DRUG RESISTANT TUBERCULOSIS IN MONTREAL 1992-1995

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ABSTRACT

DRUG RESISTANT TUBERCULOSIS (TB) IN MONTREAL, 1992-1995

OBJECTIVE: Since the 1980's the incidence of tuberculosis (TB) in Montreal has remained at 11 cases per 100,000. In order to improve TB prevention and control programs, we sought to identify predictors of tuberculosis drug-resistance and to describe the epidemiology of TB drug resistance on the island of Montreal.

STUDY DESIGN: Retrospective descriptive analysis

STUDY POPULATION: All culture proven TB patients reported to the Montreal Regional Health Board aged 0-49 for 1992-1994 and 0-18 years for 1995.

RESULTS: Drug resistant TB was found in 18.3% of culture-proven TB cases. The rate of INH resistance in our study cohort was 10.6%. Two percent of TB cases were found to have MDR-TB. Only 3 TB cases (0.9%) in our study cohort developed acquired drug resistance over the study period. Previous history of TB was associated with a 3.9 times greater risk of drug resistant TB.

CONCLUSIONS: Drug resistance is a significant problem in Montreal that continues to hinder TB treatment and control. Previous history of tuberculosis is a strong predictor of drug resistance. In addition, immigration from individual countries was not associated with an increase in the rate of drug resistance. Nonetheless, country-specific drug resistance rates may serve to predict the likelihood of drug resistant TB among the foreign-born in Canada.

ABRÉGÉ

LA TUBERCULOSE RÉSISTANTE AUX ANTIBIOTIQUES À MONTRÉAL, 1992-1995

Objectif : À Montréal, l'incidence des cas de tuberculose (TB) s'est stabilisé autour de 11 cas/100,000 population. Afin d'être en mesure d'améliorer la prévention et le contrôle de la TB nous nous proposons d'identifier et de décrire les facteurs associés à la résistance aux médicaments anti-tuberculeux de première ligne à Montréal.

Devis d'étude : Étude retrospective descriptive

Population à l'étude : Tous les cas de TB confirmé bactériologiquement et déclaré à la Direction de la santé publique de Montréal-Centre qui sont âgés entre 0-18 ans pour les années 1992-1995 et entre 19-49 ans pour les années 1992-1994.

Résultats : La résistance globale est de 18.3%. Plus de 10.6% des cas présentait une résistance à l'INH. 2% des cas (n=7) se sont révélé multi-résistant (MDR-TB). Seulement 3 cas (0.9%) ont développé une résistance en cours de traitement. Les seuls facteurs indépendamment associés avec la présence de résistance sont l'histoire antérieure de TB (OR=3.9).

Conclusion : L'histoire d'un épisode antérieur de TB est associé avec la présence de résistance. Le profil d'immigration à Montreal et le taux de résistance du pays d'origine des patients vont influencer l'incidence de résistance à Montréal.

Chapter 1: Introduction

For several decades previous to the 1980's, tuberculosis (TB) incidence steadily declined at a rate of approximately 6.0-8.0% per year in many developed countries, including Canada. [1-3] This decline was largely due to improved socio-economic conditions, the implementation of TB control programs and the introduction of effective anti-tuberculosis medications. [1,2,4,5] However, in the mid-1980's TB incidence rates increased in many regions of North America. [1-9] This resurgence of TB was attributed to the dismantling of TB control programs, the emerging HIV epidemic, increasing immigration from TB-endemic countries and higher levels of poverty and homelessness, which facilitated the development and spread of tuberculosis. [2-6,10,11] Rising levels of drug resistance have further hindered TB treatment and control. [12]

Drug resistance is an especially worrisome problem because there are few effective anti-TB medications available. [13] Moreover, the prognosis for individuals infected with drug resistant TB is substantially poorer than for TB patients infected with drug-sensitive strains. In addition, less-commonly used anti-TB medications are often considerably more expensive and can increase the cost of treatment by up to 10-fold. [8,14] Thus, due to the many complications associated with the treatment of drug-resistant TB and the potential for widespread dissemination, prevention of drug resistance should be considered a priority for TB control. In order to create effective TB control programs and public

health policies it is necessary to identify risk factors associated with drug-resistant TB.

At present there is little information available regarding risk factors for the development and transmission of TB drug resistance. Most studies have been limited to surveillance data or to localized hospital outbreaks and have provided useful, but somewhat limited information. A more comprehensive understanding of predictors of TB drug resistance is necessary to improve the ability of physicians to treat and diagnose TB patients and to allow for the creation and implementation of timely public health interventions, which will prevent the spread of drug-resistant TB.

1.1 Objectives

1.1.1 Primary Goal

The primary goal of this study was to identify sociodemographic, clinical and TB risk factors that are independently associated with resistance to 1st-line anti-tuberculosis drugs.

1.1.2 Specific objectives

1. To describe the epidemiology of TB drug resistance on the island of Montreal.

2. To determine the incidence of primary and acquired resistance on the island of Montreal.
3. To determine the incidence of resistance for the following 5 first-line drugs: isoniazid, pyrazinamide, rifampin, ethambutol, and streptomycin.
4. To determine the incidence of multi-drug resistance (MDR-TB).
5. To compare mortality rates between drug-resistant TB patients and drug-sensitive TB patients.
6. To examine longitudinal trends of TB drug resistance incidence.

1.2 Significance of this study

This is the first in-depth study performed to describe patterns of drug resistance on the island of Montreal. Additionally, this study will add to the current body of knowledge of TB drug resistance by examining potential risk factors for TB drug resistance. This includes determining whether clinical variables and risk factors for TB are associated with TB drug resistance. Lastly, information gathered on a local scale can be used to contribute to the global understanding and management of drug resistance. [15]

Chapter 2: Review of the Literature

2.1 Definition of tuberculosis

TB is an infectious disease which has plagued humanity since ancient times. In the recent past, TB was commonly known as "consumption", due to the gradual wasting of the body that often resulted as the disease progressed. [15, 16] The etiologic agent for most cases of TB in humans is *Mycobacterium tuberculosis*, with the exception of a small number of cases caused by the mycobacterium *M. africanum* and *M. bovis*. [15-17]

The lungs are the most common site of TB, although TB can affect any organ system in the body including the lymph nodes, skeleton, genitourinary tract, abdomen, central nervous system, skin and eyes. It is estimated that pulmonary TB represents approximately 60.0-80.0% of all TB cases. [4,15,17] This has important public health implications since TB is most commonly spread through the person-to-person transmission of aerosolized droplets of respiratory mucus. [15,17]

2.2 Clinical course of tuberculosis

TB can be divided into two stages: primary TB and post-primary TB. During primary TB, individuals are infected with tubercle bacilli through close contact with the respiratory secretions of an infectious TB case. Once bacilli reach the alveoli of the lungs they undergo phagocytosis by macrophages. In most cases,

macrophages are unable to destroy TB bacteria (due to the wax-coated cell wall) and bacterial replication continues within the macrophage. Antigens placed on the macrophage cell-surface alert T-cells and mount a cell-mediated reaction that results in the creation of granulomas, known as tubercles, which contain the infection and prevent clinical disease. [4,15-17]

Tubercles consist of a central core filled with TB bacilli and macrophages surrounded by an outer wall of lymphocytes, neutrophils and fibroblasts. As the immune system works to contain the infection, necrosis and subsequent calcification of the tubercle occurs allowing recovery from the primary TB infection, although viable bacteria tend to remain and can be reactivated later in life.

Most patients remain asymptomatic or experience a slight fever during the course of primary TB and recover without having clinically significant TB. Approximately 5.0-15.0% of individuals who are initially infected with TB bacterium eventually develop clinically active TB. The greatest risk of developing the disease is within the first two years post-infection. [14, 15-17]

Post-primary TB is a reactivation of the initial primary TB infection and occurs when an individual's immune system has weakened and can no longer contain dormant TB bacilli. As a result, TB bacteria are reactivated and can spread

throughout the lungs. During the post-primary stage of TB, immune hypersensitivity to TB bacteria causes an increased rate of necrosis and lung damage. Symptoms are more severe during post-primary TB and can include chest pain, anorexia, fatigue, night sweats, hemoptysis, fever and violent coughing. The onset of symptoms is usually slow and progressive. During this stage the mortality rate for untreated TB cases is estimated to be around 60.0%. [4,15,17]

2.3 Diagnosis and treatment of tuberculosis

TB is often suspected when patients present with clinical symptoms of the disease. However, a number of potential cases are also identified through routine TB screening and contact tracing. Since symptoms of TB are non-specific and may mimic other illness, such as pneumonia, additional diagnostic tools are employed.

Tuberculin skin testing (TST), chest radiology, sputum smear microscopy and mycobacterial culture are the most commonly used diagnostic methods for TB, in addition to clinical evaluation. The first three methods provide quick results and are relatively simple and inexpensive to perform, but are unable to provide conclusive evidence of TB, and more importantly drug-susceptibility profiles. Nevertheless, these tools can be used to evaluate the likelihood of TB infection,

and in the case of chest x-ray and sputum smear microscopy, can help to estimate the potential extent and severity of disease. [15-17]

In order to make a definitive TB diagnosis, isolation of *M. tuberculosis* bacteria is necessary. [15,17] Although this can be accomplished through bacterial culture, and more recently, through polymerase chain reaction (PCR), a gene amplification technique, laboratory culture is currently the only definitive technique commonly used.

Isolation of *M. tuberculosis* in pure bacterial culture has a sensitivity and specificity of 82.0% and 98.0%, respectively and is currently considered to be the most accurate and reliable method for diagnosing TB. [4,18] Using specimens obtained from infected tissues and bodily fluids, pure cultures of *M. tuberculosis* can be cultivated on selective growth medium. Egg-based mediums, such as Lowenstein-Jensen are the most popular, but other selective growth media, such as Middlebrook agar and the BACTEC® (Becton-Dickinson Diagnostic Instruments Systems, Maryland) broth system are also regularly used. In addition to bacterial identification, *M. tuberculosis* isolates are subjected to drug-susceptibility testing in order to provide information that can be used to direct therapy.

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*2nd line anti-TB drugs include: amikacin, capreomycin, clofazine, cycloserine, ethionamide, kanamycin, ofloxacine and rifabutin

Initially, cultures of *M. tuberculosis* are tested for drug susceptibility to 1st line ant-tuberculosis medications. Isolates found to be drug resistant are further tested for drug susceptibility to 2nd line anti-tuberculosis medications*. The turnaround time for laboratory culture of *M. tuberculosis* and drug-susceptibility testing can range from 2-4 weeks - presenting a major obstacle for prompt diagnosis. As a result, physicians must make a preliminary diagnosis with less definitive criteria in the interim period before culture results are made available.

Treatment of TB is accomplished through the administration of anti-tuberculosis medications for lengthy periods of approximately 6-24 months, depending on several factors including patient immune status, drug resistance profile and response to therapy. [15,17] These long treatment periods are necessary to ensure the destruction of all TB bacilli and the prevention of relapse and drug resistance. In certain cases where there is a high potential risk for non-compliance, directly observed therapy (DOT) is instituted. [19] DOT is when health workers ensure treatment compliance by directly observing ingestion of anti-TB medications.

Due to delays in obtaining laboratory culture results, the decision to initiate TB treatment is often based on less definitive criteria, such as clinical presentation, chest x-rays, TST and smear results. Therefore, the initial treatment with

multiple anti-TB drugs is necessary until drug susceptibility results are made available.

In areas, such as Montreal, where the prevalence of INH resistance is 4.0% or more, both the American and Canadian Thoracic Societies have recommended the use of four of the following 1st-line drugs for preliminary treatment: isoniazid, rifampin, pyrazinamide, ethambutol and/or streptomycin. [20-23] Once drug-susceptibility results are known, adjustments to this treatment regimen can be made accordingly. Use of 2nd-line medications is reserved for TB cases that demonstrate resistance to most 1st-line drugs.

Successful treatment is dependent on patient compliance as well as close patient monitoring to ensure that prescribed treatment is effective and does not cause any serious adverse effects. Success is indicated when repeated laboratory cultures and sputum smears produce negative results. [15,17]

2.4 General tuberculosis epidemiology

2.4.1 World

TB is an infectious and life-threatening disease found throughout the world, although the majority of cases occur in developing countries. [3,18,24] Currently, it is estimated that one-third of the world's population is infected with TB [25] and that 26.0% of all preventable deaths in the developing world can be attributed to

TB. [7,26] There are approximately 7.5 million new cases and 2.5 million deaths annually due to TB worldwide. [11,18,26] To put this in perspective, TB is considered to be the number one killer among infectious diseases and is responsible for more deaths in the world than AIDs, malaria, and leprosy combined. [18,26] Rates of TB in many countries and regions, in addition to increasing rates in the developed world, has prompted the World Health Organization to declare the current TB situation a "global emergency." [7,26]

In the developed world, this increase was most pronounced in large cities, such as New York where the TB incidence rate tripled over a 10-year period. [9,10] Surprisingly, this epidemic occurred after TB had reached such low levels that it was no longer considered to be a major public health problem. The belief that TB was a disease of the past resulted in the reduction of TB surveillance and the dismantling of the existing TB control program. The resulting lack of vigilance allowed for a significant increase in the number of TB cases before control measures could be implemented. [9,10,26] Eventually, after investing approximately $1 billion dollars (U.S.) on public health control measures, TB rates in New York were reduced closer to pre-resurgence levels. [9]

2.4.2 Canada

After many years of steady decline, the yearly TB incidence rate in Canada has stabilized at 7 cases per 100 000. [25] Although the TB rate is much lower than

that found in developing nations, TB remains a serious public health concern. [24] The fact that TB levels have not declined since the early 1990's, even though TB is a highly treatable and preventable disease, is especially disconcerting. [18, 25, 27

One of the most striking aspects of Canada's TB situation is the uneven distribution of cases among large urban centres and subgroups in the population. [28] In the last decade a large proportion of TB cases in Canada have been found in foreign-born individuals. [20,25,29] Currently, immigrants represent 60.0% of the total number of TB cases in Canada. In western Canada, foreign-born Canadians have been estimated to have a 12-fold increased risk of developing TB as compared to Canadian-born individuals. [29] An additional 13.7% of TB cases were found in the aboriginal population in Canada. [1]

Among the non-foreign born and non-aboriginal Canadian population, TB incidence was greatest among the elderly (over 65) due to reactivation of latent infection acquired much earlier in life. [1] In recent years, decreasing rates among the elderly and increasing TB incidence among those aged 25-34 have been observed. [20] The shifting age distribution of TB may be due to the greater prevalence of well-known TB risk factors found in younger individuals, such as HIV infection and immigration from TB endemic countries.

2.4.3 Montreal

In contrast to steady declining TB rates in the province of Quebec, the incidence rate of TB in Montreal has stabilized at a rate of approximately 11 cases per 100 000 per year, which is substantially higher than the rate of 5 per 100 000 for the rest of the province of Quebec. [20] This difference illustrates the way broad disparities in TB incidence can be obscured when overall rates are calculated to include both urban and rural areas. A potential reason for these differences is the elevated levels of TB risk factors that are pervasive on the island of Montreal, such as high rates of immigration from TB endemic countries, HIV infection, drug abuse, poverty and homelessness.

According to a recent survey, foreign-born patients accounted for 77.3% of all TB cases on the island of Montreal, despite representing only 25.0% of the total population. [20] When compared to the Canadian-born population in Montreal, immigrants demonstrated a 10-fold increased incidence of TB. In addition to different levels of magnitude, the age distribution of TB among foreign-born patients was highest in younger age groups, while among Canadian-born individuals, TB incidence was found to be highest among those over 65 years of age.

The majority of foreign-born TB patients originated from Haiti and Vietnam, representing approximately 38.0% of all foreign-born TB cases, with a large portion of the remainder coming from Southeast Asia, India, Latin America,

Africa and the Caribbean. [20] The large proportion of TB cases in Montreal attributed to foreign-born residents, and more specifically to particular countries of origin, is reflective of Montreal's unique immigration patterns. Moreover, it is indicative of the underlying TB risk factors and public health infrastructures existing in the originating country and thus must be considered when implementing appropriate TB control programs.

