in diabetic persons compared to non-diabetic persons; the incidence rate of reactivated TB (i.e. non-clustered) was also 6.8 times greater (95% CI 5.5-8.4) in

diabetics than non-diabetics. These findings imply that both reactivation and secondary TB cases are potentially more frequent among diabetics [74].

A more recent study by Jiménez-Corona et al.(2013) was a prospective cohort study from 1995 to 2010 that conducted epidemiological, clinical and microbiological evaluation of TB patients in 12 municipalities in the Orizaba Health Jurisdiction in Veracruz State, Mexico. All smear-positive sputum samples from previously treated TB patients were cultured, and DM patients were identified in order to evaluate clinical outcomes of diabetic vs non-diabetic TB patients. DM patients more often experienced severe clinical manifestations such as cavitation, as well as treatment failure, recurrence and relapse. Patients with DM more often had unique IS*6110* fingerprints, which was interpreted as being more likely to reflect reactivation TB rather than new transmission. If diabetic patients had two episodes of active TB, isolates from both episodes were genotyped, and the second typically involved identical strains to the first episodes (81% in recurrence, 77% in relapse). A somewhat higher proportion of diabetic patients had their second TB episode resulting from exogenous reinfection, compared to non-DM patients. Therefore, it was suggested that not only did the DM patients have higher risks of recurrence and relapse due to the original infecting organism, but they were more vulnerable to exogenous reinfection compared to non-DM patients. Transmission index or proportion of clustered TB cases was not calculated [75].

2.1.2 Contact Tracing (Tuberculin Skin Test Survey among Contacts)

The tuberculin skin test (TST) is the most frequently used test to detect latent TB infection (See Section 4.3). A higher proportion of positive TST results, interpreted as a higher prevalence of latent TB infection among contacts of one group of active cases compared to another group, suggests that the former is more contagious than the latter. There were a few studies that conducted contact investigation, but we could not find any study that compared the infectiousness of TB among diabetic vs. non-diabetic TB patients through tuberculin screening of contacts.

Trnka et al. and *Harris et al.*conducted case studies reporting contact investigation for one active TB diabetic patient without any controls. Statistical analysis on the effect of diabetes on TB infection in contacts could not be performed [76, 77].

Two studies looked for risk factors for contacts to develop active TB disease, rather than latent TB. *Grandjean et al.* (2011) investigated contacts of multidrug-resistant tuberculosis patients in Peru in 2008 and reported risk factors for development of active TB disease; the hazard ratio (HR) for those with “comorbidities” (which included diabetes and other pulmonary diseases, excluding HIV) developing active TB was 11.2 ($P<0.001$) [78]. Second, *Lee et al.* (2008), in another contact tracing study in Hong Kong, again studied risk factors associated with development of active TB in contacts of active TB patients. Diabetes mellitus was identified as a risk factor with a risk ratio of 3.44 (95% CI 1.04-11.33) [79].

Al Kubaisy et al. (2003) assessed the rate of latent TB infection among 834 household associates of 191 school children with confirmed latent TB infection in Iraq. The study identified diabetes as a risk factor for tuberculosis infection in the associates of children with LTBI, with a risk ratio of 4.04 (95% 1.51-10.74) [80]. The study by *Al Kubaisy et al.* does not satisfy the criteria to be included in the systematic review – the study did not investigate contacts of active TB patients. Although the study shows that diabetes is a risk factor for TB infection, it does not allow us to make any conclusions about transmission from persons with active TB to their diabetic contacts.

Grandjean et al., Lee et al., and Al Kubaisy identified diabetes mellitus in contacts as a risk factor for the latter to be infected or to develop active TB, but none of these studies examined the role of diabetes in the source patients.

2.2 EFFECT OF DIABETES ON HEALTH CARE COSTS FOR TB PATIENTS

Many studies have addressed the economic impact of diabetes. These studies have estimated direct healthcare costs (medication, visits to healthcare professionals, hospitalization, etc.), indirect healthcare costs (care in nursing homes, care by relatives, etc.), and productivity losses, however, no study has estimated the additional cost

associated with diabetes as a comorbid factor when coupled with other primary diagnoses. We could not find any study comparing the use of healthcare services of diabetic active TB patients vs. non-diabetic TB patients.

2.3 SUMMARY OF LITERATURE REVIEW

Several genotyping studies and contact investigations suggest that diabetes has a significant role in TB transmission. However, no genotyping study has yet performed cluster analysis that directly examines the effect of diabetes on generating subsequent cases, which could provide direct evidence regarding the association of diabetes with TB infectiousness. Also, limiting contact investigation to active TB may have missed the majority of the contacts to whom the source have transmitted, but who may not have developed active TB yet. Tuberculin skin test survey among contacts to compare frequency of latent TB infection among contacts of diabetic active TB patients with those of non-diabetic TB patients would capture TB transmission in a more complete manner.

Studies have estimated direct healthcare costs (medication, visits to healthcare professionals, hospitalization, etc.), indirect healthcare costs (care in nursing homes, care by relatives, etc.), and productivity losses associated with diabetes. Although it is clear that diabetes causes substantial economic losses, the additional cost associated with diabetes as a comorbid factor when coupled with other primary diagnoses has not been investigated.

3. METHODS

3.1 STUDY SETTING

Montreal is Canada's second largest city with a population of about 1.65 million on the Island of Montreal at the time of the last census in 2011, an increase of 1.8% from 2006. It is also the second most frequent destination for new immigrants to Canada. About 23% of the residents of the island were born outside Canada. In 2011, persons born in Haiti, Italy, France, Morocco and Algeria were the largest groups within Montreal's foreign-born population [81].

In Quebec from 2008 to 2011, the rate of tuberculosis was approximately 15 times higher in foreign-born compared to Canadian-born persons, with the foreign-born representing more than 60% of all cases. This is in part due to immigration from countries with high TB incidence including Haiti and India. More than 50% of TB patients were between of 20 and 49 years of age and 26.5% were aged 60 and over. About 80% of all cases had respiratory TB, 89% among them had pulmonary TB [82]. In Montreal, the estimated TB incidence rate in 2013 was 5.7 cases per 100 000 inhabitants [83].

In Canada, TB is a reportable disease. Accordingly in Quebec, where TB is listed among the *Maladies à declaration obligatoire* (MADO), any physician who diagnoses active TB in patient and any laboratory that identifies *M. tuberculosis* from a clinical specimen must report the case to the public health department. In turn, local public health authorities are required to report all cases of TB to their respective provincial/territorial TB programs, which voluntarily submit reports of TB cases to the Canadian TB Reporting System (CTBRS) that maintains demographic, clinical, diagnostic, treatment and outcome details of all reported active TB cases [4]. In Quebec, all *M. tuberculosis* isolates are sent to the provincial public health laboratory, the *Laboratoire de Santé Publique du Québec* (LSPQ), which conducts drug-sensitivity testing on isolates from every culture-positive case. Montreal also has an extensive TB control system that conducts contact investigation and appropriate public health

interventions including offering treatment of latent TB infection to all TST positive contacts where appropriate [26]. All TB medications, whether for treatment of active or latent TB, are provided to patients without charge.

In 2007, the study *Understanding the keys to Tuberculosis: from Exposure to Infection, and from Infection to Disease* was initiated with CIHR funding, to establish a research database (Montreal TB Research Resource Database) that contains demographic, clinical, social, and environmental information on the residents of Montreal diagnosed with culture positive TB since 1995 including information on their contacts. This research database combines information from several clinical and demographical databases, such as that of the *Maladies à déclaration obligatoire* (MADO) and of the Public Health department, and hospital/clinic records, for all culture-positive cases diagnosed between 1996 and 2007 ("retrospective cohort") and for consenting patients diagnosed between 2007 and 2012 ("prospective cohort").

The present study uses the restrospective cohort, which consists of all cases reported to have active TB on the Island of Montreal between January 1996 and May 2007 and their household or family contacts. The majority of information was retrieved from medical records of hospitals and the Public Health department. A detailed description of the study population will appear later in section 8.2.0.

3.2 EFFECT OF DIABETES ON TB TRANSMISSION

To address Objective 1, we performed a genotyping study of *M. tuberculosis* isolates and compared tuberculin skin test results among contacts of diabetic vs. non-diabetic patients.

First, *M. tuberculosis* isolates were genotyped according to the standard IS*6110* restriction fragment length polymorphism (RFLP) methodology [52] using GelCompar II (Applied Maths NV, Sint-Martens-Latem, Belgium). For isolates with less than six RFLP bands, spoligotyping was performed (Isogen Bioscience, Maarssen, The Netherlands) and identical spoligotypes were considered to be clustered if RFLP patterns were also identical [84]. For this analysis, cases with unknown diabetic status were excluded.

For each cluster, a putative index case was identified. The index case was defined as a patient with pulmonary TB whose *M. tuberculosis* genotype was new to the study population on the date of diagnosis. Therefore within each cluster, the pulmonary case with the earliest date of diagnosis was considered the index case that transmitted TB to the subsequent cases. In cases where the patient's date of diagnosis was not available, the date of case notification was used as the reference date. As extra-pulmonary TB is not infectious, clustered extra-pulmonary cases for which an index case could not be identified – either because the extrapulmonary case occurred before the cluster's first pulmonary case or because the cluster included extra-pulmonary cases only– were excluded from analysis. Their source cases were assumed to be outside our temporal or geographic limits or unavailable for genotyping [68]. However, it was possible that a patient who was initially diagnosed as having extrapulmonary TB in fact had concomitant pulmonary TB. To assess the effect of possible misclassification, we performed a sensitivity analysis where all extrapulmonary cases were included.

The transmission index (TI) was calculated by dividing the number of secondary TB cases by the sum of clustered index cases, plus cases with unique genotypes with pulmonary TB (see Section **1.3.3.2** b)). We also calculated relative transmission indices, i.e. the ratios of the indices between patient subgroups. Negative binomial regression was used to adjust for confounders [68, 85].