Although the majority of TB cases in Montreal were found in foreign-born residents, Canadian-born cases still constituted a sizeable portion of the total TB cases for the city. Moreover, interesting differences in the distribution of TB among this group were identified. For instance, when considering TB cases between the ages of 0-49 on the island of Montreal, it was found that males composed almost 80.0% of Canadian born cases, as compared to 55.7% of foreign-born cases. The higher incidence of TB in this subgroup may be due to the disproportionate representations of TB risk factors, such as homelessness, injection drug use (IDU) and HIV infection, found among Canadian born males.

2.4.4 General TB risk factors

There are two main factors involved in the development of TB: 1) infection with TB bacterium and 2) host immunity levels that allow for progression to active disease. [2,3,15,16,17] Since TB is primarily spread through airborne droplet nuclei, conditions that allow for close contact with infectious TB cases and larger

inoculations of TB bacteria increase the risk of TB infection and subsequent disease development.

Several socio-economic conditions, such as homelessness, poverty, and residence in a prison or shelter have been associated with an increased risk of contracting TB. [1-3,5,6,8,30] In these situations, overcrowding and inadequate medical services partially explain the high prevalence and increased risk of disease transmission in these populations. It is estimated that approximately one-third of individuals exposed to an active TB case become infected, as determined by a positive tuberculin skin test. [1,3,26] As mentioned before, the lifetime risk of developing active TB is 5.0-15.0% once an individual is infected with TB bacilli. [1,15,17,26] This risk is substantially magnified for individuals suffering from immunosuppressive conditions, such as HIV infection. [1,3,5,18,26]

Immunosuppression increases the risk of TB in two ways: 1) by enabling reactivation of latent infection and 2) by reducing the latency period between infection and disease. [3,8] The resurgence of TB in the early 1990's coincided with the AIDs epidemic and many TB patients were infected with HIV. [3,5,24] In some U.S. urban clinics, as many as 46.0% of TB patients were also co-infected with HIV. [31] For these reasons, HIV infection is currently considered the single most important TB risk factor. Studies have associated seropositivity with a

relative risk of 6-100 as compared to non-HIV infected individuals. [5] While HIV is definitely the most important condition, others that alter immunity, such as diabetes, immunosuppressive chemotherapy, severe malnutrition and extremes of age are also known to increase the risk of TB. [3]

In developed countries, foreign-born status is one of the most important risk factors for the development of TB and is associated with a 3-10 fold greater risk than that of non foreign-born individuals. [1,3,12,20,25,29] The majority of foreign-born individuals develop TB within 5 years of arrival, strongly suggesting TB has been imported from TB-endemic countries. [1,20] Thus, TB rates among this population are reflective of the underlying TB risk factors and public health infrastructures existing in the country of origin.

In addition to socio-economic risk factors, such as homelessness and overcrowding, extremely high rates of HIV infection in developing countries have contributed to the growing TB burden. A recent report by the World Health Organization has estimated that TB/HIV co-infected patients represent between 14.0-65.0% of all TB infected individuals in several African countries. [11] Since HIV testing is not routinely performed during pre-immigration medical screening, it is highly probable that many TB cases originating from countries with high HIV prevalence are also TB/HIV co-infected. [32] This has been shown in Montreal, where foreign-born AIDs patients originating from sub-Saharan Africa were found

to have a TB relative risk of 17.9, as compared to the Canadian born population. Therefore, HIV infection is an important TB risk factor for recent immigrants to Canada. [33]

2.5 Drug Resistance

2.5.1 Mechanisms of drug resistance development

Drug resistance occurs when bacteria mutate and develop resistance genes, or when resistance genes are transferred on plasmids from one bacterium to on another. Subsequently, drug resistant bacterial strains survive and proliferate as a response to selective pressures, such as exposure to antimicrobial medications. [15, 34] These drugs select for resistant organisms because they eliminate all susceptible bacteria, leaving only few resistant organisms. As a result of reduced competition there is accelerated multiplication of the few remaining resistant strains. In addition, this increased bacterial replication increases the probability of further genetic mutations, which may also confer resistance. [15,35,36]

In practice, there are many situations that may contribute to the generation of drug resistance. For instance, patient non-compliance, inadequate drug therapy length, excessive use of antimicrobials, inappropriate drug choices, and poor drug absorption are important factors which facilitate the development of drug resistance. [5,13,37,38). In addition, poor infection control practices and

insufficient TB control programs have exacerbated the situation by enhancing the ease of transmission to new hosts. [39]

2.5.2 Scope of the drug resistance problem

Drug resistance is a growing problem worldwide [5, 41]. The first occurrence of drug resistance was documented only a few years after the introduction of antibiotics. Today, resistance has been demonstrated for all known drugs, while the introduction of new medications has proceeded at a dramatically slower pace than drug resistance development [34]. Furthermore, increased international travel has provided an extremely quick mode of transmission for resistant organisms. According to the World Health Organization (1997), the world is the currently experiencing the fastest rate ever of emergence and dissemination of resistant pathogens. [41]

2.6 Drug resistant TB

2.6.1 Epidemiology of drug-resistant TB

To date, resistance has been demonstrated for all of the 1st line anti-tuberculosis drugs: isoniazid, rifampin, ethambutol, streptomycin and pyrazinamide, as well as for other lesser-known anti-mycobaterial medications. Resistance to 1st-line medications is an especially worrisome problem since alternative anti-TB drugs are often less effective, have higher toxicity, are less available (especially in less

developed countries), and are much more expensive than those used for standard treatment. [5,14,28,43,44]

Recently, several sensational outbreaks in the United States focused attention on a particularly troublesome pattern of resistance known as multidrug resistant TB (MDR-TB). [44,45] MDR-TB is defined as resistance to at least both isoniazid and rifampin - the two most important anti-TB drugs. These outbreaks occurred in hospital settings, where those most affected were HIV positive individuals who acquired the infection nosocomially. The most striking features of these outbreaks were the extremely high rates of treatment failure and mortality. For instance, treatment failures of up to 50.0% were observed among HIV negative individuals, while case fatality rates of up to 100.0% were seen in HIV positive individuals. Also, treatment costs per MDR-TB case were tabulated at approximately $200,000 US, a price that would be beyond the capacity of most developing nations. Thus, the potential impact of widespread transmission of MDR-TB to the population at large would be formidable from both a public health and economics point of view.

In addition to specific patterns of drug resistance, a distinction must be made between primary, initial, and acquired resistance. *Primary resistance* occurs when an individual who with certainty has never been treated for a previous episode of TB is diagnosed with a drug resistant strain. *Initial resistance* occurs

when a patient denies, but cannot be confirmed as never having had previous TB treatment is diagnosed with a resistant strain of *M. tuberculosis* bacteria. [23] The level of primary resistance in a community is believed to be an indicator of the effectiveness of existing TB control programs for preventing transmission. [37] Conversely, *acquired resistance* occurs when patients initially diagnosed with a drug-susceptible TB strain are diagnosed with resistant TB over time. [5, 23] The rate of acquired resistance in a population is considered to be an indicator of how effective existing TB treatments are for curing active TB disease. [37]

Although TB drug resistance has been found throughout the world, considerable variability in the distribution among different countries and regions has been observed. For example, while the proportion of TB cases exhibiting resistance to isoniazid alone was approximately 10.2% in Kenya, 16.9 % in Karnataka State (India), much lower proportions of 2.1%, 3.5 % and 1.6% were observed in southeastern England, Melbourne (Australia) and Argentina, respectively. Similar variability has also been observed for other patterns of anti-TB drug resistance, including both single-drug resistance and resistance to multiple anti-tuberculosis medications.

This recent review of 63 drug resistance surveys representing countries in Africa, Europe, Oceania and the America's concluded that drug resistance was indeed a

worldwide problem with demonstrated variability between countries and regions. [42] Unfortunately, several methodological problems were associated with many of the surveys reviewed.

First, only 20.0% of the surveys were representative of the population studied, thus making it difficult to compare drug resistance patterns between countries. Also, most surveys only presented basic surveillance data that did not provide information on many demographic variables, such as age, gender and country of origin or on longitudinal trends, limiting the identification of risk factors for drug resistance. In many countries, drug-resistant cases were incompletely reported. Frequently, no distinction was made between primary and secondary resistance and specific types of resistance were not differentiated. This prevented the evaluation of the respective national TB programs (NTP). Often, the lack of adequate laboratory facilities prevented comprehensive drug-susceptibility testing of *M. tuberculosis* isolates.

2.6.2 Drug resistant TB in Montreal

Between January 1, 1992 and December 31st, 1995, 16.2% of bacteriologically confirmed cases were found to be resistant to at least one anti-tuberculosis medication. The current prevalence of resistance to isoniazid on the island of Montreal is estimated to be greater than 4.0%, regardless of age group, gender or country of birth. A total of 10 cases (1.4%) were found to have MDR-TB. [20]

These statistics illustrate the significance of the drug resistance problem and, because of the complications associated with treatment of drug resistant strains of TB, emphasizes the potential obstacle faced for TB treatment and control.

2.6.3 Risk factors associated with TB drug resistance

PREVIOUS HISTORY OF TB

One of the most consistently reported risk factors for drug-resistant TB has been previous TB treatment. Several U.S studies of TB drug resistance have associated previous TB treatment with a 2-3 fold increased risk of drug resistance. [9,37]. This association has also been demonstrated in Canada, where studies of resistance trends in the western provinces of Manitoba, Alberta, Saskatchewan and British Columbia have found significantly higher rates of resistance among those individuals with a known previous history of anti-TB treatment. [29,46] Since antimicrobials exert selective pressures for resistance, it is not surprising that previous TB treatment has been associated with an increased likelihood of drug resistance. Inappropriately administered drugs, inadequate follow-up and non-compliance to treatment are factors which enhance the selective pressures that encourage drug resistance development. [17,47,48]

FOREIGN BORN STATUS

In developed countries, foreign-born status has consistently been associated with drug resistance rates 50.0-500.0% higher than that of non-foreign born patients. [37,42,9] In western Canada, foreign-born TB cases were associated with a three-fold increased risk (OR=3.2, 95% CI: 1.3 –7.8) of drug resistant TB. [46] While this pattern has been repeatedly demonstrated in many populations, resistance rates among foreign-born TB patients in Montreal have been found to be only slightly higher than rates found among Canadian-born TB cases and this difference was not statistically significant. [20] A study of TB drug resistance patterns in New York City also found no relationship between immigration and drug resistance. [9]

These inconsistent results illustrate the localized nature and variability of drug resistance patterns, which may be due to specific immigration patterns found in different parts of North America. For instance, 90.0% of drug-resistant cases in western Canada originated from five Asian countries (China, India, Vietnam, the Philippines and Hong Kong) that are known to have rates of TB resistance that are 2-3 times greater than those found in Canada. [42,46] In Montreal, individuals from these countries represented only 20.0% of all immigrants, with the remainder originating from Latin America, Africa and the Caribbean, whereas over half of immigrants to western Canada came from these five countries. [49]

In order to evaluate the impact of immigration on the rate of TB drug resistance rates in Montreal, it is necessary to take into consideration the variability of TB drug resistance found throughout the world. This includes observing patterns of TB resistance associated with immigration from *specific* countries and regions. At the present time, the impact of immigration on rates of TB resistance in Montreal has not been fully explored.

DURATION OF RESIDENCE

Several studies have found TB resistance incidence rates to be inversely proportional to the duration of residence in Canada. [29] For instance, a 10 year study of drug-resistant TB cases in Manitoba revealed that immigrants who developed TB within their first year of arrival to Canada were 9.9 times more likely than Canadian born TB patients to have drug resistance. Also, immigrants residing in Canada for 5 years or less before diagnosis were found to have a 5-fold increased risk of drug-resistant TB. [50] These findings suggest that resistant strains of TB were acquired in the originating country and reflect prevalent rates of resistance.

HIV

Although HIV seropositivity is a well-established risk factor for the development of TB, it is still unclear whether this is also true of drug resistance. [3,18,51] Many studies that have found a strong association between HIV and resistant TB

have been based on hospital outbreaks. [44,45] In these situations, it is likely a high degree of exposure combined with poor immune function, enabled rapid transmission and development of active disease.

Subsequent studies using Restriction Fragment Length Polymorphism (RFLP) techniques have identified identical strains of *M. tuberculosis* among outbreaks cases, suggesting clustering due to nosocomial infection. [5,45,51] Furthermore, small sample sizes and incomplete HIV reporting have further reduced the strength of these results.

Other studies based in geographic areas that experienced MDR-TB hospital outbreaks on HIV wards also found an association between HIV infection and TB drug resistance. [37,52,53] On closer examination, it is apparent that an overrepresentation of MDR-TB cases connected with isolated outbreaks among HIV infected populations probably explains the association between HIV infection and TB resistance. Since these studies did not control for membership in an outbreak cohort, these results must be interpreted with caution.

A population-based study by Spellman and associates (1998) determined that HIV infection was not associated with an increased risk of drug-resistant TB. [54] The highly representative nature of the study population and the completeness of HIV reporting improved the credibility of these findings. The study population

included all culture-positive cases reported to the Tarrant County Health Department in Austin, Texas over an 8-year period (802 cases) and HIV serology results were available for 92.4% of these individuals. Only 4.2 % of HIV-positive cases were resistant as compared to 8.5% of HIV-negative individuals, although these differences were not significant. This evidence supports the hypothesis that a high incidence of resistant TB found among HIV infected patients is likely due to the ease of transmission and development of disease, rather than to the virulence of resistant bacterial strains.

CLINICAL FACTORS

Clinical signs and symptoms are the most important and easily obtained diagnostic tools for physicians. Unfortunately, the clinical course of drug-resistant TB has not been sufficiently differentiated from that of drug-susceptible TB for this purpose.

The majority of research in this area has focused on determining whether lung condition is predictive of resistance. To date, a higher likelihood of drug resistance has not been observed for either respiratory or non-respiratory TB cases. [43,46,55,56] Similarly, cavitary lung disease, the presence of pulmonary infiltrates and sputum smear results were not associated with drug resistance. However, Salomon and colleagues found hilar or mediastinal adenopathy on chest radiographs to be independently associated (P=. 0009) with MDR-TB, after

controlling for potential confounders, such as HIV infection. [53] Still, because these results were based on a very small sample, this may be a spurious association. Moreover, several larger studies have not observed this same relationship. [56]

Other common clinical symptoms associated with TB, such as fever, cough, night sweats and weight loss were not found to occur more frequently in patients with resistant-TB. {43,46,55,56] Although the presence of fever was not associated with drug resistance, one study determined that patients who suffered from *persistent* fever (greater than 2 weeks) after being treated with a 4-drug regimen had an increased incidence of drug-resistant TB. [53]

Despite the importance of clinical signs and symptoms for patient management in terms of drug-resistant TB, this area has not been fully explored. Few clinical factors have been deemed predictive of drug-resistant TB and much of the existing evidence has been inconclusive. Therefore, further study in this area is needed for the enhancement of TB management.

SOCIODEMOGRAPHIC FACTORS

One of the largest impediments for TB control is non-compliance to treatment and prevention programs. Untreated TB results in longer periods of infectivity, higher TB incidence and an increased potential for the development of drug

resistance to anti-tuberculosis medications. Compliance to TB treatment is difficult to achieve because current regimens are very long (6-24 months), involve multiple medications and are often associated with unpleasant side effects. Also, because obvious symptoms are alleviated early in the course of treatment, patients tend to believe cure has been achieved and often prematurely discontinue treatment only to relapse in the future – often with acquired TB resistance.

Since adherence to TB treatment requires a substantial level of commitment, it is not surprising that socio-economic characteristics, such as homelessness, substance abuse, mental illness, and inadequate social networks (e.g. family support) have been associated with non-compliance. [57 Furthermore, membership in socio-economic groups with a high prevalence of TB and TB-resistance, may allow for greater exposure to resistant organisms.