Univariate analyses were performed on *a priori* potential confounders (such as age, sex, country of birth and smear status), as well as other relevant predictors (such as renal disease) — in addition to diabetes, which was the primary independent variable of interest. Based on the results of these univariate analyses, variables with a statistical significance level < 0.20 were initially included in the multivariate model, with variables then removed through backward selection (α_{drop}=0.15). For transmission index, covariates besides diabetic status were age, country of birth, smear status and HIV status. Time available for detection of subsequent transmission was also considered using time at risk as an offset variable.

The effects of risk factors for TST positivity among contacts of active TB cases were calculated using hierarchical logistic regression, where the two levels were characteristics of contacts and those of index cases. A multi-level design was necessary to account for the characteristics shared by contacts of a common index case (e.g. socioeconomic characteristics) [86, 87]. Patient characteristics associated with cluster membership vs. non-membership were assessed using Chi-square or Fisher's exact tests.

To assess susceptibility of diabetic contacts, the prevalence of diabetes among secondary cases, i.e. clustered but non-index by DNA fingerprint, was compared to that among index or unique TB cases, i.e. unique genotype at the time of diagnosis. Odds ratios and 95% confidence intervals were calculated using logistic regression.

3.3 EFFECT OF DIABETES ON HEALTH CARE COSTS AND TREATMENT OUTCOME

For Objective 2 of the study, we examined additional healthcare costs using the data on hospitalization and TB therapy duration and drug types from the Resource Database. By examining these indicators of health care utilization, we tested the hypothesis that the combination of diabetes and active TB is associated with higher healthcare costs, as compared to active TB alone.

Hospitalization accounted for almost half of the active TB related costs in Canada [69]. Days of hospitalization (number of days between admission date and discharge date) was compared between TB patients with DM vs. those without. Univariate linear regression analysis was performed to estimate the effect of each variable on hospitalization duration: the regression coefficients for each variable could be interpreted as additional days of hospitalization associated with that parameter. Covariates to be used in multivariate analysis were selected through backward selection using the same method as above analyses. Through hierarchical linear regression consisting of two levels – patient and hospital, a possible clustering effect by the

characteristics of different hospitals was adjusted. All cases with unknown admission date and/or discharge date were excluded from analysis.

Costs associated with TB therapy were added using data on drug prescription and on treatment duration. Univariate and multiple linear regression were performed to identify the predictors of duration of TB therapy; clinical judgment and backward selection using α_{drop} of 0.15 was used for choosing covariates to be included in multivariate analysis. The regression coefficient for each variable could be interpreted as additional months of TB therapy associated with that variable. Costs associated with hospital stay were estimated by multiplying the number of days of hospitalization by $929.96; while by attributing costs according to the drugs prescribed for TB therapy. For estimating the cost of treatment of active, latent TB and multi-resistant TB, drugs prescribed were multiplied by the corresponding daily price and number of days prescribed. Drug costs were taken from a *Public Health Agency of Canada* report prepared by Menzies and colleagues (for first-line TB drugs), and a World Health Organization publication by Gupta and colleagues (for second line drugs) [69, 88]. All costs were expressed in 2014 Canadian dollars; values from the *Public Health Agency of Canada* report were inflated, and those from the WHO publication, which were expressed in 2001 US dollars, were converted and inflated to 2014 CAD [89]. Drugs not listed in any of the two papers were excluded in this analysis.

The WHO definitions of treatment outcomes were used: a) cure was defined as a bacteriologically-confirmed TB patient who was smear- and culture-negative in the last month of treatment and on at least one previous occasion; b) failure was a patient who was initially and remained sputum culture-positive at month 5 or later during treatment. Included in this definition were patients found to have multidrug-resistant TB at any point in treatment; c) defaulted was a patient whose treatment was interrupted for two consecutive months or more; d) death was a patient who died during treatment for any reason; e) unknown was defined as a case whose treatment outcome was not known, including loss to follow-up due to the patient having moved out of Montreal or lack of microbiologic information at the end of the treatment [53]. All cases with unknown

treatment outcome were excluded from this analysis. Univariate and multivariate logistic regression were performed to identify factors associated with treatment failure and death, using the same model building method as above.

The proportion excluded due to missing values for the above variables was 7%, and that excluded due to being an extrapulmonary first case was 0.9%.

4. RESULTS

4.0 STUDY POPULATION

There were 1862 episodes of active TB in the retrospective database; among them 8 entries were relapses or recurrences, meaning individuals who were re-reported as active TB cases after recovery from their first TB episode. Therefore, 1854 subjects who had a first episode of active TB between January 3, 1996 and November 9, 2007, were included in this study (See **Figure A** in APPENDIX I). Analysis was limited to first episodes only. Mean age was 43.5 and 54.1% were male. Other characteristics of the study population are described in **Table 1**. 130 subjects (7.0%) had no documentation of diabetes status (yes/no); these subjects were excluded from analysis. Among 1724 subjects who were reported to have active TB between 1996 and 2007 and whose diabetes status was recorded, 132 (7.7%) were identified as diabetic based on their public health and/or hospital records. Diabetic TB patients were older, had a higher proportion of positive smear microscopy results, and more often suffered from liver disease when compared to non-diabetic TB patients. Difference in smear results was no longer statistically significant when restricted to pulmonary TB cases; 121 extra-pulmonary TB cases had positive smear results and 10 among them were diabetic.

Diabetic status of TB patients was significantly associated with renal disease; diabetic TB patients were 5.4 times more (95%CI 3.3-9.0) likely to have concomitant renal disease compared to non-diabetic TB patients. Among 94 TB patients who had renal diseases, 88 (93.6%) had information on their types of renal diseases: 53 (60.2%) had chronic renal insufficiency, While 19.8% of diabetic TB patients had renal diseases, the majority (91.7%; 22 out of 24 who had information on their types of renal disease) had chronic renal insufficiency. Among non-diabetic TB patients with renal diseases, only 48.4% (31 out of 64 who had information on their types of renal diseases) suffered chronic renal insufficiency. A cross-tabulation of diabetes mellitus and chronic renal insufficiency is shown in **Table 2**. Diabetic status was significantly associated with chronic renal insufficiency. Differences in other characteristics were not statistically significant.

Table 1 Characteristics of active TB cases by diabetic status

Characteristics	Diabetic n (%)	Non-diabetic n (%)	Total n = 1854	Chi-square, Fisher's exact[1] or t-test p-value
Cases	132 (7.66%)	1592 (92.34%)	1724†	
Age			1713	<0.001
<15	1(0.77%)	60(3.79%)	61(3.56%)	
15-24	0(0.00%)	263(16.61%)	263(15.35%)	
25-34	3(2.31%)	404(25.52%)	407(23.76%)	
35-44	16(12.31%)	290(18.32%)	306(17.86%)	
45-54	23(17.69%)	160(10.11%)	183(10.68%)	
55-64	25(19.23%)	121(7.64%)	146(8.52%)	
65-74	24(18.46%)	139(8.78%)	163(9.52%)	
75-84	34(26.15%)	106(6.70%)	140(8.17%)	
≥ 85	4(3.08%)	40(2.53%)	44(2.57%)	
Sex			1715	0.216
Male	79(59.85%)	859(54.26%)	938(54.69%)	
Female	53(40.15%)	724(45.74%)	777(45.31%)	
HIV status			905	0.051
Positive	2(4.35%)	130(15.13%)	132(14.59%)	
Negative	44(95.65%)	729(84.87%)	773(85.41%)	
Disease site			1721	
Pulmonary	88(66.67%)	978(61.55%)	1066(61.94%)	0.244
Extra-pulmo.	30(22.73%)	490(30.84%)	520(30.21%)	0.051
Both	14(10.61%)	121(7.61%)	135(7.84%)	0.219
Smear test			1721	0.011
Positive	69(52.27%)	649(40.84%)	718(41.72%)	
Negative	63(47.73%)	940(59.16%)	1003(58.28%)	
Pulmonary TB smear			1201	0.086
Positive	59(57.84%)	538(48.95%)	597(49.71%)	
Negative	43(42.16%)	561(51.05%)	604(50.29%)	
Place of birth			1716	0.065
Canadian	16(12.21%)	296(18.68%)	312(18.18%)	
Non-Canad.	115(87.79%)	1289(81.32%)	1404(81.82%)	
Aboriginal			173	>0.999
Yes	0(0.00%)	6(3.68%)	6(3.47%)	
No	11(100%)	157(96.3%)	168(97.1%)	
From TB endemic countries[b]			1661	0.425
Yes	97(74.6%)	1092(71.3%)	1189(71.6%)	
No	33(25.4%)	439(28.7%)	472(28.4%)	
Drug resistance[c]			1417	0.396
Yes	9(8.41%)	145(11.07%)	154(10.87%)	
No	98(91.59%)	1163(88.93%)	1263(89.13%)	
Marital status			222	0.204
Married	11(68.8%)	106(51.5%)	117(52.7%)	
Single[d]	5(31.3%)	100(48.5%)	105(47.3%)	
Working			249	0.064
Yes	2(11.1%)	78(33.8%)	80(32.1%)	
No	16(88.9%)	153(66.2%)	169(67.9%)	
Obesity			363	0.750
Yes	3(7.69%)	23(7.10%)	26(7.16%)	
No	36(92.3%)	301(92.9%)	337(92.8%)	
Previous TB diagnosis (latent/active)			1595	0.661
Yes	12(10.3%)	173(11.7%)	185(11.6%)	
No	104(89.7%)	1306(88.3%)	1410(88.4%)	
BCG vaccination			325	0.115
Yes	2(10.5%)	85(27.8%)	87(26.8%)	
No	17(89.5%)	221(72.2%)	238(73.2%)	
Comorbidities: Pulmonary condition			1706	0.111

Yes	29(22.8%)	272(17.2%)	301(17.6%)	
No	98(77.2%)	1307(82.8%)	1405(82.4%)	
Comorbidities: Liver disease			1708	0.002
Yes	18(14.1%)	105(6.65%)	123(7.20%)	
No	110(85.9%)	1475(93.4%)	1585(92.8%)	
Comorbidities: Renal disease			1713	<0.001
Yes	25(19.8%)	94(5.49%)	94(5.49%)	
No	101(80.2%)	1619(94.5%)	1619(94.5%)	
Comorbidities: Immune illnesses[e]			1706	0.577
Yes	14(11.4%)	208(13.1%)	222(13.0%)	
No	109(88.6%)	1375(86.9%)	1484(87.0%)	
History of smoking			1400	0.393
Yes	29(28.2%)	418(67.8%)	447(31.9%)	
No	74(71.8%)	879(32.2%)	953(68.1%)	

[1]Fisher's exact test when any of the cells of the contingency table is below 5.
[b]Endemic countries defined in *Albanna et al.* (2011)[63].
[c]Drug resistance to any of TB drugs.
[d]Single includes unmarried, divorced or widowed.
[e]Immune illnesses include HIV, cancer, transplantation
† The number in each category under the column "Total" represents the number of subjects with no missing information in the corresponding category.

Table 2 Diabetes mellitus and chronic renal insufficiency

		Chronic renal insufficiency		Total
Diabetes		Yes	No	
	Yes	22 (91.7%)	2 (8.3%)	24 (100%)
	No	31 (48.4%)	33 (51.6%)	64 (100%)
		35 (39.8%)	53(60.2%)	88 (100%)

Among 6553 individuals who were listed as contacts of an active TB case, 289 were contacts of index patients without information as to diabetic status; 6264 contacts were used for analysis.

4.1 INFECTIOUSNESS OF DIABETIC VS NON-DIABETIC ACTIVE TB PATIENTS

Of the 1862 reported TB cases, 1583 (85.0%) were culture-positive. 1549 (97.9%) of these isolates were successfully genotyped. According to RFLP analysis, 96 clusters were identified involving 282 persons with active TB (18.2%); 1267 active TB cases were not clustered. Most clusters were small, although cluster size ranged from 2 to 14 cases (See **Figure 1**). Patients born in Canada, especially those with Aboriginal status, were significantly more likely to be cluster members (See **Table 3**). As for age, patients

aged 14 and younger and patients aged between 35 and 44 were more likely to be part of a cluster. Positive smears and positive HIV status were also significantly associated with cluster membership. No significant association was found between diabetic status and cluster membership, even after adjustment for age, sex, Canadian birth, smear status and HIV status (aOR 1.6, 95% CI 0.7 to 3.9) (See **Table 4**).

Figure 1 Cluster count by cluster size

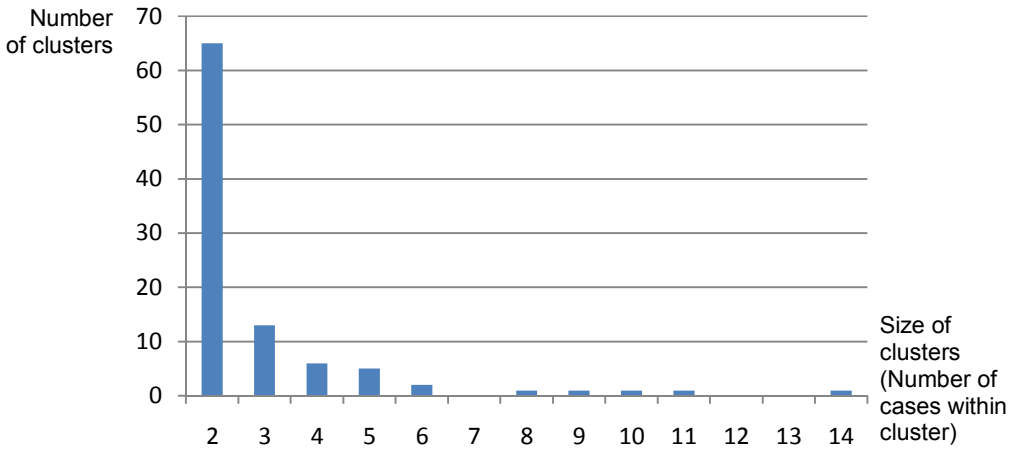

Table 3 Characteristics of TB cases by cluster membership

Characteristics	Clustered n(%)	Non-clustered n(%)		Chi-square, Fisher's exact* or t-test P-value
Age			1540	0.017[a]
<15	13(4.61%)	19 (1.51%)	32(2.08%)	0.001[b]
15-24	47(16.67%)	187(14.86%)	234(15.19%)	0.446
25-34	53(18.79%)	302(24.01%)	355(23.05%)	0.060
35-44	66(23.40%)	229(18.20%)	295(19.16%)	0.045
45-54	34(12.06%)	130(10.33%)	164(10.65%)	0.397
55-64	24(8.51%)	102(8.11%)	126(8.18%)	0.824
65-74	20(7.09%)	129(10.25%)	149(9.68%)	0.104
75-84	20(7.09%)	119(9.46%)	139(9.03%)	0.210
>= 85	5(1.77%)	41(3.26%)	46(2.99%)	0.240
Sex			1545	0.879
Male	154(54.61%)	567(44.89%)	850(55.02%)	
Female	128(45.39%)	696(55.11%)	695(44.98%)	
Country of Birth			1541	<0.001
Canadian	66(26.09%)	164(15.09%)	230(17.16%)	
Non-Canadian	187(73.91%)	923(84.91%)	1110(82.84%)	
Aboriginal				0.009
Yes	5(10.42%)	1(0.88%)	6(3.70%)	
No	43(89.58%)	113(99.12%)	156(96.30%)	

Smear test[c]			1073	0.032
Positive	127(62.25%)	469(53.97%)	596(55.55%)	
Negative	77(37.75%)	400(46.03%)	420(44.45%)	
HIV status			802	0.001
Positive	44(24.44%)	85(13.67%)	129(16.08%)	
Negative	136(75.56%)	537(86.33%)	673(83.92%)	
Diabetes			**1444**	**0.354**
Diabetic	**17(6.44%)**	**96(8.14%)**	**113(7.83%)**	
Non-diabetic	**247(93.56%)**	**1084(91.86%)**	**1331(92.17%)**	

[a]T-test for age
[b]Chi-square for age group and cluster membership
[c]For pulmonary TB cases only.

Table 4 Crude and adjusted odds ratios for cluster membership, based on patient characteristics

Characteristics	Crude odds ratio (95%CI)	Adjusted odds ratio[a] (95% CI)
Age	0.99 (0.986-0.999)	0.99 (0.978-1.005)
Male sex	0.97 (0.7-1.3)	0.8 (0.5-1.3)
Canadian birth	2.2 (1.6-2.9)	2.5 (1.6-4.1)
Aboriginal	13.1 (1.5-115.7)	
Positive smear test[b]	1.4 (1.03-1.9)	1.1 (0.7-1.7)
Positive HIV status	2.0 (1.4-3.1)	2.2 (1.4-3.7)
Diabetic	**0.8 (0.5-1.3)**	**1.6 (0.7-3.9)**

[a]Adjusted for all other variables using multivariate logistic regression. (Except for Canadian and Aboriginal due to collinearity (dropped the variable "Aboriginal" for multivariate analysis as it has more missing data))
[b]For pulmonary TB cases only

Seven clusters with extrapulmonary cases only (14 extrapulmonary cases) and 398 non-clustered extrapulmonary TB cases were excluded from the transmission index analysis. 958 active pulmonary cases were identified, among which 89 were index cases and generated 160 subsequent cases. The sensitivity analysis including all extrapulmonary cases is in **Table B** in APPENDIX I.

Overall transmission index of the study population was 0.17, i.e. 160/958. Transmission indices varied with age; it was highest in the 15 year and younger (adjusted relative transmission index 5.78, 95% CI 1.94-17.25), then peaked in the 35-44 age group. Canadian-born patients, positive smears, HIV status, pulmonary and liver comorbidities were associated with higher transmission index relative to index cases without these characteristics. After adjustment using negative binomial regression, only age was significantly associated with transmission index (See **Table 5**).

Table 5 Transmission indices for TB in Montreal, Canada, 1996-2007

Characteristics of index	Index and non-clustered pulmonary cases n	Subsequent cases generated n	Transmission index			
			Crude	Relative[a] crude	Relative adjusted[a,b]	95%CI
Total	958	160	0.17			
Age						
<15	16	27	1.69	9.49	5.78	1.94-17.25
15-24	157	12	0.076	0.43	0.67	0.55-0.81
25-34	225	40	0.18	1.00[†]	1.00[†]	
35-44	163	37	0.23	1.28	1.11	1.02-1.21
45-54	97	15	0.16	0.87	0.55	0.35-0.87
55-64	68	4	0.059	0.33	0.42	0.14-1.32
65-74	102	16	0.16	0.88	3.59	1.65-7.82
75-84	94	8	0.085	0.48	0.36	0.07-1.81
≥ 85	29	1	0.034	0.19	0.000132	0
Country of Birth						
Canada	186	58	0.31	1.00[†]	1.00[†]	
Others	771	102	0.13	0.42	0.62	0.27-1.40
Smear test						
Positive	526	92	0.18	1.11	1.02	0.52-1.99
Negative	432	68	0.16	1.00[†]	1.00[†]	
HIV status						
Positive	77	25	0.33	2.01	1.91	0.85-4.33
Negative	434	70	0.16	1.00[†]	1.00[†]	
Diabetes						
Diabetic	**77**	**2**	**0.026**	**0.14**	**0.79**	**0.13-4.63**
Non-diab.	**831**	**151**	**0.18**	**1.00[†]**	**1.00[†]**	
Pulmonary diseases						
Yes	193	36	0.19	1.15	2.16	0.95-4.92
No	719	117	0.16	1.00[†]	1.00[†]	
Liver diseases						
Yes	64	20	0.31	1.97	2.00	0.69-5.78
No	845	134	0.16	1.00[†]	1.00[†]	
Renal diseases						
Yes	52	7	0.14	0.78	0.68	0.84-5.46
No	856	148	0.17	1.00[†]	1.00[†]	

[a] Transmission indices relative to the reference category, i.e. the ratios of the indices between patient subgroups

[b]Adjusted for age, country of birth, smear status, HIV status, HIV status and person-time at risk using negative binomial regression.