For these reasons, it would be expected that socio-economic factors would influence the incidence rate of TB resistance. In Fort Worth Texas, having a history of drug use and being male was associated with an increased risk of drug resistance when univariate regression was performed. [54] However, a study of selected regions in the United States determined that homelessness, unemployed status, alcoholism and drug abuse were not associated with drug resistance, once previous history of TB was taken into consideration. [53]

2.6.4 Summary

Overall, the only factor that has consistently been associated with TB drug resistance is having a previous history of TB. Other factors, such as country of origin and number of years since arrival, have only been associated with TB drug resistance in certain regional settings. Similarly, a relationship between HIV and drug resistance has only been demonstrated in certain hospital-based and outbreak settings. In conclusion, the evidence for potential clinical and sociodemographic predictors of TB drug resistance, other than previous history of TB, has been contradictory and extremely limited in scope.

Chapter 3: Methods

This section presents a discussion of the study design, the study population and data collection procedures used. Also, a description of all exposure and outcome variables is presented in detail. The study objectives and study hypotheses were discussed previously in Chapter 1.

3.1 Study Design

The research design used was a retrospective descriptive analysis. To identify risk factors for drug resistance, comparisons were made between drug resistant and drug susceptible TB cases.

3.2 Study Population

The population for this study consisted of all incident TB cases reported to the Montreal Regional Health Board from 1992-1994 for cases aged 19-49, and from 1992-1995 for those individuals aged 0-18. A total of 387 subjects were included in this data set.

3.2.1 Background on current TB control and public health measures in Montreal

In Quebec, TB is a statutory notifiable disease mandated by provincial law (*Loi sur la protection de la sante publique).* As such, both physicians and laboratories are required to report each diagnosed TB case to the DSP, including those diagnosed at autopsy, thus making up a dual TB notification system.

While the completeness of reporting for dual notification systems has never been specifically examined for Montreal, excellent results have been reported in Wisconsin where a similar program is in place. [59] There, more than 99.0% of laboratory confirmed cases and 98.0% of hospital discharged TB cases were reported to the local TB registry.

Each TB case reported to the DSP was assigned a public health nurse who was responsible for case management and follow-up. To identify other potential TB cases, public health nurses perform additional measures, such as tracing individuals who may have had substantial contact with an infectious TB case. Also, a case file was opened and any relevant sociodemographic and clinical information that was available was recorded for each reported TB case (see Appendix B).

Due to the progressive and chronic nature of this disease, it is expected that most affected individuals will eventually seek medical attention. This is especially true in Montreal where most individuals are covered by a provincial medical plan and have free access to medical treatment. Although an accurate estimate cannot be made, it is believed only a small proportion of TB cases remain undetected for the reasons mentioned above.

3.2.2 Inclusion criteria

1. Individuals living on the island of Montreal and between the ages of 19-49 were diagnosed with TB between 1992-1994.
2. Individuals living on the island of Montreal and between the ages of 0-18 that were diagnosed with TB between 1992-1995.
3. Must be culture positive for *Mycobacterium tuberculosis.*

3.3 Data collection procedures

Dr. Kate Culman and associates at the Infectious Disease Unit of the DSP Montreal-Centre developed this data set in 1996 for the express purpose of studying HIV/TB infection. In order to capture the vast majority (90.0%) of TB/HIV infected individuals and to study TB in children - a population that has previously received little study - data collection was limited to individuals less than 50 years of age. The Laboratory Centre for Disease Control (LCDC) at Health Canada provided funding for data collection and ethics approval was obtained from the DSP ethics committee.

Information was gathered through a retrospective review of both medical and public health charts for all reported TB cases. To collect information on a wide range of potentially relevant variables, a standardized chart abstraction instrument was created (see Appendix 1) by Kate Culman and associates. Using this standardized abstraction form, data was collected on: 1) demographic

variables 2) clinical symptomology 3) therapeutic regimen 4) TB risk factors 5) laboratory results, and 6) previous TB history.

Permission was sought and obtained from the Director of Professional Services at each hospital on the island of Montreal that reported having at least one TB case during the study period. After permission was granted, charts were obtained for all study subjects. TB cases reported to the public health department were identified using the provincial MADO database (*maladies a declaration obligatoire*) and all respective public health charts were retrieved. Once all public health and medical charts were matched for each study subject, two research assistants specially trained in reviewing TB charts abstracted all pertinent information listed on the standardized data abstraction form.

The design of the data abstraction instrument, collection of the data, and creation of the database was done by Dr. Kate Culman and associates. Subsequently, we analyzed this existing database to answer the objectives of our study.

3.3.1 Reliability of data collection

To ensure information was collected in a reliable and consistent manner, the principal investigator, Dr. Kate Culman, and both research assistants *each* reviewed 10 of the same patients' charts. The abstracted data collected by each reviewer was compared for completeness and consistency. At this point, the

principal investigator clarified areas of misunderstandings among members of the research team and made any appropriate changes to the measurement instrument.

This pre-test was done to minimize inter-observer variation and to ensure that all charts were reviewed in the same consistent manner regardless of the outcome status of the study subject. In addition, reliability was enhanced since the data abstracted from medical charts was mostly objective in nature (i.e., clinical symptoms, sociodemographic variables, etc.) and required little additional interpretation.

3.3.2 Data storage

Once charts were reviewed, data recorded on each abstraction form was entered into a database using the statistical package Epi Info (CDC V.6.06) and was then converted into a SAS database for statistical analyses purposes. The database was designed to have the same format as the questionnaire and contained the same categories and variable titles. All study subjects were given a unique identification number to maintain privacy and confidentiality and access to the database was limited to designated research staff.

3.4 Outcome measures

3.4.1 Primary outcome measures

DRUG RESISTANCE

Drug resistance was defined as bacteriologically confirmed resistance to one or more 1st-line anti-tuberculosis medications. Drug susceptibility results were obtained from the Laboratoire de Sante Publique du Quebec (LSPQ), where culture confirmed cases of *M. tuberculosis* were tested for susceptibility to isoniazid (INH), rifampin (RIF), streptomycin (SM), ethambutol (EMB), and pyrazinamide (PZA). [60]

3.4.2 Secondary Outcome Measures

INITIAL RESISTANCE

Since data on previous TB episodes were unavailable, patients who reported never having a previous episode of TB and were diagnosed with a drug resistant strain of TB were considered to have initial drug resistance. Primary resistance can only be assessed when the past history of TB can be verified. [5,23, 42,47]

ACQUIRED DRUG RESISTANCE

Acquired resistance occurs when a TB patient that is initially diagnosed with a non-resistant strain of *M. tuberculosis* develops drug resistance over time, indicating inadequate treatment. [5,23,42,47]

SPECIFIC PATTERNS OF RESISTANCE

In this study we will describe the specific patterns of drug resistance that occurred among TB patients in our study population for the following 1st-line drugs: isoniazid, rifampin, streptomycin, ethambutol and pyrazinamide. The overall prevalence of resistance to each of these drugs (with or without resistance to other 1st-line anti-TB drugs) will be presented, as well as for single drug resistance (also known as monoresistance) and specific combinations that were demonstrated in our study population.

MULTIDRUG RESISTANCE

Multidrug resistant TB is when TB patients are diagnosed with resistance to both INH and RIF, with or without resistance to other anti-TB medications. [5,42.47]

3.5 Exposure Variables

3.5.1 Table 1: Demographic variables

Variable	Definition	Scale of Measurement	Characteristics
Age	Age at time of TB diagnosis.	Years (0-49) Age categories in years: 1. 0-18 2.19-29 3.30-39 4.40-49	Continuous Variable Ordinal Variable
Gender	Sex	1. Male 2. Female	Dichotomous Variable
Foreign-born Status	Based on country of birth.	1. Foreign-born 2. Canadian-born	Dichotomous Variable
# Years in Canada Post-Immigration	Based on the total number of years immigrants have lived in Canada from the 1st day of arrival until date of TB diagnosis.	1: 5 years or more 2: Less than 5 years	Dichotomous Variable
Marital Status	Marital status at the time of diagnosis	1: Single/Divorced/ Widowed 2: Married/Free Union	Dichotomous Variable

3.5.2 Table 2: Clinical variables

Variable	Definition	Scale of Measurement	Characteristics
Site of disease	Site of disease defined by the ICD-9 classification and grouped into respiratory or non-respiratory.	1. Respiratory Infection* 2. Non-respiratory Infection only	Categorical Variable
Clinical Symptomology	Number of symptoms reported in medical chart: TB symptoms include: 1. Fever 2. Sweats 3. Weight Loss 4. General Malaise 5. Cough 6. Sputum production 7. Hemoptysis 8. Chest Pain	Specific clinical symptom: 1: Yes 2: No Number of clinical symptoms: 1: None 2: 1-3 3: 4 or more	Dichotomous Variable Ordinal Variable
Previous History of TB	Previously diagnosed with TB. Information obtained from public health/ medical charts.	1. Previously had TB 2. Never had TB before. 3. Unknown	Categorical Variable
HIV Status	HIV status as reported in Medical chart.	Positive Negative Unknown	Categorical Variable

*this category includes TB cases that had extrapulmonary infection in addition to pulmonary infection

3.5.3 Table 3: TB risk factors

Variable	Definition	Scale of Measurement	Characteristics
TB Risk Level	Total # of TB risk factors reported in patients' charts. Known risk factors include: 1. Alcoholism 2. Diabetes 3. Chronic Renal Failure 4. Illicit Drug Use 5. Homelessness 6. Stay in a TB endemic country 7. Malnutrition	1. None 2. 1-2 TB risk factors 3. More than 3 risk factors Risk Level: 1. Hi-risk =3 or more risk actors 2. Low-risk= less than 3 risk factors	Ordinal Variable Dichotomous Variable

3.5.4 Rationale for selection, measurement and categorization of selected study variables

POTENTIAL CONFOUNDERS

Age and sex were considered to be likely confounders due to their relationship with the presence of TB risk factors. Furthermore, the association between age and the clinical course of TB further supports the inclusion of this factor as a potential confounder. As likely confounders these two variables were retained in all final models.

MARITAL STATUS

Some studies have found single individuals to be more non-compliant to medical treatment than partnered individuals. [57,61] It has been suggested that significant partners play a supportive role, such as reinforcing routines and reminding and encouraging partners to adhere to medication schedules and treatments.

Since noncompliance to TB treatment is one of the main selective factors for drug-resistant organisms and relapse, it is possible that married TB patients may be less likely to have drug-resistant TB than single patients. To determine whether the incidence of drug resistance was related to marital status, this variable was included in the present study.

YEARS IN CANADA

Recent immigrants from less developed countries have been found to have a substantially higher rate of TB incidence within the first five years of arrival (See Chapter 2). For both practical purposes of comparison, and because this division can serve as a useful guide for the practice of public health, we have elected to dichotomize years in Canada in the same manner as previous studies.

Chapter 4 – Statistical analysis

All data was analysed using the SAS (SAS Inc., Cary, North Carolina) computer statistical package and Epi Info (Centers for Disease Control, Atlanta, v. 6.06).

4.1 Descriptive analyses

Descriptive statistics were provided for all outcome and independent variables. The mean, median, and standard deviation were reported for all continuous variables, while proportions were reported for all dichotomous and categorical variables. Pearson correlation coefficients were calculated for continuous variables.

4.2 Univariate analyses

As a first step, univariate analyses were performed to assess the relationship between each independent exposure variable and the outcome of drug resistance. The Pearson Chi-square test was used for categorical independent variables. The Fisher's exact test was used when the value of any cell of a contingency table was less than 5. Univariate logistic regression was used to obtain odds ratios and the Wald statistics for all continuous and categorical variables.

Variables attaining the p=0.05 level were deemed to have a significant crude association, although all independent variables determined to have a p-value <

0.25 were included in the multivariate modelling process. Age and sex were included in all final models to control for their potential confounding effects.

4.3 Multivariate analysis

A multivariate analysis was performed to identify independent risk factors for TB drug resistance, after controlling for the effect of potential covariates. As the outcome variable of our study was dichotomous, unconditional logistic regression was employed. Using this technique, parameters for each independent variable were estimated using the maximum likelihood method.

4.3.1 Testing for effect modification and confounding

Variables that were deemed to be potential effect modifiers or confounders based on *a priori* information and biological plausibility were tested using a trivariate analysis; this involved determining whether the exposure–outcome (drug resistance) association varied across different levels of another factor – the potential effect modifier.

Effect modification was considered to be likely when the crude odds ratios fell within the range of the stratum-specific odds ratios for another variable, and the Breslow-Day test of homogeneity had a probability of less than p= 0.10. Potential confounding was suspected when: 1) the crude odds ratio for the exposure-outcome relationship fell outside the range of stratum-specific odds

ratios for another factor; and 2) there was a difference of 10% or greater between the crude and adjusted (Maentel-Haenszel) odds ratio.

All potential effect modifiers suggested by the trivariate analyses were further tested in the multivariate analysis to see if they significantly improved the fit of the full model at the $\alpha = 0.05$ level. Potential confounders were further assessed in the multivariate analysis by examining their effect on covariate odds ratios when added to the model. Variables that did not affect odds ratio estimates, but improved the precision of the model (by reducing residual error) were retained.

4.3.2 Multivariate modelling process

Included in the initial model were all independent variables selected in the univariate analysis, in addition to the potential confounders - age and sex. Using this full model, potential interactions identified in the trivariate analysis were tested. To maintain a hierarchically well-formulated model, higher ordered variables (interactions) that were not significant ($p < 0.05$ level) were excluded first. For interactions that demonstrated significance, all lower order components were retained in all further models regardless of their individual significance.

Once interactions were tested, the remaining independent exposures and potential confounders were tested for significance using the Likelihood Ratio (LR) and Wald significance tests. A hierarchical backward elimination approach was used to obtain the most parsimonious final model.

According to this approach, variables that were found to significantly improve the model (LR test $p < .05$) were retained, while those that did not contribute to the overall fit of the model were excluded in a stepwise fashion.

Goodness-of-fit was assessed for all final models using the Hosmer-Lemeshow probability test statistic. A final model was chosen according to goodness-of-fit and biological plausibility, in light of *a priori* knowledge.

Once the final model was chosen, continuous variables were assessed for assumption of linearity in the logit. This was done by dividing each continuous variable into quartiles and graphically plotting the median value of each quartile against the logit to visually observe the linearity of the graph.

4.4 Time trends for TB drug resistance

The incidence of TB drug resistance for each year was tabulated and plotted on a graph for each year. The X^2 test for linear trend was used to detect significant differences in the incidence of TB drug resistance over the study period.

4.5 Sample size and statistical power considerations

The statistical power of a study is dependent on the following factors:

1) Sample size
2) Magnitude of the difference to be detected
3) The ratio of cases to controls
4) The population prevalence of exposure in the population
5) The level of confidence one requires

For our study, there were a fixed number of subjects that met the eligibility criteria - a total of 349 culture-positive TB cases. Because this study examined several potential risk factors, we have estimated the power for several scenarios of exposure prevalence and relative risk values (Table 4).

Table 4: Power to detect increased relative risk for different levels of exposure prevalence among controls

Relative Risk	Number of cases	Exposure Prevalence				
		1%	5%	10%	25%	50%
1.5	64	.09	.17	.24	.38	.43
2.0	64	.15	.36	.53	.75	.79
2.5	64	.21	.55	.76	.93	.94
3.0	64	.27	.71	.90	.98	.98
4.0	64	.41	.91	.99	.999	.999

In table 4, we have highlighted relative risk and exposure prevalence combinations that have achieved 80.0% power – a level that is commonly accepted as being adequate. Based on previous studies, we expect that the

exposure prevalence for all variables examined will be at least 10.0%. Therefore, we expect that our sample size will be large enough to provide an adequate level of power to detect relative risks of 2.5 or greater.

Chapter 5 - Results

This chapter presents the results of the analyses described previously in the methods section (Chapter 3). A description of the sociodemographic and clinical characteristics is presented initially, for both the total study population, and sub-groups of interest. Also, a comparison of included and excluded study subjects is described. Next, the results of the univariate analyses are presented for all sociodemographic and clinical characteristics, as well as for the stratified analysis. Lastly, the results of the multivariate analyses describe the relationship between sociodemographic and clinical characteristics and tuberculosis drug resistance.

5.1 Description of the study cohort

5.1.1 Sociodemographic characteristics

Between 1992 and 1995, a total of 349 out of 387 TB cases reported to the Montreal DSP met the specified eligibility criteria and were included in the present study. The mean age for the entire study cohort was 31.4 years (SD=9.6) and 57.6% of all subjects were female (table 5). Children (under 18 years of age) only made up 6.6% (n=22) of the total study population. A comparison of included and excluded TB cases is presented in section 5.1.3.

A large portion of the study cohort was of foreign origin (84.8%), with the majority of foreign-born cases originating from Haiti (23.5%), Vietnam (12.0%), the

Philippines (6.0%), Peru (3.4%), and China (3.4%). The average time of residence in Canada before diagnosis was 6.0 years (S.D.=6.0).
Approximately forty-two percent of foreign-born cases (123/293) arrived in Canada less than 5 years before being diagnosed with tuberculosis (table 5).

Almost half all the study subjects (41.8%) were in a partnered relationship defined as marriage or free union (common-law). For 10 cases, marital status was not recorded in either medical or public health charts and was consequently coded as missing.

In this study we were interested in assessing the relationship between predominant TB risk factors and the likelihood of drug resistance. Initially we wanted to observe the association for each TB risk factor, however, because of insufficient sample sizes we decided to categorize study subjects into high and low-risk categories. Individuals that had more than 2 TB risk factors recorded in their medical charts were classified as high-risk, while those with less than 3 TB risk factors were considered to be low-risk. In fact, the number of TB risk factors an individual had was not associated with a greater likelihood of drug resistance. To further characterize our study population, the distribution of individual TB risk factors is described in the next section (5.1.2).

Table 5: Sociodemographic description of tuberculosis (TB) patients and drug resistance in Montreal

Characteristic	Total number of patients n=349	Number of patients with drug resistant TB (%)	Crude OR (95% CI)
Sex			
Female	201	36 (17.9)	Referent
Male	148	28 (18.9)	1.1 (0.6-1.8)
Age in years			
Less than 18	22	3 (13.6)	Referent
18-29	117	27 (23.1)	1,9 (0.5-6.9)
30-39	140	24 (17.1)	1.1 (0.6-2.2)
40-49	70	10 (14.3)	1.0 (0.6-1.6)
Country of origin			
Canadian-born	53	10 (18.9)	Referent
Foreign-born	296	54 (18.2)	1.0 (0.5-2.0)
Time since arrival in Canada*			
5 years or more			
Less than 5 years	123	21 (17.1)	Referent
	170	32 (18.8)	1.1 (0.6-2.1)
Marital Status**			
Married / Free Union	146	22 (15.0)	Referent
Single/Divorced/ Widowed	193	39 (20.0)	1.4 (0.8-2.5)
Number of TB risk factors			
2 or less	302	57 (18.9)	Referent
3 or more	47	7 (14.9)	0.8 (0.3-1.8)

*Foreign-born subjects only – missing 3 subjects for time since arrival
** Missing 10 subjects

5.1.2 Predominant TB risk factors

The distribution of well-known TB risk factors can be seen below in table 6. It should be noted that in most cases TB risk factors were only reported in patients' charts when they were present; therefore, unless explicitly stated otherwise, they were assumed to be absent.

The most common risk factors reported in our study population were: stay in a TB-endemic country, contact with a known TB case, immunosuppression and having another type of debilitating disease. As the majority of TB cases in Montreal originated from countries known to have a high prevalence of TB, it was not surprising that 86.0% of our study population were reported to have stayed in a TB–endemic country.

Approximately 8.0% (29 cases) of our study subjects were classified as alcoholics or substance abusers and 10 (2.9%) cases were reported to have spent time in a prison. Interestingly, homeless individuals only accounted for 5 cases (1.4%) of the total study population. Occupational TB exposure was only reported for 6 cases (1.7%) of the total study population.

In general, most TB risk factors were distributed similarly among both resistant and non-resistant TB cases and any slight disparities were not statistically significant (α= 0.05 level).

Table 6: Frequency of TB risk factors among TB cases in Montreal (1992-1995)

TB Risk Factor	N (%) of total study population (N=349)	N (%) of total resistant TB cases (N=64)	N (%) of total non-resistant TB cases (N=285)
Alcoholism	14 (4.0)	4 (6.3)	10 (3.5)
Diabetes	6 (1.7)	0 (0.0)	6 (2.1)
Silicosis	0 (0.0)	0 (0.0)	0 (0.0)
Gastrectomy	1 (0.3)	0 (0.0)	1 (0.4)
Malnutrition	9 (2.6)	3 (1.6)	6 (2.1)
Chronic renal failure	3 (0.9)	0 (0.0)	3 (1.1)
Drug addict	15 (4.3)	2 (3.1)	13 (4.6)
Homeless	5 (1.4)	0 (0.0)	5 (1.8)
Sex trade worker	2 (0.6)	0 (0.0)	2 (0.7)
Stay in an endemic country	300 (86.0)	57 (89.1)	243 (85.3)
Immunosuppression	52 (14.9)	8 (12.5)	44 (15.4)
Occupational exposure	6 (1.7)	2 (3.1)	4 (1.4)
Other debilitating disease	58 (16.6)	12 (18.8)	46 (16.1)
Known TB contact	74 (21.2)	11 (17.2)	63 (22.1)
Prisoner	10 (2.9)	1 (1.6)	9 (3.2)

5.1.3 Comparison of culture-positive and culture-negative TB cases

As mentioned earlier, 38 TB cases were excluded from this study because they did not meet the eligibility criteria – namely they did not have bacterial culture results. Culture positive cases were compared to culture negative cases for several sociodemographic variables in order to assess whether any appreciable differences existed between these two groups. According to these results, females were more highly represented among culture-negative cases (52.6%) than among culture-positive cases (42.4%). Similarly, a higher proportion of

Canadian-born individuals were found among culture negative cases (21.1%) than culture positive cases (15.2%). However, differences between culture-negative and culture-positive cases were not significant for any of the variables examined.

5.1.4 Comparison of foreign-born and Canadian-born TB cases

The characteristics of foreign-born and Canadian-born culture-positive TB cases were compared to determine whether there were any differences between these two sub-groups in Montreal. Factors examined included age, sex, number of TB risk factors, HIV seropositivity and marital status.

Our analysis showed that foreign-born TB cases were significantly more likely to be partnered than Canadian-born TB cases (48.6% versus 15.2%). Other than marital status, there were no significant differences between foreign-born TB cases and Canadian-born TB cases for any of the remaining variables tested.

5.1.5 Clinical characteristics

Clinical signs and symptoms were mainly obtained through our review of patient medical charts, although some information may also have been obtained from public health charts, which contained the *questionnaire epidemiologique – tuberculose* for each TB case reported to the DSP. This questionnaire included information on the date of diagnosis, the site of disease, clinical presentation, the clinical characteristics in our study population is presented in Table 7.

Table 7: Clinical characteristics of tuberculosis (TB) patients and drug resistance in Montreal

Characteristic	Total number of patients n=349	Number of patients with drug-resistant TB (%)	Crude OR (95% CI)
HIV status			
Negative	119	20 (16.8)	Referent
Positive	52	9 (17.3)	1.0 (0.4-2.5)
Unknown	178	35 (19.7)	1.2 (0.7-2.2)
Previous TB			
No	182	28 (15.4)	Referent
Yes	18	7 (38.9)	3.5 (1.3-9.8)
Unknown	149	29 (19.5)	1.3 (0.8-2.4)
Site of disease*			
Non- respiratory	101	20 (19.8)	Referent
Respiratory	246	43 (17.4)	0.9 (0.5-1.5)
Number of clinical symptoms			
None	97	18 (18.6)	Referent
1-3	125	29 (23.2)	1.3 (0.7-2.6)
4 or more	127	17 (13.3)	0.7 (0.3-1.4)

*Missing 2 subjects

As can be seen in table 7, a much higher proportion of patients with a previous history of TB were drug resistant compared to patients without a previous history of TB (38.8% versus 15.4%). Due to missing information, previous history of TB was only known for 200 subjects, of which 18 were classified as having had a previous history of TB and 7 of those were drug-resistant. To assess the impact

of these missing values for previous history of TB (n=149 missing) a sensitivity analysis was performed and is discussed later in section 5.6 (table 16).

Positive HIV status was reported for 14.8% (n=52) of the total study population, but it is important to note that HIV status was only known for 49.0% of the total study population. When considering only those individuals with known HIV status, the proportion of HIV positive individuals increased to 30.4%. As with previous history of TB, a sensitivity analysis was performed to further assess the impact of missing values on the relationship between HIV and drug resistance and can also be seen in section 5.6 (table 15). In addition, for both HIV status and history of previous TB, a comparison between study subjects with reported and non-reported status was done to see if there were any significant differences between these two groups and is discussed further in the next section (5.1.2).

In terms of clinical presentation, 18.6% of study subjects were reported to be asymptomatic, 23.0% exhibited between one and three symptoms, and another 13.0% of subjects exhibited four or more symptoms. Over 70.0% of our TB cases had respiratory involvement, with or without extrapulmonary disease. The distribution of individual symptoms can be seen in table 8.

Table 8: Clinical symptoms among TB patients in Montreal

Symptom	Total Cohort (N=349)	Drug resistant (N=64)	Non drug resistant (N=285)
Fever	167 (47.9)	31 (48.4)	136 (47.7)
Sweats	98 (28.1)	15 (23.4)	83 (29.1)
Malnourishment	153 (43.8)	23 (35.9)	130 (45.6)
Cough♦	179 (72.8)	35 (81.4)	144 (70.9)
Sputum Production♦	135 (54.9)	26 (60.5)	109 (53.7)
Hemoptysis♦	57 (23.2)	12 (28.0)	45 (22.2)
Chest pain♦	79 (32.1)	8 (18.6)	71 (35.0)

♦- Only includes subjects with respiratory TB with or without extrapulmonary involvement (total n= 246; resistant n=43; non-resistant n=203)

None of the clinical symptoms in Table 8 were found to be significantly more prevalent among either drug resistant or drug susceptible TB cases. The denominator for the following symptoms: cough, sputum production, hemoptysis and chest pain only included respiratory TB cases, thus the proportion of subjects suffering these symptoms is higher than it would have been if the denominator used was the total study cohort.

5.1.6 Comparison of TB cases with known and unknown status for HIV and previous history of TB

As mentioned previously, because there were such a high proportion of missing values for both HIV status (51.0%) and previous history of TB treatment (42.7%), individuals with known status were compared to individuals with unknown status for several sociodemographic variables. This analysis was performed in order to

determine whether any systematic differences existed between these two groups that might bias our results. The results of this comparison can be seen in table 9.

As can be seen in table 9, gender and marital status were the only factors associated with reporting of HIV status ($p<.05$). Individuals who were single were 70.0% more likely to have their HIV status reported in their medical chart than partnered individuals, while females were 50.0% less likely to have their HIV test results reported than males.

In terms of rates of reporting for previous history of TB, Table 9 shows that TB cases who had lived in Canada for less than 5 years at the time of diagnosis were almost twice as likely to have their previous history of TB reported than TB cases diagnosed more than five years after arrival ($p< .05$).

Table 9: Comparison of TB patients in Montreal with known and unknown status for HIV and previous history of TB

Independent Variable	Known HIV status (N=171)	Unknown HIV status (N=178)	Crude OR (95% CI)	Known previous TB (N=200**)	Unknown previous TB (N=149**)	Crude OR (95% CI)
Age						
Median	32.0	31.6	1.0	30.7	32.9	1.0
(25-75%)	(25.6-37.4)	(24.7-38.5)	(.97-1.0)	(24.5-37.2)	(26.2-39.0)	(0.95-1.0)
Gender						
Male	112 (65.5)	89 (50.0)	Referent	120 (60.0)	81 (54.4)	
Female	59 (34.5)	89 (50.0)	0.5 (0.3-0.8)	80 (40.0)	68 (45.6)	0.8 (0.5-1.2)
Country of origin						
Canadian-born	29 (17.0)	24 (13.5)	Referent	33 (16.5)	20 (13.4)	
Foreign-born	142 (83.0)	154 (86.5)	0.8 (0.4-1.4)	167 (83.5)	129 (86.5)	0.8 (0.4-1.4)
# of years in Canada post-immigration[a]						
Greater than 5 years	66 (46.8)	57 (37.5)	Referent	60 (36.1)	63 (49.6)	
5 years or less	75 (53.2)	95 (62.5)	0.7 (0.4-1.1)	106 (63.9)	64 (50.4)	1.7 (1.1-2.8)
Marital Status[b]						
Married/Free Union	61 (36.7)	85 (52.1)	Referent	79 (39.5)	65 (44.8)	
Single/Widowed/ Divorced	105 (63.3)	88 (47.9)	1.7 (1.1-2.6)	113 ()	80 (55.2)	1.1 (0.7-1.7)

[a] Assessment made with foreign-born subjects only (3 missing values for year of arrival); HIV known n=141, HIV not known n=152; Previous history of TB known n=166, Previous history of TB unknown n=167

[b] Missing 10 subjects; HIV known n=166, HIV not known n=173; Previous TB history known n=194, Previous TB history unknown n=145

5.2 The prevalence of drug resistance in Montreal

Overall, 18.3% of all TB cases demonstrated resistance to at least one 1st-line anti-TB medications (table 10). In terms of patterns of resistance, the large majority (78.1%) of resistant cases demonstrated SM resistance. Resistance to INH, with or without resistance to other 1st-line anti-TB medications was 10.6%. In our study cohort, only 8 cases (2.3%) demonstrated any resistance to RIF.

Although approximately half of all resistant TB isolates were monoresistant, there were no cases of RIF or INH monoresistance. Single drug resistance only occurred for SM (23 cases), EMB (9 cases) and PZA (2 cases). Since monoresistant PZA TB is unusual, we investigated these two cases further and discovered that both these cases were foreign-born and originated from Vietnam and Haiti, respectively. All Canadian-born TB cases that were resistant to PZA (n=2) were also resistant to INH.

Multidrug resistant TB (resistance to at least both INH and RIF) was diagnosed in only 7 patients (2.0% of TB patients) over the entire study period. Two foreign-born TB cases diagnosed with MDR-TB exhibited resistance to all five 1st-line anti-TB medications.

Table 10 also shows the proportion of the study population, stratified by both previous history of TB and country of origin. In terms of overall drug resistance (at least one 1st-line anti-TB drug) rates, there was little difference between

foreign-born and non-foreign born TB cases, however, for several specific drug resistance patterns, different rates were observed between the two groups. For instance, a much higher proportion of Canadian-born TB cases exhibited resistance to RIF than foreign-born TB cases (5.7% versus 1.7%). Also, the proportion of Canadian-born TB patients with MDR-TB was approximately 40.0% higher than that of foreign-born TB patients.

In terms of previous history of TB, rates of resistance for all combinations of anti-TB drugs were considerably higher for cases that previously had an episode of TB. Overall, 38.9% of patients who had a previous tuberculosis episode were resistant to at least one 1stline anti-TB drug compared to 15.4% of first-time TB patients.