[†]Reference category

Of 77 diabetic patients with pulmonary TB who had a unique genotype at their time of diagnosis, only two transmitted TB to others. Of 755 non-diabetic pulmonary TB patients with a unique genotype, 76 were transmitters. The comparison between transmitters and non-transmitters among pulmonary TB patients with unique genotypes is shown in **Table C** in the APPENDIX I. Diabetic active TB patients generated slightly less subsequent cases (adjusted TI 0.79, 95% CI 0.13-4.63) relative to the same reference

group, but the difference was not statistically significant and confidence intervals were wide.

Contacts of diabetic TB patients were more likely to be male and family or household members of the index case. Overall, one-third of contacts were treated for latent TB infection. Differences in other characteristics were not statistically significant (See **Table 6**). For about 77% of all contacts, records of isoniazid (INH) prescription (yes/no) were available. As a single TST result may not be an accurate indicator of recent TB infection and INH treatment may better reflect the physician's diagnosis of recent TB infection, data on whether or not the contact was put on isoniazid were also used as another indicator of TB infection.

Among contacts, 41.0% had a positive tuberculin skin test result. Positive TST was positively associated with age of contact, age of index patient, and family or household contact with the index case. Positive TST results were also associated with pulmonary TB and foreign birth in the index case. Crude logistic regression found no significant association between TST results in contacts and diabetic status of TB index cases: crude odds ratio was 1.1 (95% CI 0.9-1.3). When adjusted for age of both index and contact, the adjusted OR was 1.4 (95% CI 1.1-1.7). When adjusted for age of both index and contact, and family or household relationship, the adjusted OR was 1.3 (95% 1.1-1.6). Hierarchical logistic regression was performed to adjust for characteristics shared by contacts of common index cases: adjusted OR was 1.4 (95% CI 1.0-1.9). When INH treatment was used as a surrogate for latent infection, crude logistic regression yielded an odds ratio of 1.6 (1.3-2.0), comparing the odds of INH treatment in contacts of diabetics vs. non-diabetics. Increasing age of both contact and index was associated with INH treatment, OR=0.996 (0.993-0.999) for every additional year and OR=0.979 (0.974-0.982) respectively, which can be translated into an OR of about 0.8 for a 10-year increase in age of the index case. Age-adjusted OR for INH treatment and diabetic status of index was 1.8 (1.4-2.3). When clustering among contacts of common index was considered, OR remained 1.8 with wider confidence interval (1.2-2.7).

Table 6 Characteristics of contacts of the active TB cases by diabetic status of index

Characteristics of contacts	Diabetic index case n(%)	Non-diabetic index case n(%)	P-value*	Positive TST contacts of diabetic index n(%)	Positive TST contacts of non-diabetic index n(%)	P-value
Contacts	565 (9.0%)	5699 (91.0%)		235(9.6%)	2225(90.4%)	
N. of contacts per index	4.3	3.6				
TST result			0.437			
Positive	235(42.2%)	2225(40.5%)				
Negative	322(57.8%)	3270(59.5%)				
Age			0.283			<0.001
<15	123(29.0%)	1146 (27.7%)		24(12.8%)	326(17.8%)	
15-24	70(16.5%)	796(19.3%)		21(11.2%)	341(18.6%)	
25-34	62(14.6%)	675(16.3%)		39(20.7%)	380(20.8%)	
35-44	62(14.6%)	618(15.0%)		44(23.4%)	337(18.4%)	
45-54	48(11.3%)	430(10.4%)		29(15.4%)	232(12.7%)	
55-64	27(6.4%)	247(6.0%)		14(7.5%)	135(7.4%)	
65-74	21(5.0%)	137(3.3%)		12(6.4%)	56(3.1%)	
75-84	10(2.4%)	66(1.6%)		4(2.1%)	18(1.0%)	
≥ 85	1(0.2%)	16(0.4%)		1(0.5%)	5(0.3%)	
Sex			0.008			0.331
Male	231(51.3%)	1515(44.7%)		97(47.5%)	668(44.0%)	
Female	219(48.7%)	1871(55.3%)		107(52.5%)	852(56.0%)	
Country of birth			0.016			0.683
Canada	103(45.0%)	572(36.7%)		16(15.8%)	111(14.3%)	
Others	126(55.9%)	987(63.3%)		85(84.2%)	664(85.7%)	
Relationship						
Family/ Household	436(80.2%)	3642(66.5%)	<0.001	199(85.4%)	1644(74.8%)	<0.001
Friend	10(1.8%)	305(5.6%)	<0.001	2(0.9%)	138(6.3%)	0.001
School/Work	24(4.4%)	757(13.8%)	<0.001	8(3.4%)	173(7.9%)	0.014
Other	74(13.6%)	774(14.1%)	0.736	24(10.3%)	242(11.0%)	0.740
Put on INH			<0.001			<0.001
Treated	181(43.4%)	1385(32.0%)		133(75.6%)	1028(61.5%)	
Not treated	236(56.6%)	2939(68.0%)		43(24.4%)	645(38.5%)	

* Chi-square, Fisher's exact* or t-test p-value

4.2 SUSCEPTIBILITY TO TB DISEASE OF DIABETIC VS NON-DIABETIC CONTACTS

Among 908 index cases with known diabetic status, 77 (8.48%) were diabetic; while 15 among 155 subsequent cases – presumed secondary cases within clusters – were diabetic (9.68%). Although the prevalence of diabetes is higher among subsequent cases compared to index cases, the association was not statistically significant: OR = 1.2 (95%CI 0.6-2.1). Canadian-born, Aboriginal persons in particular, were also overrepresented among secondary as compared with index cases (See **Table 7**).

Table 7 Characteristics of active TB cases by index VS subsequent

Characteristics	Index n(%)	Subsequent n(%)		Chi-square, Fisher's exact* or t-test p-value
Cases	958(85.6%)	160 (14.3%)	1118	
Age			1111	0.167
<15	16(1.7%)	7 (4.4%)	23(2.1%)	0.027
15-24	157(16.5%)	31(19.4%)	188(16.9%)	0.371
25-34	225(23.7%)	26(16.3%)	251(22.6%)	0.038
35-44	163(17.1%)	38(23.8%)	201(18.1%)	0.044
45-54	97(10.2%)	16(10.0%)	113(10.2%)	0.938
55-64	68(7.2%)	14(8.8%)	82(7.4%)	0.474
65-74	102(10.7%)	13(8.1%)	115(10.4%)	0.318
75-84	94(9.9%)	11(6.9%)	105(9.5%)	0.229
>= 85	29(3.1%)	4(2.5%)	33(3.0%)	0.705
Sex			1115	0.061
Male	565(59.2%)	82(51.3%)	647(58.0%)	
Female	390(40.8%)	78(48.7%)	468(42.0%)	
Country of Birth			1117	<0.001
Canada	186(19.4%)	55(34.4%)	241(21.6%)	
Others	771(80.6%)	105(65.6%)	876(78.4%)	
Aboriginal			140	0.005
Yes	1(1.0%)	5(13.5%)	6(4.3%)	
No	102(99.0%)	32(86.5%)	134(95.7%)	
Smear test***			1073	0.224
Positive	526(54.9%)	70(60.9%)	596(55.6%)	
Negative	432(45.1%)	45(39.1%)	477(44.4%)	
HIV status			621	0.082
Positive	77(15.1%)	24(21.8%)	101(16.3%)	
Negative	434(84.9%)	86(78.2%)	520(83.7%)	
Diabetes			**1063**	**0.624**
Diabetic	**77(8.5%)**	**15(9.7)**	**92(8.7%)**	
Non-diabetic	**831(91.5%)**	**140(90.3%)**	**971(91.3%)**	

Therefore, when susceptibility to TB disease is estimated by comparing the prevalence of the characteristic among subsequent vs. index TB cases, Canadian birth and aboriginal status were significantly associated with susceptibility.

4.3 EFFECT OF DIABETES ON HEALTH CARE COSTS FOR TB PATIENTS

4.3.1 Hospitalization Duration

1581 cases with records on hospitalization and known DM status were used for analysis. 102 cases with unknown admission date and/or discharge date were excluded from the analysis. Hospital stays less than <24 hours were counted as one day. The mean hospitalization duration was 25.12 days (range 1-1130); this is about $23,360 when multiplied by $929.96 per day of hospital stay.

When adjusted for age, smear-positive pulmonary TB was associated with 11.19 days longer hospitalization duration, which can be translated into $10 406.25. Among comorbidities, when adjusted for age and positive smear pulmonary TB, renal disease was the strongest predictor of longer hospitalization duration: 14.42 days more when diagnosed with renal condition, i.e. about $13 410.02. Diabetes was not a significant predictor of hospitalization duration. Its crude coefficient value was +3.23d (95% CI -5.71d to 12.17d; $3 003.77). The effect disappeared when adjusted for age and smear status (adjusted coefficient= -0.71d, 95% CI -12.34d to 26.69d). When hierarchical linear regression was performed to adjust for clustering effect by hospital, the effect of diabetes on hospitalization duration was even closer to zero (regression coefficient= -0.53d, 95% CI -6.24d to 5.19d).

Table 8 Regression Coefficients for Variables on Hospitalization Duration in Days

Variables	Coefficient (additional days)	95% Confidence Interval	Adjusted Coefficient[b] (additional days)	95% Confidence Interval
Age (per year older)	0.17	0.047 to 0.30	0.069	-0.09 to0.23
Male	-0.73	-6.39 to 4.93	-1.05	-8.45 to 6.34
Canadian	0.40	-6.27 to 7.07	-2.23	-10.54 to 6.08
Aboriginal	5.74	-17.03 to 28.51	8.90	-15.12 to 32.91
Pos. smear PTB	11.19	3.87 to 18.51	11.41	4.05-18.76
Drug resistant	4.93	-5.40 to 15.27	6.68	-6.04 to19.39
Homeless	11.45	-11.67 to 34.57	6.05	-19.53 to 31.64
HIV positive	0.999	-8.85 to 10.84	-0.66	-13.34 to 12.02
Any comorbidity[a]	5.95	0.21 to 11.69	-0.27	-8.85 to 8.31
Pulmonary	1.61	-4.85 to 8.06	-3.47	-12.05 to 5.12
Liver	1.62	-7.65 to10.90	0.86	-11.20 to12.92
Cardiac	5.29	-1.60 to 12.19	1.52	-9.01 to12.05
Renal	16.66	7.01 to 26.31	14.33	1.03 to 27.63
Immunosuppressive	0.40	-6.58 to 7.38	-1.38	-10.14 to 7.38
Diabetic	**3.23**	**-5.71 to12.17**	**-0.71**	**-12.34 to26.69**

Regression coefficients could be interpreted as additional days of hospitalization if risk factor present.
[a]Case with any comorbidity including HIV, any pulmonary, liver, cardiac, renal, immunosuppressive or diabetic conditions.
[b]Adjusted for age and positive smear PTB

Table 9 Regression Coefficients for Variables on Therapy Duration in Months

Variables	Coefficient (months)	95% Confidence Interval	Adjusted Coefficient (months)[b]	95% Confidence Interval
Age (per year older)	-0.004	-0.014 to.0064	0.0098	-0.0086 to 0.028
Male	-0.68	-1.11 to -0.24	-1.06	-1.67 to -0.43
Canadian	-0.40	-0.94 to 0.14	0.17	-0.63 to 0.97
Aboriginal	0.51	-2.73 to 3.76	-1.54	-5.48 to 2.40
From endemic region	0.72	0.24 to1.20	-0.21	-0.95 to 0.53
Pos. smear PTB	0.63	0.19 to 1.08	0.28	-0.35 to 0.92
Extrapulmonary TB	1.44	0.96 to 1.91	1.57	0.75 to 2.39
Drug resistant	2.68	1.92 to 3.45	3.72	2.80 to 4.64
Homeless	1.19	-0.83 to 3.21	0.81	-1.20 to 2.8
HIV positive	2.87	2.05 to 3.70	2.09	1.30 to 8.52
Any comorbidity[a]	0.44	-.0001 to 0.88	0.72	0.17 to 1.28
Pulmonary	-0.78	-1.31 to -0.24	0.26	-0.54 to 1.07
Liver	0.66	-0.13 to 1.45	1.23	0.16 to 2.30
Cardiac	-0.38	-0.96 to 0.20	0.06	-1.12 to 1.24
Renal	-0.15	-0.98 to 0.69	-0.10	-1.56 to 1.36
Immunosuppressive	1.41	0.82 to 2.00	-0.44	-2.48 to 1.59
Diabetic	**-1.12**	**-1.87 to -0.37**	**-0.66**	**-2.04 to 0.73**

Regression coefficients could be interpreted as additional months of TB therapy if risk factor present.
[a]Case with any comorbidity including HIV, any pulmonary, liver, cardiac, renal, immunosuppressive or diabetic conditions.
[b]Adjusted for age, sex, smear status, HIV status and drug resistance,

4.3.2 TB Therapy Duration

The mean therapy duration in months was 7.97 months, ranging from 0 to 66 months. According to univariate linear regression, TB therapy was longer when the patient was female, had positive smear pulmonary TB, had TB in an extrapulmonary site, had drug resistance, had immunosuppressive conditions or was HIV positive (See Table 8). Diabetes was not associated with longer treatment. After multivariate analysis, female sex, extrapulmonary TB, drug resistance, HIV status, liver disease and having any comorbidity were associated with longer therapy duration. Drug resistance (adjusted coefficient +3.72 months, 95%CI 2.80 to 4.64 mo) and HIV positive status (+2.09 mo, 1.30 to 8.52 mo.) were the strongest predictors of TB therapy duration. Diabetes was associated with somewhat shorter treatment (-1.12 mo).

4.3.3 Cost of TB Drugs for Treatment

The most commonly prescribed drugs were isoniazid ($0.07 for 300mg daily), rifampin ($2.28 for 600mg daily), pyrazinamide ($1.80 for 1500mg daily), ethambutol ($0.97 for

1200mg daily) and vitamin B6 ($0.12 for 25mg daily) [69]. Total cost for TB drugs for treatment of an active case ranged from $38.73 to $33 929.52, and the average cost was $2155. In the univariate analysis, drug resistance, HIV positive status, any immunosuppressive condition, liver disease and endemic origin were associated with higher costs of drug treatment, in decreasing order of effect size. In the multivariate analysis including age, sex, drug resistance, and HIV status, drug resistance was the strongest predictor of treatment cost, with an additional cost of $6300. Diabetes was not associated with higher TB drug treatment cost. Adjusted regression coefficients for each variable are given in **Table 10**.

4.3.4 TB Therapy Outcome

Among 1724 TB patients with known treatment outcome, 1439 (87.6%) were cured, 114 (6.94%) died during treatment, 24 (1.46%) were defaulted, 1 (0.06%) failed, and 65 (3.96%) have moved. According to univariate logistic analysis, predictors of unfavorable outcome (death or failure) were age, male sex, Canadian birth, homelessness and positive HIV status. Having any comorbidity increased the odds of having treatment failure by about 9-fold. Of comorbidities, renal conditions were the strongest predictor of adverse outcome. Diabetes mellitus was associated with 2.8 fold increase in odd of treatment failure (95%CI 1.7 to 4.8).

For multivariate logistic regression, age and renal conditions remained significantly associated with treatment failure or death. Diabetes was no longer a statistically significant risk factor (aOR=1.6, 95%CI 0.4-6.1). As the most common cause of renal failure is diabetes, the interaction of the two was assessed. When diabetes and renal failure were both present, this was the strongest risk factor for treatment failure, resulting in an adjusted odds ratio of 13.6 (See **Table 13**).

Table 10 Regression Coefficients for Cost of TB Drugs for Treatment

Variables	Coefficient ($)	95% Confidence Interval	Adjusted Coefficient ($)[b]	95% Confidence Interval
Age (per year older)	-3.44	-13.50 to 6.63	-1.79	-18.31 to 14.73
Male	298.24	-120.39 to 716.87	549.90	-4.44 to 1104.24
Canadian	-498.33	-1035.37 to 38.72	-168.78	-952.85 to 615.29
Aboriginal	-144.54	-3147.06 to 2857.98	-930.42	-3426.46 to 1565.63
From endemic region	555.48	82.37 to 1028.58	147.92	-540.28 to 836.12
Pos. smear PTB	214.74	-339.44 to 768.91	-202.11	-904.17 to 499.96
TB sites:				
Pulmonary only	130.48	-304.30 to 565.27	128.61	-459.63 to 716.85
Extrapulmonary	-309.95	-772.35 to 152.44	-218.00	-853.22 to 417.22
Both	478.77	-316.15 to 1273.69	195.25	-882.34 to 1272.83
Drug resistant	4178.53	3535.23 to 4821.83	6300.00	5314.80 to 7285.21
Homeless	-773.18	-3014.85 to 1468.48	-1245.06	-3662.42 to 1172.29
HIV positive	1800.58	720.51 to 2880.64	995.14	65.03 to 1925.24
Any comorbidity[a]	261.59	-154.18 to 677.36	-159.96	-880.85 to 560.93
Pulmonary	-451.75	-1022.37 to 118.87	-300.65	-1114.75 to 513.46
Liver	918.00	103.70 to 1732.30	-288.26	-1306.31 to 729.80
Cardiac	-240.73	-810.73 to 329.28	18.42	-1158.40 to 1195.24
Renal	-533.43	-1442.59 to 375.72	-417.98	-2117.48 to 1281.51
Immunosuppressive	1232.47	545.87 to 1919.06	851.71[c]	195.12 to 1508.30
Diabetic	**158.26**	**-638.56 to 955.09**	**31.58**	**-1241.18 to 1304.33**

Regression coefficients could be interpreted as additional months of TB therapy if risk factor present.
[a]Case with any comorbidity including HIV, any pulmonary, liver, cardiac, renal, immunosuppressive or diabetic conditions.
[b]Adjusted for age, sex, drug resistance and HIV status.
[c]Adjusted for age, sex and drug resistance.

Table 11 Treatment outcomes by diabetic status

Treatment outcomes	Diabetic TB patients n(%)	Non-diabetic TB patients n(%)	Chi-square or Fisher's exact p-value
	129(100%)	1514(100%)	
Cured	100(77.5%)	1339(88.4%)	<0.001
Defaulted	2(1.6%)	22(1.5%)	0.930
Died	20(15.5%)	94(6.2%)	<0.001
Failed	0(0.0%)	1(0.1%)	1.000
Moved	7(5.4%)	58(3.8%)	0.372

Table 12 Predictors of unfavorable outcome (death or failure)

Variables	Crude Odds Ratio	95% Confidence Interval	Adjusted Odds Ratio[a]	95% Confidence Interval
Age (per year older)	1.1	1.04-1.07	1.04	1.01-1.07
Male	1.5	1.03-2.3	1.8	0.8-4.5
Canadian	2.6	1.7-3.9	1.1	0.4-3.0
Aboriginal	1.5	0.2-15.0		
From endemic region	0.3	0.2-0.4		
Pos. smear PTB	1.5	0.95-2.2	1.7	0.8-4.0
Extrapulmonary TB	0.5	0.3-0.8		
Drug resistant	0.7	0.3-1.4		
Homeless	3.8	1.04-14.1	2.2	0.4-12.1
HIV positive	4.1	2.2-7.8	2.2	0.4-12.6
Any comorbidity	9.0	5.3-15.2		
Pulmonary	3.3	2.2-4.9	1.1	0.4-2.7
Liver	2.5	1.4-4.3	0.5	0.2-1.8
Cardiac	5.9	3.9-8.8	1.7	0.5-5.3
Renal	9.7	6.0-15.8	4.1	1.2-14.0
Immunosuppressive	5.0	3.3-7.5	3.2	0.6-16.4
Diabetic	**2.8**	**1.7-4.8**	**1.6**	**0.4-6.1**

[a]Adjusted for age, sex, Canadian birth, smear status, homelessness, HIV status, and all comorbidities.