Table 10: Frequency of drug resistance to 1st-line anti-TB drugs in Montreal (1992-1995) for selected drug resistance patterns

Resistance Pattern	Total Population	Previous TB		Country of Origin	
	N=349 (%)	Yes N=18 (%)	No N=182 (%)	Foreign-born N=296 (%)	Canadian-born N=53 (%)
Any resistance*					
Any resistance overall	64 (18.3)	7 (38.9)	28 (15.4)	54 (18.2)	10 (18.9)
Any INH resistance	37 (10.6)	5 (27.8)	16 (8.8)	31 (10.5)	6 (11.3)
Any RIF resistance	8 (2.3)	2 (11.1)	4 (2.2)	5 (1.7)	3 (5.7)
Any SM resistance	50 (14.3)	5 (27.8)	23 (12.6)	42 (14.2)	8 (15.1)
Any EMB resistance	6 (1.7)	2 (11.1)	4 (2.2)	5 (1.7)	1 (1.9)
Any PZA resistance	7 (2.0)	1 (5.6)	3 (1.6)	5 (1.7)	2 (3.8)
Single drug resistance					
Overall single drug resistance	34 (9.7)	3 (16.7)	13 (7.1)	30 (10.1)	4 (7.5)
INH only	9 (2.6)	1 (5.6)	2 (1.1)	8 (2.7)	1 (1.9)
RIF only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
SM only	23 (6.6)	2 (11.1)	10 (5.5)	20 (6.7)	3 (5.7)
EMB only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PZA only	2 (0.6)	0 (0.0)	1 (0.6)	2 (0.7)	0 (0.0)
Multidrug resistance					
Any multidrug resistance	7 (2.0)	2 (11.1)	3 (1.6)	5 (2.7)	2 (3.8)
INH+RIF only	1 (0.3)	1 (5.6)	0 (0.0)	1 (0.5)	0 (0.0)
INH+RIF+SM only	2 (0.6)	0 (0.0)	1 (0.6)	2 (0.7)	0 (0.0)
INH+RIF+SM+EMB only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
INH+RIF+EMB+PZA only	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
INH+RIF+SM+EMB+ PZA only	2 (0.6)	1 (5.6)	1 (0.6)	2 (0.7)	0 (0.0)
Other resistance patterns*					
INH+SM	25 (7.2)	3 (16.7)	12 (6.6)	21 (7.1)	4 (7.6)
RIF+SM	6 (1.7)	1 (5.6)	3 (1.7)	4 (1.4)	2 (3.8)
INH+SM+EMB	5 (1.4)	2 (11.1)	3 (1.7)	4 (1.4)	1 (1.9)
INH+SM+PZA	3 (0.9)	1 (5.6)	1 (0.6)	2 (0.7)	1 (1.9)
INH+SM+EMB+PZA	2 (0.6)	1 (5.6)	1 (0.6)	2 (0.7)	0 (0.0)

*with or without resistance to other 1st-line drugs

5.2.1 Proportion of the study cohort resistant to different numbers of anti-TB drugs

This analysis was done to find out the proportion of the study population resistant to different numbers of 1st-line anti-TB drugs. For this analysis we also stratified the study population by previous history of TB to determine whether higher proportions of TB cases with a previous history of TB were resistant to multiple 1st-line anti-TB drugs.

Table 11 shows the proportions of the total and stratified study population resistant to different numbers of anti-TB medications. As indicated in the table, 9.7% of the study population was resistant to two or more anti-TB drugs. The proportion of the population represented in each category declined as the number of drugs increased. Only three TB cases (0.9%) in our study cohort were resistant to all 5 anti-TB drugs. When comparing TB cases with and without a previous history of TB, a higher proportion of patients with a previous history of TB were represented in each category, but none of these differences reached the level of significance α=0.05.

Table 11: Proportion of the study cohort resistant to different numbers of 1st-line anti-TB drugs

Number of drugs	Total cohort N=349	Previous history of TB		
		Previous TB N=18	No previous TB N=182	Unknown N=149
0	285 (81.7)	11 (61.1)	154 (84.6)	120 (80.5)
1	30 (8.6)	3 (16.7)	12 (6.6)	15 (10.1)
2	15 (4.3)	1 (5.5)	6 (3.3)	8 (5.4)
3	12 (3.4)	1 (5.5)	7 (3.8)	4 (2.7)
4	4 (1.1)	1 (5.5)	1 (0.5)	2 (1.3)
5	3 (0.9)	1 (5.5)	2 (1.1)	0 (0.0)

5.2.2 Drug resistance over time

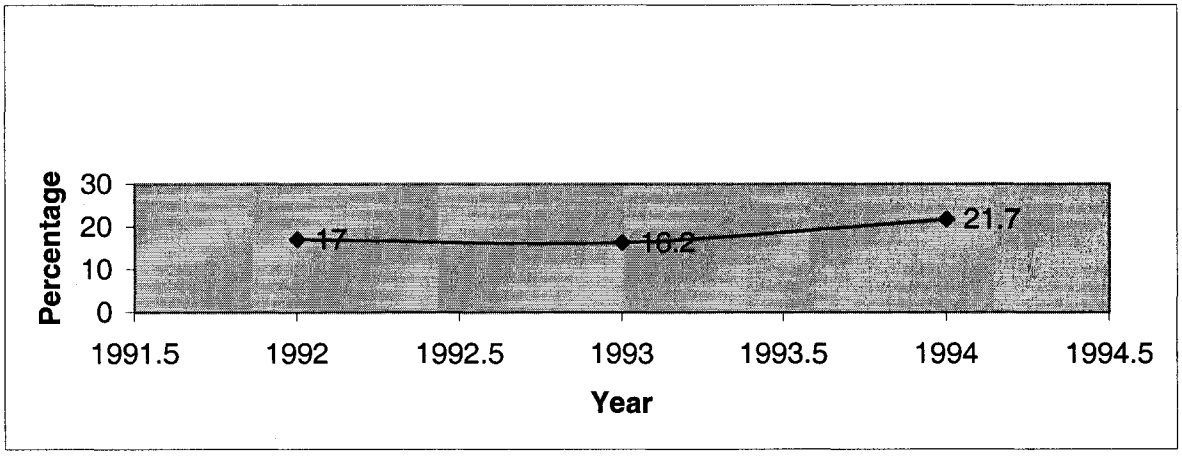
During the study period drug resistance increased from 17.0% in 1992 to 22.0% in 1994 (table 12 and figure 1). Increasing rates were also observed for each of the 1st-line anti-TB medications. For example, resistance to INH increased by 6.0% (from 10.0% in 1992) to over 16.0% in 1994, while the proportion of isolates resistant to rifampin increased by 4.5% during the study period. The rate of MDR-TB steadily increased during the study period from less than 1.0% in 1992 to over 3.0% in 1994.

Since we only had information for paediatric cases in 1995, we decided to exclude this information from our analysis of overall drug resistance time trends. However, 25.0% of paediatric cases in 1995 were drug resistant and one of these cases was diagnosed with MDR-TB.

Table 12: The yearly prevalence of specific drug resistance patterns in Montreal between 1992-1994

Year	*N*	INH	RIF	SM	EMB	PZA	Any drug	MDR-TB
1992	112	7.1	0.9	14.3	0.0	1.8	17.0	0.9
1993	99	11.1	1.0	12.1	2.0	0.0	16.2	1.0
1994	115	13.0	4.4	16.5	2.6	3.5	21.7	3.5

Figure 1: The proportion of yearly incident TB cases in Montreal resistant to at least one 1st-line anti-TB drug (1992-1994)



Using the chi-squared test for linear trend it was determined that there was no significant increase in the year-to-year incidence rate of drug resistance (X^2=0.9, p=0.4) between 1992-1994.

5.2.3 Prevalence of initial and acquired drug resistance

TB patients diagnosed with drug resistance were classified as having initial resistance if they never had a previous episode of TB. According to this definition, 14.0% (28/200) of our study population was diagnosed with initial resistance. Acquired resistance was only observed in three cases (0.8%) during the study period.

5.3 Univariate analyses: factors associated with drug-resistant TB

Univariate analyses were carried out for all exposure variables of interest to identify factors that were significant predictors of drug resistance. The results of the univariate analyses can be seen in table 5 for sociodemographic factors and table 7 for clinical factors. Included are the number and proportion of patients resistant to anti-TB medications in each variable category, as well as the crude odds ratio and 95% CI's.

A patient's previous history of TB was the only significant predictor of drug resistant TB. In this case, patient's who had a previous TB episode were more than three times as likely as first-time TB patients to be diagnosed with drug resistance (OR=3.5; 95% CI: 1.3, 9.8).

The following sociodemographic exposure variables were not associated with an increased risk of anti-TB drug resistance: age, sex, country of origin, number of years in Canada before diagnosis, marital status, number of TB risk factors. Likewise, the following clinical characteristics were not associated with drug-resistant TB: HIV status, site of TB infection and number of TB symptoms.

Although country of origin was not found to be associated with an increased risk of drug resistance, we initially decided to examine this variable further by categorizing countries according to TB prevalence, as published by the World Health Organization. [41]

As the majority of our TB cases originated from countries with either high or low TB prevalence this categorization did not substantially differ from the original categorization of our population (Canadian-born versus foreign born), and was not considered to provide useful additional information. Instead, we decided to limit this analysis to those that represented a substantial portion of our TB cases: Haiti, Vietnam, the Philippines, Peru and China. Of these countries, only immigration from Vietnam was significantly associated with drug-resistant TB (OR=2.3; 95% CI=1.1-4.6) of being diagnosed with drug-resistant TB.

5.4 Stratified Analyses

Before performing the multivariate analyses, stratified analysis was performed to assess for potential confounding and effect modification of the association between some exposures and covariates and drug resistance.

As can be seen in table 13, the adjusted (M-H) odds ratio remained within the range of the stratum-specific odds ratios for each interaction tested, indicating a lack of a confounding effect between the variables tested. In terms of effect modification, substantial heterogeneity (Breslow-Day probability <0.10) between stratum-specific odds ratios was only observed for the association between previous history of TB and drug resistance when stratified by gender (table 13).

Table 13 shows that males with a previous history of TB were almost eight times more likely to have drug resistance than females with a previous history of TB. This potential interaction was tested further in the multivariate analysis.

Table 13: Stratified analysis to check for confounding and effect modification among TB patients in Montreal

Variable	Stratification Variable	Odds Ratio	95% CI	OR (M-H)	95% CI	Breslow-Day Probability
Marital Status	*Crude*	1.4	(0.8-2.5)			
	Males	1.7	(0.8-3.8)	1.4	(0.8-2.6)	0.463
	Females	1.1	(0.5-2.7)			
Previous TB	**Crude**	5.8	(1.7-19.3)			
	Male	8.0	(1.9-33.2)	3.3	(1.3-8.6)	0.092
	Female	1.3	(0.2-6.8)			
TB Risk Factors	**Crude**	0.7	(0.4-1.2)			
	Male	0.9	(0.4-1.9)	0.6	(0.4-1.2)	0.267
	Female	0.4	(0.1-1.2)			
Previous TB	**Crude**	5.8	(1.7-19.3)			
	Married/ Free Union	7.0	(1.3-37.7)	4.2	(1.6-11.2)	.470
	Single / Divorced / Widowed	3.1	(0.8-12.3)			

5.5 Multivariate analysis

Multivariate analyses were performed to assess the associations between different exposure variables and drug resistance, after adjusting for other factors. Based on the criterion for inclusion in the multivariate analyses that was discussed earlier, the following variables were included in the multivariate modelling process: age, sex, previous history of TB, marital status and country of origin.

In addition, we decided to include originating from Vietnam in the final modeling process because of the strong association with drug resistance that was demonstrated in the univariate analysis. Also, age and sex were forced into all multivariate models to control for their potential confounding effects. All potential interactions were forced into the full model, but were found to be insignificant and were excluded from all further models.

As can be seen in the final model (table 14), only previous history of TB was a significant predictor of drug resistance after controlling for age and sex.

Table 14: Risk factors associated with TB drug resistance: unconditional logistic regression analysis (Final Model; n=349)

Variable	Adjusted OR	95% CI
Age range (years)		
0 to 18	Referent	N/A
19 to 29	1.8	0.5-6.8
30 to 39	1.2	0.3-4.7
40 to 49	1.0	0.2-4.0
Sex		
Male	Referent	N/A
Female	1.0	0.6 - 1.8
Previous TB History		
No	Referent	N/A
Yes	3.4	1.2-9.7
Unknown	1.4	0.8-2.5
Country of Origin		
Canada	Referent	N/A
Vietnam	0.6	0.2-1.6
Other	0.8	0.4-1.9

5.6 Missing values analysis

Missing data that are independent of both the exposure and response variable are considered to be missing completely at random (MCAR) and do not bias the measure of effect. Because we could not be certain that unknown values in our study were MCAR we decided to perform sensitivity analyses for all exposure variables that were missing responses for at least 20.0% of the total study cohort.

In our study, HIV status and previous history of TB treatment were missing information for approximately half of the total number of study subjects. To assess the potential impact of these missing values on the results of our study we performed sensitivity analyses for both of these variables (Table 15 and 16).

Three potential scenarios were tested:

1) Complete subject analysis: All unknown variables were coded as missing and not calculated in the total population.
2) Case #1: All unknown values were coded as being positive for the exposure variables HIV and previous history of TB.
3) Case #2: All unknown values were coded as being negative for the exposure variables HIV and previous history of TB.

Sensitivity Analysis: the implications of missing values

Table 15: Sensitivity analysis: The association of HIV status with TB drug resistance (3 scenarios to assess the effect of missing values for HIV status)

HIV test status	% HIV Positive	OR	95% CI
Complete subject analysis	14.9*	1.0	0.4 – 2.5
Case #1	65.9	1.2	0.7 - 2.1
Case #2	14.9	0.9	0.4 - 2.0

Case #1 – subjects with unknown HIV status are assigned HIV positive status
Case #2 – subjects with unknown HIV status are assigned HIV negative status
*Based on total number of subjects n=171

As can be seen in table 15, regardless of the assignment of the status for the exposure variable HIV, no relationship with drug resistance was demonstrated.

Table 16: Sensitivity analysis: The association of previous history of TB treatment with TB drug resistance (3 scenarios to assess the effect of missing values for previous history of TB)

Previous history of TB	% Having previous history of TB	OR	95% CI
Complete subject analysis	5.1	3.5	1.3 – 9.8
Case #1	47.9	1.5	0.9 – 2.6
Case #2	5.1	3.1	1.1 – 8.2

Case #1 – assigned subjects with unknown previous history of TB treatment as having treatment
Case #2 – assigned subjects with unknown previous history of TB treatment as never had treatment
*Based on total # subjects n=200

In table 16, assigning all of the TB cases with an unknown history of previous TB as either missing or having a negative status did not have a large impact on the overall measure of effect. In both the complete subject analysis and case number two, having a previous history of TB demonstrated a three-fold increased risk of having drug resistance. However, in case number one, the measure of effect was in the same direction as the previous two scenarios described, except that it was marginally insignificant. (P = .05 level).

5.7 Comparison of mortality between drug-resistant and drug-susceptible TB cases in Montreal

In our study cohort a total of 6 TB cases (1.7%) were reported to have died as a result of their TB infection during the study period. A higher proportion of drug-resistant TB cases (4.7%) died compared to drug susceptible TB cases (1.0%), but this difference was not significant. Treatment outcome could not be determined for 57 patients in our study cohort because they were either lost to follow-up, transferred to other jurisdictions or because they were still in treatment at the time of chart review.

Chapter 6- Discussion

This chapter contains a discussion of the patterns of drug resistance on the island of Montreal and the relationship between different sociodemographic and clinical factors and TB drug resistance. In addition, we discuss the limitations of this study.

6.1 Incidence of TB drug resistance and time trends

In Montreal the rate of resistance among culture-positive TB cases (less than 50 years of age) was 18.3% (64/349) over the study period. This rate was considerably higher than that observed for the Canadian population (11.8% in 1998), in the western provinces (7.0%) and in Ontario (12.6%). [46,51,52] The inclusion of TB cases from all age groups and from both urban and rural areas may partially explain the discrepancies between Montreal and other regions of Canada. However, the overall rate of drug resistance in Montreal for all age groups was only slightly lower at 16.2%, suggesting that our results are reflective of those found in the general Montreal population. [20]

Overall a significant increasing trend in drug resistance was not observed in our study, although there was an increase from 16.2% in 1993 to 21.0% in 1994. A longer period of observation would be necessary to determine whether this increase was important or was strictly due to chance.

In terms of drug-specific rates, resistance to INH increased by almost 5.5% over the study period from 7.1% in 1992 to 13.0% in 1994. Nevertheless, due to limited statistical power a significant trend was not discernible. However, similar increases in drug-specific rates have also been observed in Ontario where the rate of INH resistance increased from 7.1% (1987-1990) to 11.2% (1991-1995). [52] In contrast, between 1993 and 1996 the United States experienced an overall decreasing trend in TB drug resistance (Moore), although rates of drug resistance substantially varied by region. [37] Further monitoring of trends over time is needed to determine whether the drug resistance rates are indeed increasing.

Regarding the prevalence of drug resistance for specific 1st-line anti-TB drugs, the highest rates were observed for SM (14.3%) and INH (10.6%). In comparison, lower rates of INH resistance were found among the Canadian population (8.4%), in Ontario (9.6%) and in the United States (8.4%). [37,62,63] The association between these drugs and higher levels of drug resistance was not surprising since they have been used the longest for the treatment of TB and, as discussed before in Chapter 2, increased exposure to antimicrobials facilitates the development of drug resistance.

Today in Canada SM is rarely used for TB treatment because it is associated with serious side effects, is inconvenient to administer and is not readily

available. [32,47] As a result, SM resistance does not greatly impact current TB treatment. On the other hand, because INH is one of the most effective anti-TB drugs available and is a cornerstone of modern TB treatment, the high rate of INH resistance demonstrated in Montreal can have implications for the future effectiveness of TB treatment and the need to identify alternative treatment options.

6.1.1 Resistance to multiple anti-TB drugs

Resistance to multiple drugs (greater than one 1st-line anti-TB drug) was observed for 9.7% of our total study cohort. Among drug resistant cases, over half were resistant to more than one 1st-line anti-TB drug. The rate of resistance to multiple numbers of anti-TB drugs in Montreal (9.7%) was higher than the rates observed in Ontario (4.3%) and Alberta (2.2%). [29,63] Also, a higher proportion of patients with a previous history of TB were more likely to be resistant to multiple 1st-line anti-TB drugs than first-time TB sufferers.

These findings emphasize the need to start TB patients off with at least four 1st-line anti-TB drugs until drug susceptibility results are available. Even these precautions may not always suffice as was demonstrated in our study population where 2.0% of our total study cohort were resistant to 4or more 1st-line anti-TB drugs. In three cases (0.9%), resistance was exhibited for all five 1st-line anti-TB drugs. A recent study in Montreal found that only 60.0% of TB cases were initially treated with four 1st-line anti-TB drugs. Given the current prevalence of

drug resistance in Montreal (INH>4.0%), inadequate initial TB treatment suggests a lapse in the current TB control program that may increase the likelihood of the development of acquired drug resistance. [64]

MDR-TB

In terms of MDR-TB, only 7 cases (2.0%) in our study cohort were resistant to (at least) both INH and RIF. Our findings reflect those found in other North American studies, where the rate of MDR-TB has remained at a level generally ranging between 1.0-3.0%. [37,46,58,62] A relatively low rate of this pattern of resistance is an indicator of the adequacy of the current TB control program – most particularly the prevention of relapse and the subsequent development of acquired resistance.

Despite relatively low rates, the high economic and clinical burden of MDR-TB demands continued vigilance. The importance of continued surveillance and aggressive management of MDR-TB can best be exemplified by the experience of New York City between 1987-1991 when lapses in the local TB control program allowed for the rapid spread of MDR-TB. [55] At one point it was estimated that one of every three TB cases was infected with MDR-TB.

Recently, MDR-TB "hot zones" have been identified in several countries throughout the world – most particularly Eastern European countries, such as

Estonia, Latvia and Russia, where the medical and public health systems have drastically deteriorated. Other hot zones include parts of China and the Islamic Republic of Iran. Rates of MDR-TB in these regions have been reported to be between 5.0 and 14.1%. [65]

Increasing international travel and migration further increases the likelihood MDR-TB rates will increase in Montreal. Improved TB screening procedures for recent immigrants as well as aggressive management of prevalent cases will help to prevent similar situations to those observed in identified "hot zones".

6.1.2 Initial resistance

Among study subjects who had their previous history of TB reported, 14.0% (28/200) were diagnosed with initial resistance, indicating that they were infected with a drug resistant TB isolate. When assuming that previous history of TB was negative for those that did not have their previous history of TB reported, the level of initial resistance increased to 16.3% (57/349). We estimate that the true level of initial resistance in our study population was somewhere between 14.0-16.3%. In western Canada initial resistance rates were lower at 5.1%.

6.1.3 Acquired drug resistance

Only three TB cases acquired drug resistance during the time period of this study, indicating that in most cases drug treatment was appropriate.

Nonetheless, due to the limited observation period, the results of our study may underestimate the true incidence of acquired resistance in Montreal. Since this study period only spanned 4 years, it is possible that not all acquired cases were captured by the chart review. This is especially true for cases that were diagnosed towards the end of the study period and could not be followed for a long enough time to determine whether they eventually developed resistance.

Unfortunately, we were unable to determine the past drug resistance profiles of TB cases in our database that were reported to have had a previous history of TB. Therefore, it is highly possible that drug resistant TB cases that were previously treated for TB also had acquired drug resistance, even though resistance did not develop after the diagnosis of the present TB episode. For the purposes of this study the term "acquired resistance" referred to TB cases that developed resistance after the time of diagnosis.

6.1.4 Drug resistance in children

Altogether there were 22 paediatric (under age 18) TB cases between 1992 and 1995, of which 9 were Canadian-born. In 1995 alone there were 12 paediatric cases, demonstrating a large increase in frequency compared to previous years. Overall, three paediatric cases demonstrated drug resistance during the study period and all of these cases were diagnosed in 1995. This represented 25.0% of the TB cases in children in 1995 - a much higher proportion than observed in

years that included the full age range of the study cohort. These three resistant paediatric cases originated from Haiti, Somalia and Canada.

Due to the lengthy latency period associated with TB, it is less likely that the prevalence of drug resistance observed in this age group was due to reactivation of an older infection; this is especially true for those under 5 years of age. Six paediatric TB cases in total were less than 5 years of age and 4 of these cases were Canadian-born. The ages of the drug-resistant paediatric cases were 8, 12 and 17 years of age, with the youngest resistant paediatric case originating from Canada.

The high rate of resistance among this age group is indicative of the potential for recent TB transmission and suggests a failure of the TB control program, either in Canada or in the country of origin. The fact that there was a Canadian-born drug-resistant case is of particular concern since it indicates that domestic transmission of drug-resistant TB has occurred. In fact, this particular Canadian-born paediatric case was known to have a close TB contact.

Similar to some North American studies, we failed to find an increased risk of drug resistance among children; however, many of these studies (including the present one) were limited by small sample sizes, which prevented the attainment of adequate statistical power to observe an association. [54,55,58] However an

increased risk of TB among children was observed among foreign-born TB cases in Alberta and among all TB cases in the United States. [29,37]

Nonetheless, the high proportion of children who demonstrated TB drug resistance in Montreal in 1995 warrants further evaluation of this sub-group and of the adequacy of current TB control measures.

6.2 Identification of risk factors for TB drug resistance

In addition to describing the epidemiology of TB-resistance in Montreal, a main focus of this research was to identify predictors, which could ultimately be used to enhance the management, treatment and prevention of TB.

6.2.1 Sociodemographic factors

Several factors influenced our decision to include certain sociodemographic variables in our analyses and included: 1) findings of previous studies 2) biological plausibility 3) markers for risk factors that were difficult to measure directly 4) well-known TB risk factors 5) data availability.

COUNTRY OF ORIGIN

As was expected, our study population was mainly comprised of foreign-born TB cases (84.8%). The proportion of foreign-born cases in our study population was slightly higher than that observed for all age groups in Montreal, suggesting that

a higher proportion of foreign-born TB cases were younger. [20] In terms of geographical origin, 57 countries were represented although the following five countries (in descending order) were the most represented: Haiti (23.5%), Vietnam (12.0%), Philippines (6.0%), Peru (3.4%) and China (3.4%).

We found, contrary to other Canadian studies, simply being foreign-born was not significantly associated with an increased risk of drug resistance in Montreal, although the rate of resistance to at least one 1st-line anti-TB drug was 34.0% higher among foreign-born TB cases. [29,46] We most likely did not observe the same association that was observed in western Canada because of different immigration patterns between these two regions.

Although a relationship was not demonstrated for country of origin as a whole, or for any individual country, substantially higher rates of resistance were observed for TB cases that originated from Vietnam than for other individual countries. Over 30.0% of all TB cases from Vietnam were found to be drug resistant. The majority (12 out of 13) of these cases from Vietnam were resistant to streptomycin – a drug that has been commonly used in many developing countries, but is no longer routinely used in Canada or much of the developed world. Of the 13 resistant cases from Vietnam, 7 were resistant to streptomycin alone and another 5 cases were resistant to streptomycin and isoniazid.

This has important clinical implications because knowing that someone is from Vietnam may not be useful for determining an initial drug regimen since streptomycin is no longer routinely used. Nevertheless, the high prevalence of SM drug resistance among this population is probably an indicator of the drug resistance situation in Vietnam.

Unfortunately, because the samples from each individual country were small, we were unable to identify countries of origin that were significantly associated with increased risk of drug resistance. All the same, country of origin may be a useful predictor of drug resistance when there are high resistance rates in the originating country. Future studies with larger samples may help to uncover countries of origin that best predict an increased risk of developing drug resistant TB in Canada.

Recent studies in the United States have found higher rates of INH and SM resistance in foreign-born TB cases. [37,42] In our study, rates of resistance to these two drugs were similar for both foreign-born and Canadian-born cases. However, foreign-born TB cases had higher overall drug resistance while Canadian-born TB cases had higher rates of RIF and PZA resistance. Due to small sample sizes these differences were not significant

Some studies have found that foreign-born TB cases were at higher risk for drug resistance if they were diagnosed with TB within five years of arrival. [29,46,50]

In Alberta, foreign-born TB cases were found to be at greater risk of having drug resistant TB for up to 15 years after arrival. [29] Although more than half of the foreign-born TB cases in our study cohort were diagnosed with TB within five years of arrival to Montreal, we did not observe an increased risk of drug resistance with the number of years between diagnosis and arrival.

MARITAL STATUS

Almost half of our study population (41.8%) were married or in a common-law relationship. As discussed earlier, marital status has been associated with increased compliance to medical treatment for a variety of ailments. Since compliance to drug regimens is one of the most critical factors for the prevention of acquired drug resistance and relapse, we hypothesized that marital status might impact drug resistance rates. Since we only observed 3 cases of acquired drug resistance in our cohort during the study period we could not determine whether single individuals were more likely to develop acquired drug resistance.

6.2.2 Clinical Factors

PREVIOUS HISTORY OF TB

Our findings were consistent with those of other North American studies, confirming that a previous history of TB is a strong predictor of drug resistance. [29,37,46,50,54,58,66] This was also the only known risk factor for TB that was also a risk factor for TB drug resistance.

Since we did not know the previous TB history of almost 50.0% of our study population we performed a sensitivity analysis. The results from this analysis were consistent with our findings, except in the case where we classified all subjects with an unknown status for this variable as having had a previous episode of TB. In this case, our measure of effect remained in the same direction as all other cases, but was marginally insignificant.

While this analysis does somewhat call into question the validity of our findings, the logical nature of the association between previous history of TB and drug resistance and the consistency of our findings with past studies support our initial findings. Moreover, it is highly unlikely that the extreme case actually occurred in our study population.

It is interesting to note that among foreign-born TB patients, those TB cases that had their previous TB history reported were 70.0% more likely to have been diagnosed with TB within 5 years of arrival. This shows that there may have been an overrepresentation of recently arrived foreign-born TB cases among those with reported status for previous history of TB.

HIV

Contrary to the results of past studies, HIV infection was not associated with an increased risk of drug resistance in our study cohort. A sensitivity analysis also

revealed that this result did not change regardless of how subjects with unknown HIV status were classified.

SITE OF DISEASE

The likelihood of having drug resistant TB was not higher for individuals with either respiratory or non-respiratory disease. This is important to know because those with respiratory disease are more infectious and would more readily spread drug resistant strains throughout the population. Long et al also found that the site of disease was not associated with drug-resistant TB. [50]

CLINICAL SYMPTOMATOLOGY

An association between individual clinical TB symptoms and drug resistance was not found in our study. Likewise, higher numbers of symptoms did not increase the risk of having drug resistant TB. Although an association was not observed, it is possible that our results were limited by the data available. There is a strong possibility that there was underreporting of clinical symptoms in medical charts. This may have resulted in some misclassification bias since we assumed that no report indicated absence of symptoms. Therefore it was difficult for us to reach a definite conclusion regarding the relationship between clinical TB symptoms and drug resistant TB.

6.3 Mortality among TB cases in Montreal

Although a higher proportion of drug resistant TB cases died, a significant difference in the mortality rate between drug resistant and drug susceptible cases was not found. Other studies have found that drug resistant TB is associated with a greater risk of death, especially when there is HIV coinfection. [43,44,55] It is likely that the small number of deaths in our study population prevented a satisfactory assessment of this relationship. Surveillance of TB mortality over the long term may reveal the same association observed in other regions.

6.4 Limitations

6.4.1 Source of data

Although medical and public health charts were a readily available source of information, incomplete reporting may have introduced a certain degree of misclassification bias. This problem may have been most pronounced in the cases of HIV status and previous history of TB. In our study population only 49.0% and 57.3% of subjects had their HIV status and their history of previous TB reported, respectively, in their medical charts.

In the first case, the highly sensitive and confidential nature of information regarding HIV status may have prevented full disclosure by both patients and physicians. Another reason may be that physicians selectively request HIV

testing from patients perceived to be at highest risk, such as I.V. drug users and males.

This selectivity was observed in the present study where a significantly greater number of single patients had HIV test results reported than married TB patients. Using the same database as our study, Geduld and associates (1999) also found the following factors to be predictors of HIV testing among TB patients in Montreal: positive smear, having at least 1 clinical symptom, being aged 30-39, having 1 or more HIV risk factors reported, and being diagnosed by a microbiologist or infectious disease specialist. [68]

Clearly, this finding suggests physicians may introduce a selection bias testing despite the strong recommendation by the Canadian and American Thoracic Societies that all TB patients undergo HIV testing.

Similarly, low reporting of previous history of TB may have been due to poor patient recall or selective reporting by physicians. In some cases, this information may not have been requested from patients or was simply not recorded. In other cases, patients may have elected to withhold information or to report erroneously because of a fear of discriminatory repercussions. Selection bias may have also occurred if some patients were asked about their past TB history more often or more thoroughly than others.

6.4.2 Generalizability

Since our study was set in a large North American city, it was difficult to compare our result to other studies that included both urban and rural areas. As TB is more prevalent in urban regions, it is possible that the inclusion of rural regions diluted the overall rate of TB in these other studies. More importantly, since recent immigrants tend to settle in large North American cities, there may be a chance that drug resistant TB is also more prevalent in urban areas. This may partially explain why we found higher rates of drug resistance compared to other Canadian regions.

6.4.3 Study period limitations

Since information available in medical charts was generally limited to the present TB episode and did not necessarily include information from past TB episodes, we could not fully assess the level of primary and acquired resistance in our population. Also, depending on stage of disease at the time of the chart review, information pertinent to this study may not have been available and therefore was not considered in this study. For instance, many symptoms and outcomes of TB occur over long time periods and may have occurred outside the scope of this study. This may have led to an underestimation of certain outcomes, such as mortality and acquired resistance.

6.4.4 Power limitations

Limited sample sizes in different sub-groups prevented the attainment of sufficient statistical power to detect an association, for several variables in our study. This problem was most pronounced in the case of individual symptoms and TB risk factors where, for each individual factor, only a small number of positive responses were present. This may be partially due to incomplete reporting, but for this study we assumed no report in the medical charts was an indication of absence of that factor. As a result, we were not able to fully assess the association of individual symptoms and TB risk factors with the outcome of TB drug resistance.

Chapter 7 – Conclusions

These conclusions summarize the principle results of our study in relation to the objectives stated earlier in Chapter 1.

1) The rate of overall resistance to at least one anti-TB drug and to INH in Montreal is higher than other Canadian and North American regions. High levels of resistance to multiple 1st-line anti-TB drugs, in addition to INH resistance, reinforces the need for initially treating all TB cases with at least four 1st-line anti-TB drugs to prevent the development of acquired resistance.