Table 13 Test for interaction between diabetes mellitus and renal failure

	N (%)	Crude odds ratio -	95% CI	Adjusted odds ratio[a]	95% CI
DM+RF+	45(2.1%)	11.1	4.7-26.3	13.6	1.6-119.4
DM+RF-	142(6.6%)	2.3	1.1-4.5	1.9	0.5-7.2
DM-RF+	114(5.3%)	9.9	5.7-17.4	3.5	1.02-12.2
DM-RF-	1857(86.1%)	1.0		1	

[a]Adjusted for age, sex, Canadian birth, smear status, homelessness, and HIV status.

5. DISCUSSION

5.1 SUMMARY

This study examined the clinical and economic impact of diabetes on tuberculosis in Montreal over an 11-year period (from 1996 to 2007). First, the impact of diabetes on the transmission dynamics of *Mycobacterium tuberculosis* (MTB) was assessed using molecular epidemiologic methods and tuberculin skin testing among contacts. Second, the additional health care burden caused by diabetes was examined through comparing length of hospital stay, length of TB therapy, cost of TB treatment, and treatment outcomes.

Over an 11-year period, patients with diabetes mellitus did not generate significantly more subsequent active TB cases. Canadian-born patients, younger patients (<15), patients with sputum smear positive pulmonary TB and HIV co-infection were associated with more secondary cases compared to those without these characteristics. Based on TST results among contacts, contacts of diabetics with active pulmonary TB were more likely to be TST positive and to be treated with isoniazid. A weak, but statistically significant association was found between diabetes and being a subsequent TB patient within a cluster, i.e. a transmittee.

TB patients with diabetes did not have longer hospital stays than those without diabetes. Concomitant renal disease was the strongest predictor of length of hospitalization in TB patients. Drug resistance and HIV co-infection were the two strongest predictors of treatment duration; diabetes was not associated with treatment duration. Likewise, it was not associated with higher treatment costs, while drug resistance and HIV co-infection were strongly associated with higher cost. Diabetes increased the risk of death or failure during treatment by 2.8-fold (95%CI 1.7-3.9). After adjustment for other characteristics, diabetes was no longer associated with adverse outcomes, while renal disease remained the strongest predictor of death or treatment failure. The effect of diabetes on the risk of death or failure during treatment was relatively modest in this study compared to others.

5.2 INTERPRETATION

Two indicators were used to compare infectiousness of diabetic vs. non-diabetic active TB patients. Based on genotyping of *M. tuberculosis* isolates, diabetic active TB patients generated less subsequent cases than non-diabetic active TB patients, though this difference was no longer evident after adjustment for confounders. However, tuberculin skin test results among contacts suggested that diabetic TB patients may transmit TB infection more frequently than non-diabetics.

There are two reasons why the results of contact tracing would better reflect the infectiousness of diabetic TB patients. First, the contact tracing had far greater number compared to genotyping study, therefore had much greater power to detect the effect of diabetes on TB transmission dynamics. There were only two diabetic active TB patients who were transmitters, compared to 76 non-diabetic transmitters (See APPENDIX I **Table C**). Second, the transmission index is affected by factors other than the infectiousness of the source case. Characteristics shared by the contacts of a common source that increase the risk of developing active TB inflates the transmission index. For example, several studies have identified that transmission index varied considerably between nationalities [62, 68, 90, 91]. In the same Montreal population used in this study, *Rossi et al.* identified that Haitian-born patients had a disproportionate share of transmission, resulting in a relative adjusted transmission index of 3.58. The authors explained this difference by possibilities of extended social networks and delays in obtaining suitable diagnosis and treatment [68]. In Borgdorff et al. (1998), authors suggested that the difference between nationalities may be due to different living conditions, such as crowding, and differences in patient's or doctor's delay [91]. There is no such risk factor for disease progression shared by contacts of diabetic patients, but health-seeking behaviors or proximity to health care may be shared. Also, as shown by the large number of contacts in the database, extensive contact investigation for latent TB may have prevented disease progression in our study setting. Therefore, detecting differences in proportions of contacts with TB infection, but not in proportions of contacts with TB disease, is not surprising in our study setting. This suggests that

investigation for latent TB should be emphasized among contacts of diabetic TB patients, which is also suggested by other studies that used different designs [73, 75, 92].

Given a positive TST result, contacts of diabetic index TB cases were more likely to receive isoniazid prescription compared to those of non-diabetic index TB cases. The examining physician may decide to treat a contact of active TB patient if 1. The person has increased risk of developing active TB, 2. The person is determined to have recent infection – e.g. documented TST conversion while being in contact with active contagious TB patient [52], A higher proportion of INH treatment among positive TST contacts of diabetic index compared to those of non-diabetic index can thus be interpreted as a judgment that the likelihood of recent infection was higher.

Subjects born in Canada, especially Aboriginal persons, were significantly more likely to be cluster members. This relates to the study's limited sampling by geography – the study population is limited to the island of Montreal. While Canadian born TB patients are more likely to be part of clusters of locally acquired and transmitted TB, foreign born are more likely to be part of clusters involving TB acquired outside of Canada and related networks, that are truncated due to relocation.

Canadian birth and Aboriginal status were also associated with increased likelihood of being secondary cases. This can be explained by several issues. First, behavioral risk factors such as substance use (such as alcohol and tobacco), homelessness, use of shelters or other congregate settings are not well captured in the database, which all tend to correlate with Canadian-born and Aboriginal status among TB cases and contacts. Second, there were two recognized outbreaks during the study period: the first at a drop-in centre with a largely Aboriginal clientele [93, 94], and the second at the Université de Montréal where a foreign-born university student diagnosed with active bilateral cavitary and laryngeal TB was the index case and seven Canadian-born secondary cases were subsequently identified [94]. Third, child contacts are at higher risk of progression to active disease, and are more likely to be born in Canada.

It has been suggested that HIV-infection is associated with decreased TB infectiousness [48], but this point is controversial. In our study, HIV-infected TB patients generated about twice as many subsequent cases as did HIV-negative patients. In a molecular study in San Francisco from 1991 to 2002, although a transmission index was not calculated, HIV-infected source cases generated 2.3 HIV-negative secondary cases on average compared to HIV-negative source who generated 1.6 on average, though no statistical testing was provided [68, 95]. Genotypic clusters that had at least one HIV-positive patient were significantly larger, lasted longer, and had a shorter time between successive cases relative to those with only HIV-uninfected patients [95]. In another study in the Netherlands, HIV-infected TB patients who were born in the Netherlands generated close to 1.5 times more subsequent TB cases relative to the HIV-negative Dutch-born TB patients [90]. The impact of HIV infection on transmission was highlighted by other molecular studies in Malawi [96, 97].

Young adults under the age of 45 were also associated with high transmission, as in other molecular epidemiological studies [95, 98], which can be explained by their tendency to socialize extensively with others of similar age. The highest adjusted relative transmission index of 5.78 was associated with the youngest age group – 15 years and younger, which was unexpected as children are known to be less contagious as they usually cannot produce airborne infectious droplets [52]. In our study, the high transmission index could be possibly explained by a few highly infectious adolescents or children who were diagnosed first before the true adult source cases.

The diabetic status of contacts was not available in our study, which would have been the ideal exposure variable to detect susceptibility to TB infection. Instead, we compared the difference in the prevalence of diabetes among index VS subsequent TB patients. Although not statistically significant, there was a higher prevalence of diabetes among secondary active cases compared to index cases. Hospitalization was longer for persons with diabetes and those with renal disease in univariate analysis, but only renal disease was independently associated in longer hospitalization in multivariate analysis. This may reflect generally high-quality care for diabetes in Canada. In our study,

unfavorable outcomes, notably death, were significantly associated with diabetes, concordant with the meta-analysis by *Baker et al.* which estimated a pooled risk ratio of 1.69 for failure and death combined [34]. The particularly strong association of poorer outcomes with the combination of diabetes and renal failure likely reflects more severe immune suppression, advanced diabetes, and poor general condition [35, 36]. In fact, it is suggested that poorly controlled type 2 diabetes impairs both innate and adaptive immune responses. Proper management of both tuberculosis and diabetes seems important in controlling TB [99, 100].

Drug resistance was the single strongest factor associated with cost of TB drugs for treatment as expected [88, 101]. In contrast, diabetes was not associated with longer TB therapy or higher cost of drug. In part, this can be explained by higher mortality during the course of treatment among diabetic TB patients, and therefore by shortened duration of TB therapy. However, diabetes was still not associated with higher treatment cost when all patients experienced death during treatment were excluded from analysis.

5.3 LIMITATIONS

5.3.1 Limitations Relating to Study Design

First, the study is based on the population in Montreal, which is a high-income setting with relatively low incidence of tuberculosis, as previously noted [68]. Less than one-fifth of the TB patients in our study were members of genotypic clusters, i.e. shared the same strain of *M. tuberculosis* with others, while only about 7% of our sample was diabetic. Hence comparisons between diabetics and non-diabetics with respect to genotypic findings (clustering, transmission indices) were hampered by limited power. For example, a two-fold difference in transmission could be detected with a power of less than 30% with given sample sizes (See APPENDIX I **Table A**). Also, because the the sample remains limited by the geographical setting – i.e. the island of Montreal – secondary cases related to a Montreal index case who were diagnosed and reported outside the island are missed. This potentially biases inference about secondary cases, and can lead to misclassification of a potential index case as “unique”. It is known that

as the sampling fraction decreases, the proportion of isolates identified as clustered is underestimated and the variability in the results obtained is larger – especially for populations with small clusters [102].