2) The only clinical predictor of TB drug resistance identified in our study was previous history of TB. Contrary to previous studies, HIV status was not shown to be associated with TB drug resistance.

3) A similar proportion of foreign-born and Canadian-born TB cases in our study cohort were drug resistant. A significant increased risk was not observed for any individual country of origin, although this may be partly due to small sample sizes. The use of country-specific drug resistance data may aid in the prediction of drug resistance among foreign-born TB cases.

4) A higher proportion of drug resistant TB cases in our study cohort died during the study period, however because the total number of deaths experienced was small we could not adequately assess the relationship between drug resistance and mortality. Future studies that span longer time periods may accrue greater numbers of deaths, improving statistical power to evaluate this relationship.

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Appendix A

THE EPIDEMIOLOGY OF TUBERCULOSIS IN MONTREAL

idnum_____
Date of chart reviews PHU ___/___/___ Hosp 1 _________ Hosp 2 _________
d m y d m y d m y
No. LSPQ _____
Hosp 1 _____ no dossier _____ Hosp 2 _____ no dossier _____

GENERAL INFORMATION AND DEMOGRAPHICS

Last name _____ First name _____

Date of birth ___/___/___ Sex male ☐$_1$ female ☐$_2$
d m y

Postal code _____

Country of birth Canada ☐ Other ☐ Specify _____

Arrival year _____ Country of last permanent address _____

Ethnic background
- Inuit ☐$_{01}$
- Native indian ☐$_{02}$
- White ☐$_{03}$
- Black ☐$_{04}$
  - Specify: African ☐$_{05}$ Haitian ☐$_{06}$ Caribbean ☐$_{07}$
- East Asian ☐$_{08}$
- Hispanic ☐$_{09}$
- South asian ☐$_{10}$
- other ☐$_{11}$
- unknown ☐$_{99}$

If Canadian aboriginal
- On reserve ☐$_1$
- Off reserve ☐$_2$
- Unknown ☐$_3$

Marital status

single	☐01	widowed	☐05
married	☐02	free union	☐06
separated	☐03	unknown	☐07
divorced	☐04	not stated	☐99

Occupation

food handler	☐01	health care worker	☐02
day care worker	☐03	student	☐04
correction worker	☐05	unemployed	☐06
unknown	☐99		
other	☐98	Specify _____	

Has this person ever worked in a

prison	☐(yy)	☐(nn)	☐(uk)
health care setting	☐(yy)	☐(nn)	☐(uk)
nursing home or chronic care institution	☐(yy)	☐(nn)	☐(uk)

At time of diagnosis was this person living in a

correctional facility	☐1
long term chronic care facility	☐2
neither	☐3
unknown	☐4

CLINICAL INFORMATION

Type of contact

household	☐1
close friend or family	☐2
care giver of TB patient	☐3
shared the same room in institution	☐4
work	☐5
school	☐6
unknown	☐7
other	☐8
specify_____	

Comment_____

_____

Date of onset of symptoms ___/___/___ or wks before diagnosis ___
d m y

Date of onset of cough ___/___/___ or wks before diagnosis ___
d m y

Clinical presentation		
	fever	☐(yy) ☐(nn) ☐(uk)
	sweats	☐(yy) ☐(nn) ☐(uk)
	weight loss	☐(yy) ☐(nn) ☐(uk)
	general malaise	☐(yy) ☐(nn) ☐(uk)
	cough	☐(yy) ☐(nn) ☐(uk)
	sputum production	☐(yy) ☐(nn) ☐(uk)
	hemoptysis	☐(yy) ☐(nn) ☐(uk)
	chest pain	☐(yy) ☐(nn) ☐(uk)
	asymptomatic	☐(yy) ☐(nn) ☐(uk)

Comment_____

_____

PMH and risk factors for TB

Alcoholism	☐(yy) ☐(nn) ☐(uk)
Diabetes	☐(yy) ☐(nn) ☐(uk)
Silicosis	☐(yy) ☐(nn) ☐(uk)
Gastrectomy	☐(yy) ☐(nn) ☐(uk)
Malnutrition	☐(yy) ☐(nn) ☐(uk)
Chronic renal failure	☐(yy) ☐(nn) ☐(uk)
Drug addict	☐(yy) ☐(nn) ☐(uk)
Homeless	☐(yy) ☐(nn) ☐(uk)
Prisoner	☐(yy) ☐(nn) ☐(uk)
Sex trade worker	☐(yy) ☐(nn) ☐(uk)
Stay in endemic area (>3 mos)	☐(yy) ☐(nn) ☐(uk)
Immunosuppression	☐(yy) ☐(nn) ☐(uk)
Specify _____	
Occupational exposure	☐(yy) ☐(nn) ☐(uk)
Specify _____	
Other debilitating disease	☐(yy) ☐(nn) ☐(uk)
Specify _____	
Known TB contact	☐(yy) ☐(nn) ☐(uk)
Specify _____	
Body weight (kgs)_____	height(cm)_____

Previous hospitalisations for any reason prior to dx of TB ☐(yy) ☐(nn) ☐(uk)

hosp 1 ___/___/___ to ___/___/___ hospital_____Dx_____
d m y d m y

hosp 2 ___/___/___ to ___/___/___ hospital_____Dx_____
d m y d m y

hosp 3 ___/___/___ to ___/___/___ hospital_____Dx_____
d m y d m y

Previous chemoprophylaxis ☐(yy) ☐(nn) ☐(uk) date ___/___/___ to ___/___/___
d m y d m y

If yes, drugs used INH ☐$_1$ RIF ☐$_2$ Other ☐$_3$ Specify_____

Previous BCG ☐(yy) ☐(nn) ☐(uk) date ___/___/___
d m y

Ever placed on medical surveillance for inactive TB ☐(yy) ☐(nn) ☐(uk)

Previous TB ☐(yy) ☐(nn) ☐(uk) If yes, Completed medical treatment ☐(yy) ☐(nn) ☐(uk)

Date of previous TB diagnosis ___/___/___
d m y

Site of infection pulmonary ☐$_1$ extra-pulmonary ☐$_2$ unknown ☐$_3$

Medical treatment (list drugs)_____

Dates of treatment ___/___/___ to ___/___/___ or duration in months_____
d m y d m y

Country where treatment given_____

Comment_____

_____

Sites of infection

Pulmonary
- Tuberculous pulmonary infiltrate ☐011.0
- Cavitary pulmonary tuberculosis ☐011.2
- Pulmonary ass. silicosis ☐502.0

Pleural (secondary) ☐012.0

Miliary ☐018.0

CNS
- Tuberculous meningitis ☐013.1
- Other (tuberculoma) ☐013.8
- Specify_____

Abdominal ☐014.0
(Small intestine, Colon, Rectum, Anus
Mesenteric lymph nodes, Retroperitoneal
lymph nodes, Peritoneal)

Bones and joints
- verterbral body ☐015.0
- thigh ☐015.1
- knee ☐015.2
- osteomyelitis ☐730.0
- arthritis ☐711.4

Genito-urinary
- kidney ☐016.0
- other urinary tract organs (bladder, ureters) ☐016.1
- epididimitis ☐016.2
- other male genital (prostate, testicle) ☐016.3
- female genital organs (ovary, salpingitis) ☐016.4

Primary ☐010.0
- pleurisy of primary infection ☐010.1

Adenitis (peripheral) ☐017.2
- Specify_____

Other non-respiratory
- Cutaneous ☐017.0
- Ocular ☐017.3
- other (heart, esophagus) ☐017.8

Other respiratory
- Intra-thoracic lymph nodes ☐012.1
- Laryngitis ☐012.3
- Bronchitis ☐012.2
- other respiratory (nose, sinus) ☐012.8

Comment (other ICD9 coding from 010-018 documented) _____

LABORATORY

Diagnostic radiology (only in relation to TB)

Normal	☐01	Abnl cavitary	☐02
Abnormal	☐03	Not done	☐04
Not stated	☐05		

Comment_____

_____

PPD_____mm date ___/___/___ (d m y) Not done ☐99 Unknown ☐98

Anergy testing ☐(yy) ☐(nn) ☐(uk) date ___/___/___ (d m y)

Result Anergic ☐1 Not anergic ☐2

Comment (Ags used)_____

Source of culture specimen (first positive by date of collection)

Sputum	☐01	BAL, B-scope	☐02
Lymph node	☐03	CSF	☐04
Urine	☐05	Gastric lavage	☐06
Peritoneal Fluid	☐07	Induced sputum	☐08
Pleural biopsy	☐09	Blood	☐10
Tissue biopsy	☐11	Specify _____	
Other	☐12	Specify _____	

			source
Smear 1	☐(ps) ☐(ng) ☐(uk) ☐(nd)	date ___/___/___ (d m y)	_____
Smear 2	☐(ps) ☐(ng) ☐(uk) ☐(nd)	date ___/___/___ (d m y)	_____
Smear 3	☐(ps) ☐(ng) ☐(uk) ☐(nd)	date ___/___/___ (d m y)	_____

			source
Culture 1	☐(ps) ☐(ng) ☐(uk) ☐(nd)	date	___/___/___ d m y _____
Culture 2	☐(ps) ☐(ng) ☐(uk) ☐(nd)	date	___/___/___ d m y _____
Culture 3	☐(ps) ☐(ng) ☐(uk) ☐(nd)	date	___/___/___ d m y _____
PCR	☐(ps) ☐(ng) ☐(uk) ☐(nd)	date	___/___/___ d m y _____

First culture resistant to:

INH	☐(yy) ☐(nn) ☐(uk)	Ciprofloxacin	☐(yy) ☐(nn) ☐(uk) ☐(nd)
Rifampin	☐(yy) ☐(nn) ☐(uk)	Ofloxacin	☐(yy) ☐(nn) ☐(uk) ☐(nd)
Ethambutol	☐(yy) ☐(nn) ☐(uk)	Kanamicin	☐(yy) ☐(nn) ☐(uk) ☐(nd)
Streptomycin	☐(yy) ☐(nn) ☐(uk)	Ethionomide	☐(yy) ☐(nn) ☐(uk) ☐(nd)
Pyrazinamide	☐(yy) ☐(nn) ☐(uk)	PAS	☐(yy) ☐(nn) ☐(uk) ☐(nd)
		Capriomycin	☐(yy) ☐(nn) ☐(uk) ☐(nd)

Development of resistance during therapy ☐(yy) ☐(nn) ☐(uk)

INH	☐(yy) ☐(nn) ☐(uk)	Ciprofloxacin	☐(yy)☐(nn)☐(uk)
Rifampin	☐(yy) ☐(nn) ☐(uk)	Ofloxacin	☐(yy) ☐(nn) ☐(uk)
Ethambutol	☐(yy) ☐(nn) ☐(uk)	Kanamicin	☐(yy) ☐(nn) ☐(uk)
Streptomycin	☐(yy) ☐(nn) ☐(uk)	Ethionomide	☐(yy) ☐(nn) ☐(uk)
Pyrazinamide	☐(yy) ☐(nn) ☐(uk)	PAS	☐(yy) ☐(nn) ☐(uk)
		Capriomycin	☐(yy) ☐(nn) ☐(uk)

Comment_____

TREATMENT

Name of treating Physician_____

Specialty Microbiology\infectious disease ☐$_1$ Pneumonologie ☐$_2$ Other ☐$_3$_____

Hospitalisations related to current TB ☐(yy) ☐ (nn) ☐(uk)

hosp 1 ___/___/___ to ___/___/___ hospital_____
d m y d m y

isolation ___/___/___ to ___/___/___ not done ☐$_1$ unknown ☐$_2$
d m y d m y

hosp 2 ___/___/___ to ___/___/___ hospital_____
d m y d m y

isolation ___/___/___ to ___/___/___ not done ☐$_1$ unknown ☐$_2$
d m y d m y

hosp 3 ___/___/___ to ___/___/___ hospital_____
d m y d m y

isolation ___/___/___ to ___/___/___ not done ☐$_1$ unknown ☐$_2$
d m y d m y

Site of follow-up therapy after initial discharge

Pulmonary clinic	☐$_1$
TB clinic	☐$_2$
ID clinic	☐$_3$
HIV clinic	☐$_4$
Primary MDs clinic	☐$_5$
Other	☐$_6$

Specify_____

Medical Treatment duration (mos)

INH ☐(yy) ☐(nn) ☐(uk) date ___/___/___ to ___/___/___ _____
d m y d m y

Rifampin ☐(yy) ☐(nn) ☐(uk) date ___/___/___ to ___/___/___ _____
d m y d m y

Pyrazinamide ☐(yy) ☐(nn) ☐(uk) date ___/___/___ to ___/___/___ _____
d m y d m y

Ethambutol ☐(yy) ☐(nn) ☐(uk) date ___/___/___ to ___/___/___ _____
d m y d m y

Streptomycin ☐(yy) ☐(nn) ☐(uk) date ___/___/___ to ___/___/___ _____
d m y d m y

PAS ☐(yy) ☐(nn) ☐(uk) date ___/___/___ to ___/___/___ _____
d m y d m y

Ethionamide ☐(yy) ☐(nn) ☐(uk) date ___/___/___ to ___/___/___ _____
d m y d m y

None ☐(yy) ☐(nn) ☐(uk)

Other ☐(yy) ☐(nn) ☐(uk) date ___/___/___ to ___/___/___ _____
d m y d m y

Specify _____

Comment _____

DOT ☐(yy) ☐(nn) ☐(uk) date ___/___/___ Total weeks _____

Daily ☐(yy) ☐(nn) ☐(uk) Intermittent ☐(yy) ☐(nn) ☐(uk)

Where Hospital ☐(yy) ☐(nn) ☐(uk) CLSC ☐(yy) ☐(nn) ☐(uk)
Private clinic ☐(yy) ☐(nn) ☐(uk) home ☐(yy) ☐(nn) ☐(uk)
Hosital clinic ☐(yy) ☐(nn) ☐(uk)
Other ☐(yy) ☐(nn) ☐(uk) Specify _____

Comment _____

_____

Side effects ☐(yy) ☐(nn) ☐(uk)

S1 generalized skin ☐$_{01}$ date__/__/__ (d m y) mild ☐$_1$ moderate ☐$_2$ severe ☐$_3$ NS ☐$_4$

S2 fever ☐$_{02}$ date__/__/__ (d m y)

S3 nausea ☐$_{03}$ date__/__/__ (d m y)

S4 vomiting ☐$_{04}$ date__/__/__ (d m y)

S5 abdominal pain ☐$_{05}$ date__/__/__ (d m y)

S6 increased LFTs ☐$_{06}$ date__/__/__ (d m y)

S7 jaundice ☐$_{07}$ date__/__/__ (d m y)

S8 hematologic ☐$_{08}$ date__/__/__ (d m y)

S9 headaches ☐$_{09}$ date__/__/__ (d m y)

S10 arthralgias ☐$_{10}$ date__/__/__ (d m y)

S11 optic neuritis ☐$_{11}$ date__/__/__ (d m y)

S12 peripheral neuropathy ☐$_{12}$ date__/__/__ (d m y)

S13 flushing ☐$_{13}$ date__/__/__ (d m y)

S14 other ☐$_{14}$ date__/__/__ (d m y)

specify _____

Medication stopped or dose lowered due to side effects ☐(yy) ☐(nn) ☐(uk)

Drug Dced or changed	date stopped or changed	reason (side effect)	date full tx restarted	drugs resumed	drugs stopped
_____	__/__/__ d m y	_____	__/__/__ d m y	_____	_____
_____	__/__/__ d m y	_____	__/__/__ d m y	_____	_____
_____	__/__/__ d m y	_____	__/__/__ d m y	_____	_____

COMPLIANCE

Appointment attendance

Attended greater than 80% of appointments ☐1
Attended 50-80% of appointments ☐2
Attended less than 50% of appointments ☐3
Unknown ☐4

Overall compliance

Compliant, 80% or more of therapy taken ☐1
partially compliant ☐2
not compliant ☐3
unknown ☐4