Second, the study was limited to the data in the Resource Database, which was not initially created for this specific study. While most subjects had documentation of their diabetic status (yes vs. no), values for other covariates were sometimes missing, and may have been misclassified in some cases. The clinical conditions and behavioral history of patients, which includes our exposure variable and covariates were retrieved from the medical records of patients at their treating hospital and at the public health department. Although past medical history is usually routinely collected while evaluating a patient, collection approach and completeness differ among different hospitals. The number of patients with non-missing data is shown in the results tables. The impact of these data gaps on inference about covariates such as HIV is unpredictable; it is possible that patients involved in clusters and/or suspected transmission episodes may have been questioned more closely about characteristics such as HIV, homelessness, substance use, etc. This may have resulted in a bias away from the null, inflating the transmissibility associated with the above characteristics. To estimate the potential information bias and determine accuracy of available medical records, a validity study could be conducted.

Third, there were critical limitations associated with contact tracing. Some limitations that were mentioned earlier include selection bias and limitations related to the use of the tuberculin skin test (See **Section 1.3.3.2** a)). Contact investigation depends on the identification and compliance of the contacts. Also, the tuberculin skin test does not differentiate a new recent from longstanding infection.[102].

To obtain more valid results regarding the role of diabetes in TB transmission, a prospective cohort study with more systematic data collection could be proposed. This would maximize the chances that necessary data are collected properly and comprehensively. However, the challenge with such prospective design is that potential cases and contacts can refuse to consent, which creates bias and compromises

generalizability and validity of genotyping study. In addition, if possible, use of a diagnostic tool with higher sensitivity and specificity, such as QFT or T.SPOT.TB assays, can improve the diagnostic accuracy of TB infection in contacts of active TB patients.

5.3.2 Limitations Relating to Methods of Analyses

In our cluster analysis using genotypes of TB isolates, our study was constrained by three key assumptions. First, we assumed that a unique DNA fingerprint in the population at the time of diagnosis arose from endogenous reactivation or from in-migration, and subsequent patients with the same genotype were considered secondary cases – i.e. transmittees – from the source case. A true source case risks being misclassified as secondary, if his/her diagnosis was substantially delayed. However, most clusters were small, and the median time between the first two infectious cases in a cluster exceeded 20 months, this suggests that misclassification of the source case was uncommon. Secondly, the assumption that a single source is responsible for all other cases within its cluster would be less valid if a cluster spreads over a long period [67, 68]. The average duration of the clusters in our study was four years, ranging from six days to ten years. A sensitivity analysis by *Rossi et al.* using 3-year time window for clustering showed that all transmission index ratios were similar, showing that the assumption did not cause a significant bias [68]. Third, although about 98% of culture-positive cases were genotyped, we could have missed a small number of linked cases, which may explain the seven clusters involving extra-pulmonary cases only. Finally, we excluded all clustered extrapulmonary cases without a pulmonary index case, as we assumed their index to be outside our temporal and geographical limits [62, 90, 91, 95]. However, it is possible that a patient initially diagnosed as extrapulmonary TB in fact have concomitant pulmonary TB, which occurs in 25% of extrapulmonary TB cases. However, a sensitivity analysis that included all extrapulmonary cases – including those originally excluded in the main analysis – did not affect substantially the transmission index of diabetic TB patients (See APPENDIX II **Table B**).

Another limitation relates to our use of standard costs from two publications of *Public Health Agency of Canada and* World Health Organization. To avoid inconsistency, we

did not include patients who were treated with other drugs that those listed in these two publications; about 10% of all patients were prescribed with other drugs, which include rifapentine, apohydrazine, etc. However, it is possible that some patients with diabetes may have been treated with uncommon medication or underwent a longer TB therapy with different drugs than the standard drugs listed in above publications. It is suggested that there is drug-drug interaction between anti-TB and anti-diabetic drugs, which aggravates both diseases [31, 46]. Excluding patients treated with uncommon drugs is expected to result a bias towards the null. Attributing the same daily cost of hospitalization for diabetic and non-diabetic patients could also have resulted a bias towards the null as diabetics may require additional medical care relative to non-diabetics.

5.4 STRENGTHS

One of the strengths of the study is its ability to account for important confounders such as age and other clinical and socio-economic characteristics such as comorbidities and homelessness. Many of the previous studies on the effect of diabetes on TB outcomes have not properly adjusted for confounding variables. Only 4 studies out of 23 studies on risk of death during treatment in the meta-analysis by *Baker et al.* had adjusted for age. The pooled effect estimate for death in diabetics vs. non-diabetic TB patients among studies that adjusted for age and other confounding factors was higher than that among the unadjusted studies, suggesting that confounding factors led to underestimation of the diabetes effect [34]. With control of covariates, the present study could provide a more accurate estimate of the impact of diabetes on TB outcomes. In addition, although the study concentrates on the relationship between TB and diabetes, the use of covariates provided us with information useful for other aspects of tuberculosis in Montreal. For example, finding predictors of length of hospital stay and treatment duration identified issues that could be explored further.

Another strength is its time span of eleven years, and the inclusion of nearly 98% of all culture-positive TB cases in a setting where TB incidence has been stable and registration and management of TB patients have been well established. With such high

coverage, the clustering analyses are expected to be very accurate. High coverage also increases the chance of finding the true source case [102]. Given the strong health care infrastructure, for management of both TB and diabetes, our findings may reflect a “best case” scenario for the impact of diabetes on TB epidemiology and outcomes, which may be more pronounced in lower-income countries.

By identifying the potential source cases by genotyping, we could estimate the effect on transmissibility of various patient characteristics. This provided additional insights beyond the traditional molecular epidemiologic analyses that simply compared members vs. non-members of genotypic clusters. By separating potential transmitters from transmittees, this approach can provide useful information for targeted public health interventions, in low-incidence settings such as Canada. In our transmission index analysis, we also accounted for the variable duration of time during which each source case could transmit. The more subsequent time there is for secondary cases to develop, the more likely an index case is to appear as a transmitter. This accounting was absent in most of the earlier transmission studies [68].

To our knowledge, there is no publication to date on the effect of diabetes among index patients on risks of latent infection among contacts. In fact, the *WHO Collaborative Framework for Care and Control of Tuberculosis and Diabetes* (2011) has recommended to assess whether DM influences the transmission of TB infection through the study of household contact tracing of diabetic vs. non-diabetic patients [36]. The biggest strength in our contact investigation is the size; over 6500 contacts were included in the study, among which 563 were contacts of diabetic TB patients. A hierarchical, multi-level model, accounted for the characteristics shared by contacts of each case to give a less biased estimate along with appropriate standard errors. Few contact tracing studies have used this multi-level approach, even though there may be intra-household or intra-community risk factors affecting transmission dynamics [87]. Moreover, TST results were complemented by considering isoniazid treatment provided to contacts. This study also relates to another key research question that was prioritized by the *WHO Collaborative Framework for Care and Control of Tuberculosis and*

Diabetes (2011): the rates of hospitalization and additional medical costs associated with diagnosis and management of dual disease [36].

5.5 DIRECTIONS FOR FUTURE RESEARCH

Producing strong evidence about diabetes and transmission dynamics of TB is difficult in a setting with low TB incidence. A study in a setting with a high incidence of TB coupled with a high prevalence of diabetes would be useful. There have been several bidirectional screening studies for TB and diabetes in different countries [103] and nation-wide bidirectional screening for TB and diabetes is ongoing in China and India [104]. In these projects, patients with newly diagnosed TB are screened for diabetes, and diabetics are periodically screened for TB symptoms, with further investigation as appropriate. These projects could be supplemented by tuberculin skin test surveys among contacts of active TB patients, and potentially by molecular epidemiological studies, which could better estimate the impact of diabetes on TB transmission dynamics.

No previous studies have examined the effect of diabetes on costs of TB care. Tuberculosis control is not as restricted by financial constraints in Canada as in many countries with high TB burden. While diabetics increase in number in many parts of the world including low- to middle- income countries [11], it would be important to weigh the economic impact of two diseases combined as suggested in the *WHO Collaborative Framework* [36].

6. CONCLUSION

Our study, conducted among Montreal TB patients over an 11-year period, suggests that diabetes among active TB patients was associated with increased transmission of TB infection, but not with increased number of secondary cases of active TB disease. Diabetes was also associated with adverse clinical outcomes in TB patients.

We recommend further prospective studies on transmission of tuberculosis in settings with a greater burden of tuberculosis. With a higher power, these studies will allow a more accurate estimation of the effect of diabetes on TB transmissibility. We also suggest more attention to contact investigation among contacts of diabetic TB patients, which could be an effective public health intervention to reduce mortality, morbidity and economic loss related to TB in countries where the dual burden of tuberculosis and diabetes is present.

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APPENDIX I

Figure A Flow chart for TB cases in Montreal, Canada

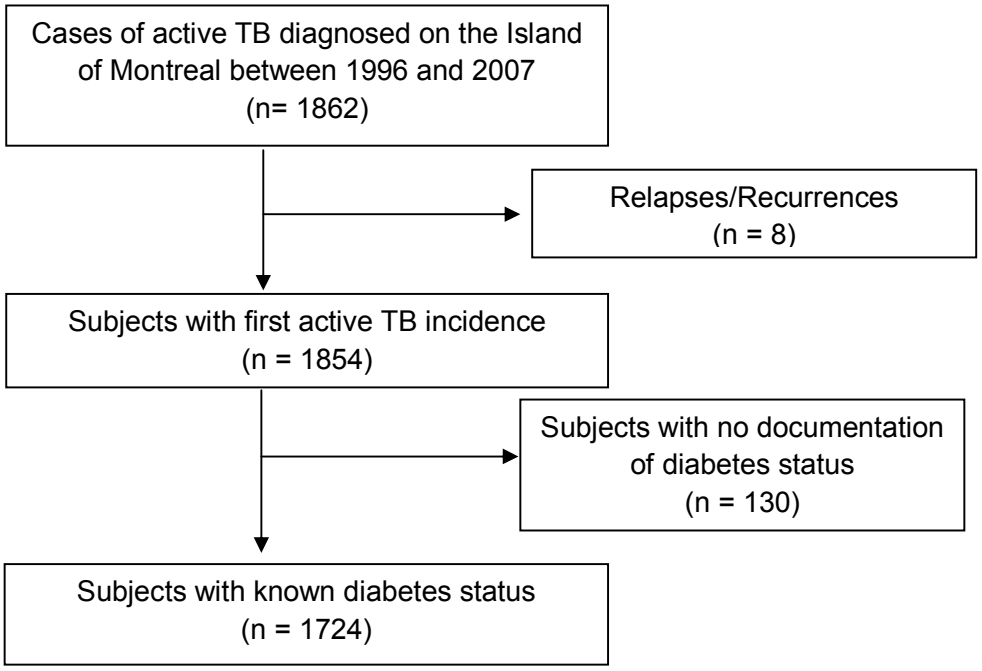

Figure B Flow chart for contacts of TB cases in Montreal, Canada

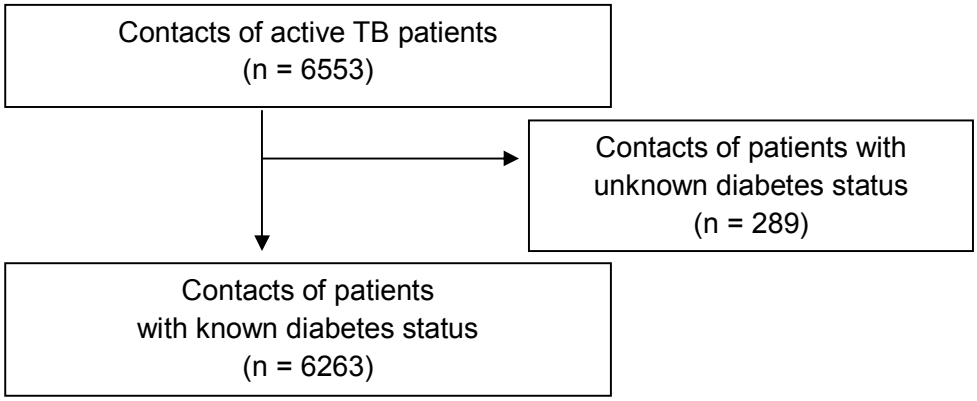

Table A Power calculation for transmission index

◉ **Two-Tail Test** (Hypothesis that the Average for Sample 1 is greater than the Average for Sample 2 or Average 1 is less than Average 2, but not both)

Enter the average value for Sample 1 and the average value for Sample 2. Also enter the sample sizes and standard deviations for each sample or rough estimates of them. For reference, a 5-pt. scale may typically have a standard deviation of 0.8 to 1.2 and a 10-pt scale may have a standard deviation between 3.0 and 4.0 for most items. The larger the standard deviation, the larger the sampling error.

Average Value for Sample 1:	0.16	(Value measured from Sample 1 or expected from it)
Average Value for Sample 2:	0.32	(Value measured from Sample 2 or expected from it)
Size of Sample 1:	831	(Size of Sample 1 or desired number of respondents)
Size of Sample 2:	77	(Size of Sample 2 or desired number of respondents)
Standard Deviation for Sample 1:	1.0	
Standard Deviation for Sample2:	1.0	
Alpha Error Level or Confidence Level:	5% ▼	(Probability of incorrectly rejecting the null hypothesis that there is no difference in the average values). An Alpha of 5% corresponds to a 95% Confidence Interval.

Statistical Power: 26.9%

Calculate Sample Size

Table B Transmission indices for TB including all extrapulmonary cases in Montreal, Canada, 1996-2007

Characteristics of index	Index and non-clustered pulmonary cases n	Subsequent cases generated n	Transmission index			
			Crude	Relative crude	Relative adjusted	95%CI
Total	1363	186	0.14			
Age						
<15	25	31	1.24	9.15	4.01	1.66-9.65
15-24	201	17	0.085	0.62	0.78	0.65-0.93
25-34	325	44	0.14	1.00†	1.00†	
35-44	250	37	0.15	1.09	0.60	0.53-0.68
45-54	144	34	0.24	1.74	1.64	1.30-2.08
55-64	107	5	0.047	0.35	0.14	0.03-0.68
65-74	134	8	0.06	0.44	0.34	0.07-1.77
75-84	126	9	0.071	0.53	0.46	0.09-2.49
>= 85	42	1	0.024	0.18	0.00000001	0
Country of Birth						
Canada	220	48	0.22	1.00†	1.00†	
Others	1136	137	0.12	0.55	1.25	0.49-3.19
Smear test						
Positive	625	77	0.12	0.83	0.996	0.54-1.85
Negative	738	109	0.15	1.00†	1.00†	
HIV status						
Positive	103	27	0.26	2.07	2.15	0.997-4.64
Negative	576	73	0.13	1.00†	1.00†	
Diabetes						
Diabetic	**98**	**2**	**0.02**	**0.14**	**0.88**	**0.16-5.00**
Non-diab.	**1170**	**165**	**0.14**	**1.00†**	**1.00†**	
Pulmonary diseases						
Yes	229	26	0.11	0.85	1.03	0.42-2.55
No	1048	140	0.13	1.00†	1.00†	
Liver diseases						
Yes	96	19	0.20	0.64	2.28	0.84-6.23
No	1178	149	0.13	1.00†	1.00†	
Renal diseases						
Yes	76	8	0.11	0.80	0.59	0.08-4.25
No	1196	158	0.13	1.00†	1.00†	

*Adjusted for age, country of birth, smear status, HIV status and person-time at risk using negative binomial regression.

†Reference category

Table C Characteristics of transmitters VS non-transmitters among index (pulmonary TB patients with unique *M. tuberculosis* genotype to the study population on the date of diagnosis)

Characteristics	Transmitters n(%)	Non-transmitters n(%)		Chi-square, Fisher's exact or t-test p-value
Cases	84(8.8%)	874 (91.2%)	958	
Age			951	0.04
<15	5(6.0%)	11 (1.3%)	16(1.7%)	0.001
15-24	11(13.1%)	146(16.5%)	157(16.5%)	0.377
25-34	21(25.0%)	204(23.5%)	225(23.7%)	0.762
35-44	20(23.8%)	143(16.5%)	163(17.1%)	0.089
45-54	10(11.9%)	87(10.0%)	97(10.2%)	0.589
55-64	4(4.8%)	64(7.4%)	68(7.2%)	0.506
65-74	6(7.1%)	96(11.1%)	102(10.7%)	0.266
75-84	6(7.1%)	88(10.2%)	94(9.9%)	0.378
≥ 85	1(1.2%)	28(3.2%)	29(3.1%)	0.299
Sex			955	0.762
Male	51(60.7%)	514(59.0%)	565(59.2%)	
Female	33(39.3%)	357(41.0%)	390(40.8%)	
Country of Birth			957	0.440
Canada	19(22.6%)	167(19.1%)	186(19.4%)	
Others	65(77.4%)	706(80.9%)	771(80.6%)	
Aboriginal			103	1.000
Yes	0(0.0%)	1(1.0%)	1(1.0%)	
No	8(100.0%)	94(99.0%)	102(99.0%)	
Smear test			958	0.042
Positive	55(65.5%)	471(53.9%)	526(54.9%)	
Negative	29(34.5%)	403(46.1%)	432(45.1%)	
HIV status			511	0.004
Positive	15(28.3%)	62(13.5%)	101(16.3%)	
Negative	38(71.7%)	396(86.5%)	520(83.7%)	
Diabetes			**908**	**0.054**
Diabetic	**2(2.6%)**	**75(9.0%)**	**77(8.5%)**	
Non-diabetic	**76(97.4%)**	**755(91.0%)**	**831(91.5%)**	

APPENDIX II

Ethics Approval

Centre universitaire de santé McGill | McGill University Health Centre

Bureau d'éthique de la recherche
Research Ethics Office

December 17, 2013

Dr. Kevin Schwartzman
MUHC - MCI
Room K1.23

Re: "Impact of Diabetes on Tuberculosis in Montreal from 1995 to 2007"

Dear Dr. Schwartzman:

We have received an Application for Continuing Review of the Biomedical A (BMA) Research Ethics Board (REB) for the research study referenced above and the report was found to be acceptable for ongoing conduct at the McGill University Health Centre. At the MUHC, sponsored research activities that require US federal assurance are conducted under Federal Wide Assurance (FWA) 00000840.

Approval for the study was provided via expedited review of the Chair on December 16, 2013 will be reported to the Research Ethics Board (REB) at its meeting of January 15, 2014 and will be entered accordingly into the minutes.

All research involving human subjects requires review at a recurring interval and the current study approval is in effect until **December 15, 2014**. It is the responsibility of the principal investigator to submit an Application for Continuing Review to the REB prior to the expiration of approval to comply with the regulation for continuing review of "at least once per year".

However, should the research conclude for any reason prior to the next required review, you are required to submit a Termination Report to the Committee once the data analysis is complete to give an account of the study findings and publication status.

Should any revision to the study, or other unanticipated development occur prior to the next required review, you must advise the REB without delay. Regulation does not permit initiation of a proposed study modification prior to REB approval for the amendment.

We trust this will prove satisfactory to you.

Sincerely,

Jean-Pierre Routy, MD
Chair,
BMA REB

Cc: 12-311-BMA

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