Compliance assessed by

pill count ☐1
verification with pharmacy ☐2
urine drug levels ☐3
patient's word of mouth ☐4
family or friend observer ☐5
attendance at appointments ☐6
other ☐7
specify_____
unknown ☐8

Treatment outcome

cure	treatment completed	☐1
default	treatment interrupted > 2 mos	☐2
died	died on treatment from TB	☐3
	died on treatment from other cause	☐4 Specify_____
transfer	pt transferred out of MTL on therapy	☐5
lost	pt lost without treatment plan	☐6
not stated	not stated in the charts	☐7

Did the patient ultimately achieve a curative completion of treatment ☐(yy) ☐(nn) ☐(uk)

If no, specify	side effects	☐(yy) ☐(nn) ☐(uk)
	lost to follow-up	☐(yy) ☐(nn) ☐(uk)
	non-compliance	☐(yy) ☐(nn) ☐(uk)
	Other	☐(yy) ☐(nn) ☐(uk)
	Specify _____	

Results of smear > 3 mos after tx culture > 3 mos after tx date___/___/___
d m y

positive	☐1	positive	☐1
negative	☐2	negative	☐2
not done	☐3	not done	☐3
unknown	☐4	unknown	☐4

Results of chest x-ray at treatment completion

improvement	☐1	date___/___/___
deterioration	☐2	d m y
stable	☐3	
not done	☐4	
unknown	☐5	

HIV status

positive	☐1	Date of testing ___/___/___
negative	☐2	d m y
tested, result unknown	☐3	
not stated	☐4	
stated, not tested	☐5	

Testing done in relation to TB diagnosis

before	☐(y) ☐(n)
after (>1mo)	☐(y) ☐(n)
same time (<1 mo)	☐(y) ☐(n)

HIV risk factors

-Sexual relations with men	☐(yy) ☐(nn) ☐(uk)
-Sexual relations with women	☐(yy) ☐(nn) ☐(uk)
-Use needles for self-injection of drugs not prescribed by MD	☐(yy) ☐(nn) ☐(uk)
-Receive any blood products (factor VIII, IX, cryoprecipitate or fibrinogen) for treatment of coag disorder	☐(yy) ☐(nn) ☐(uk)
before Nov. 1985	☐(yy) ☐(nn) ☐(uk)
after Nov. 1985	☐(yy) ☐(nn) ☐(uk)
-Receive a transfusion of blood or blood components	☐(yy) ☐(nn) ☐(uk)
before Nov. 1985	☐(yy) ☐(nn) ☐(uk)
after Nov. 1985	☐(yy) ☐(nn) ☐(uk)
-Sex trade worker	
_Person born or resident of a country where heterosexual transmission predominates	☐(yy) ☐(nn) ☐(uk)
-Work in a health care or clinical laboratory	☐(yy) ☐(nn) ☐(uk)
-Have any other exposure which could have been the source of contact (organ transplant, tissue transplant, artificial insemination, breast milk)	☐(yy) ☐(nn) ☐(uk)

Specify _____

For cases attributed to sexual contact, did the case have sex with:

-Injection drug user	☐(yy) ☐(nn) ☐(uk)
-Homosexual man	☐(yy) ☐(nn) ☐(uk)
-Bisexual man	☐(yy) ☐(nn) ☐(uk)
-Person with coagulation disorder requiring transfusion of blood products	☐(yy) ☐(nn) ☐(uk)
-Blood or blood component transfusion recipient	☐(yy) ☐(nn) ☐(uk)
-Person born or resident of a country where heterosexual transmission predominates	☐(yy) ☐(nn) ☐(uk)
Specify country _____	
-Sex trade worker	☐(yy) ☐(nn) ☐(uk)
-Is the sex partner also a person with confirmed HIV infection or AIDS	☐(yy) ☐(nn) ☐(uk)

Diseases indicative of AIDS (at time of TB diagnosis)

		date (d/m/y)
Candidiasis-bronchi trachea or lungs	☐(y) ☐(n)	---/---/---
Candidiasis, esophageal	☐(y) ☐(n)	---/---/---
Coccidiodomycosis, disseminated or extra-pulmonary	☐(y) ☐(n)	---/---/---
Cryptococcosis, extrapulmonary	☐(y) ☐(n)	---/---/---
Cryptosporidiosis, chronic intestinal	☐(y) ☐(n)	---/---/---
CMV disease, other than liver, spleen, or nodes	☐(y) ☐(n)	---/---/---
M. tuberculosis, disseminated or extra-pulmonary	☐(y) ☐(n)	---/---/---
Mycobacterium of other species or unidentified species, disseminated or extra-pulmonary	☐(y) ☐(n)	---/---/---
Pneumocystis carinii pneumonia, PCP	☐(y) ☐(n)	---/---/---
Progressive multifocal leukoencephalopathy	☐(y) ☐(n)	---/---/---
Salmonella septicemia, recurrent	☐(y) ☐(n)	---/---/---
Toxoplasmosis of brain	☐(y) ☐(n)	---/---/---
Wasting syndrome due to HIV	☐(y) ☐(n)	---/---/---
Pulmonary TB	☐(y) ☐(n)	---/---/---
Cervical cancer	☐(y) ☐(n)	---/---/---
Recurrent pneumonia	☐(y) ☐(n)	---/---/---

CD4 count at time of TB diagnosis (or most recent prior to TB diagnosis)

_____ Not done ☐$_{9999}$ Unknown ☐$_{8888}$ date ___/___/___
d m y

CD4\CD8 ratio _____ Not done ☐$_{9.9}$ Unknown ☐$_{8.8}$

CD4 counts during treatment

_____ date ___/___/___ _____ date ___/___/___
d m y d m y

_____ date ___/___/___ _____ date ___/___/___
d m y d m y

CD4 count at end of treatment

_____ Not done ☐$_{9999}$ Unknown ☐$_{8888}$ date ___/___/___
d m y

Long term outcome if known

date of last follow-up note ___/___/___
d m y

Death	☐1
Alive, no other diseases indicative of AIDS	☐2
Alive, new diseases indicativie of AIDS	☐3
Unknown	☐4

Appendix B

QUESTIONNAIRE ÉPIDÉMIOLOGIQUE - TUBERCULOSE

Nom de l'enquêteur : _____#_____ Date début de l'enquête : _____
(1er contact)

Nom : _____ Prénom : _____

No. dossier MADO :_____ Date d'épisode : ____/____/____

No. dossier Hosp. : _____ No. ass.-mal. : _____

Déclaration initiale : ☐[1] Médecin ☐[2] Lab. local ☐[2] LSPQ ☐[1] Autre _____

DÉMOGRAPHIE

Date de naissance : ____/____/____ ☐ Inconnue Âge : _____ Sexe : ☐[1] masc. ☐[2] fém.

Occupation :
☐[1] Manip. aliments ☐[2] Trav. de la santé ☐[3] Trav. en garderie ☐[4] Étudiant niv. ind.
☐[5] Enfant en garderie ☐[6] Sans emploi ☐[7] Étudiant prim. ☐[8] Étudiant sec.
☐[9] Étudiant collégial ☐[10] Étudiant univ. ☐[11] Étudiant maternelle ☐[99] Inconnu
☐[98] Autre spécifiez : _____

Adresse : _____
No. Rue Municipalité Code postal

Tél. domicile : _____ Tél. travail _____ Autre tél. : _____

CLSC : _____

Lettre envoyée au médecin **Oui** ☐ **Date** _____
Non ☐

MILIEUX DE VIE : Garderie, école, travail, refuge pour itinérants, C.A., C.H.S.L.D., sans domicile fixe (SDF)

Nom de l'établissement : _____ Personne-ressource : _____

Adresse : _____ Tél. : _____

Niveau scolaire (si indiqué) : _____ Classe (si indiqué) : _____

Occupation : _____ Dernière présence : ____/____/____

HOSPITALISATION : Oui ☐ Non ☐ Du : ____/____/____ Au : ____/____/____

Hôpital : _____ No. chambre : _____ Tél. : _____

Md traitant : _____ Tél. : _____

Adresse : _____
No. Rue Municipalité Code postal

Md traitant : _____ Tél. : _____
(suivi TB)

Adresse : _____
No. Rue Municipalité Code postal

RAPPORT DE LA MALADIE

Début de la maladie : ____/____/____ Maladie : 77-Tuberculose Micro-org./Agent : 54-Mycob. tub.

Évolution pour cette maladie : ☐[1] Récupération ☐[2] Décès

Commentaires : _____

_____

DÉMOGRAPHIE

CA ou CHSLD de résidence : _____

Province de déclaration : _____ Pays de naissance : _____ ☐ Inconnu

Année d'arrivée : _____ ☐ Inconnue Pays précédant l'arrivée : _____ ☐ Inconnu

Origine ethnique :
☐[1] Inuit
☐[2] Indien
☐[3] Immigrant
☐[4] Autres
☐ Inconnu

État civil :
☐[1] Célibataire
☐[2] Marié
☐[3] Séparé
☐[4] Divorcé
☐[5] Veuf
☐[6] Droit commun
☐[7] Inconnu
☐[98] Non précisé

Pays de naissance des parents si enfant < 20 ans : Canada ☐ Autres ☐ Inconnu ☐

Spécifiez _____

RENSEIGNEMENTS CLINIQUES

Diagnostic clinique :
☐[1] Pulmonaire
☐[2] Pulmonaire ass. silicose
☐[3] Miliaire
☐[4] Pleurésie
☐[5] Syst. nerv. central
☐[6] Abdominal : _____
☐[7] Os et articulation : _____
☐[8] Génito-urinaire : _____
☐[9] Primaire
☐[10] Ganglions : _____
☐[98] Autre non-resp. : _____
☐[99] Autre resp. : _____

Date du diagnostic : ____/____/____ Inconnue ☐

Mode de traitement

Médication	Posologie DIE	Posologie TOD	Début du traitement	Fin du traitement	☐ non ☐ inc. Résistance
☐[1] Isoniazide	____	____	____/____/____	____/____/____	☐ oui
☐[2] Rifampine	____	____	____/____/____	____/____/____	☐ oui
☐[3] Streptomycine	____	____	____/____/____	____/____/____	☐ oui
☐[4] Ethambutol	____	____	____/____/____	____/____/____	☐ oui
☐[5] Ac. p-amino-sal.	____	____	____/____/____	____/____/____	☐ oui
☐[6] Pyrazinamide	____	____	____/____/____	____/____/____	☐ oui
☐[7] Ethionamide	____	____	____/____/____	____/____/____	☐ oui
☐[99] Aucune	____	____	____/____/____	____/____/____	☐ oui
☐[100] Autre	____	____	____/____/____	____/____/____	☐ oui

RADIOGRAPHIE DU DIAGNOSTIC

☐[1] Normal ☐[2] Anorm. cav. ☐[3] Anorm. ☐[4] Non fait ☐ Résultat inconnu ☐ Information non disponible

Rapport de radiologie (date : _____) _____

_____

_____

Rx pulmonaire de fin de traitement Date : _____ Résultat _____

☐ Non faite : Précisez _____

ÉTAT BACILLAIRE

	Frottis			Culture		
	Pos.	**Nég.**	**Date du prélèvement**	**Pos.**	**Nég.**	**Date du rapport**
☐[1] Expectorations	☐	☐	_____	☐	☐	_____
☐[2] Lav. des bronches ☐	☐	☐	_____	☐	☐	_____
☐[3] Lav. gastrique	☐	☐	_____	☐	☐	_____
☐[4] Urine	☐	☐	_____	☐	☐	_____
☐[5] Biopsie _____	☐	☐	_____	☐	☐	_____
☐[99] Autre _____	☐	☐	_____	☐	☐	_____

PCR : Positif ☐ Négatif ☐ Date : _____ Non fait ☐
Spécimen : _____

DÉTECTION

☐[1] Sympt. ☐[2] Examen de contact ☐[3] Dépistage ☐[4] Enquête spéciale ☐[5] Post mortem ☐[6] Autre

Commentaires : _____

_____

SITUATION DU CAS

Résistance : _____ (cf liste des médicaments page 2)
Statut ☐[1] Nouveau cas ☐[2] Récidive ☐ Inconnu
Année de l'épisode antérieur : _____ ☐ Inconnue
Médication antérieure : _____ ☐ Inconnue ☐ Aucune
Vaccination (BCG) : ☐[1] Oui ☐[2] Non ☐[3] Inconnue
Si Oui, année : _____ ☐ Inconnue
Chimioprophylaxie (date du début) Durée en mois : _____
Date du décès : ____/____/____ Cause du décès : ☐[1] TB est la cause initiale du décès
☐[2] TB a contribué au décès sans le causer
☐[3] TB n'a pas contribué au décès

HISTOIRE DE LA MALADIE ACTUELLE PLUS ANTÉCÉDENTS

	OUI	NON	INC.	si OUI, date du début
Fièvre :	☐	☐	☐	___/___/___
Perte de poids :	☐	☐	☐	___/___/___
Atteinte de l'état général :	☐	☐	☐	___/___/___
Toux :	☐	☐	☐	___/___/___
Expectorations :	☐	☐	☐	___/___/___
Hémoptysie :	☐	☐	☐	___/___/___
Autres :	☐	☐	☐	___/___/___

(Précisez) _____

_____

_____

Épreuve tuberculinique : ☐ Faite (Date) ___/___/___ Résultat _____ mm ☐ Inconnu
☐ Non faite

Contagiosité : ☐ Oui ☐ Non Du ___/___/___ au ___/___/___

ANTÉCÉDENTS MÉDICAUX ET FACTEURS DE RISQUE

	OUI	NON	INC.	Précisez PRN :
Alcoolisme	☐	☐	☐	_____
Toxicomanies	☐	☐	☐	_____
Conditions médicales prédisposantes : diabète, cancer, silicose, gastrectomie, insuffisance rénale chronique, dérive jéjunoiléale	☐	☐	☐	_____
Immunosuppression (autre que VIH)	☐	☐	☐	_____
Itinérance	☐	☐	☐	_____
Malnutrition	☐	☐	☐	_____
Travailleur de la santé	☐	☐	☐	_____
Travailleur du sexe	☐	☐	☐	_____
Histoire d'incarcération	☐	☐	☐	_____
Contact connu avec cas de tuberculose	☐	☐	☐	_____
Si oui : Nom _____ # MADO _____				
Séjour en zone endémique	☐	☐	☐	Pays : _____ Année : _____ Durée séjour : _____

Dépistage VIH

fait date : _____ ☐ résultats pos. ☐ Déclaration faite au programme
nég. ☐ de surveillance du sida
inc. ☐ ☐ Oui ☐ Non

non fait ☐ déjà connu positif ☐
non demandé par médecin ☐
refusé par patient ☐

inconnu ☐

SOURCES ET DATES

Médecin déclarant : _____

Date du rapport : ____/____/____ Mode : ☐[1] Formulaire Date reçu par la DSP : ____/____/____
☐[2] Téléphone
☐[3] Lettre
☐[4] Rapport laboratoire
☐[5] Autre

Spéc. envoyé au labo ? ☐[1] Oui Date du 1er prélèvement : _____
☐[2] Non
☐[3] Non-spécifié

LABORATOIRE

Laboratoire déclarant : _____

Date du rapport : ____/____/____ Mode : ☐[1] Formulaire Date reçu par la DSP : ____/____/____
☐[2] Téléphone
☐[3] Lettre
☐[4] Rapport laboratoire
☐[5] Autre

Laboratoire de référence : ☐ LSPQ ☐ Autre Date du rapport : ____/____/____

No. de référence : _____

STATUT DU CAS

Cas validé ☐[1] Oui Nature de la validation ☐[1] Confirmée Date : ____/____/____
☐[2] Non ☐[2] Clinique

Date de relance : ____/____/____

Données complémentaires : _____

_____

_____

_____ Date de fermeture du dossier : ____/____/____
Signature de l'enquêteur

Information pour saisie (1er commentaire)
☐ SurCL ☐ TODCL Autre ☐ Précisez : _____
☐ SurIT ☐ TODIT
☐ SurTC ☐ TODTC