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AN EVALUATION OF RADIOGRAPHIC SCREENING FOR TUBERCULOSIS IN IMMIGRANTS TO CANADA

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ABSTRACT

INTRODUCTION: Foreign-born persons applying for permanent residence in Canada must undergo radiographic screening for tuberculosis (TB). As a screening tool for TB, however, the chest x-ray has a number of limitations.

OBJECTIVES: To evaluate the reliability of chest radiographic screening as well as its ability to detect prevalent active TB and predict future incident disease in immigrants to Canada.

METHODS: Immigration screening x-rays were categorized by 12 physicians experienced in TB; observer agreement was calculated using the kappa coefficient. The prevalence and incidence of active TB diagnosed among applications screened at the Montreal Chest Institute between 1995 and 1998 was measured.

RESULTS: Intra- and inter-observer agreement was fair to moderate. Among 36,433 applicants screened, 53 prevalent cases were detected (0.145%) and 19 incident cases were reported post-screening (25.7 per 100,000 person-years).

CONCLUSION: Radiographic screening successfully detects immigrants with active TB but is limited in preventing future incident cases. Observer agreement needs to be improved.

RÉSUMÉ

INTRODUCTION : Les personnes nées à l'étranger demandant la résidence permanente au Canada doivent subir un dépistage radiographique pour permettre de déceler la tuberculose. Toutefois, en tant que moyen de dépistage de la tuberculose, la radiographie de la cage thoracique présente un certain nombre de limitations.

OBJECTIFS : Évaluer la fiabilité du dépistage par radiographie de la cage thoracique ainsi que sa capacité à déceler la tuberculose prévalente active et à prédire la future maladie incidente chez les immigrants à destination du Canada.

MÉTHODES : Douze médecins expérimentés en tuberculose ont classé les radiographies de dépistage des immigrants. La concordance entre observateurs a été calculée à l'aide du coefficient Kappa. La prévalence ainsi que l'incidence de tuberculose active diagnostiquée parmi les postulants dépistés à l'Institut thoracique de Montréal entre 1995 et 1998 ont été mesurées.

RÉSULTATS : La concordance interne et réciproque des observateurs s'est révélée suffisante à moyenne. Parmi les 36 433 postulants examinés, 53 cas prévalents ont été dépistés (0,145 %) et 19 cas incidents ont été rapportés après le dépistage (25,7 pour 100 000 années-personnes).

CONCLUSION : Le dépistage radiographique réussit à détecter les immigrants atteints de tuberculose active, mais ne prévient les futurs cas incidents que de manière limitée. Il faut améliorer la concordance entre observateurs.

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ABBREVIATIONS

AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
CIC	Citizenship and Immigration Canada
CMI	Cell-mediated immunity
CXR	Chest x-ray
EMB	Ethambutol
HIV	Human immunodeficiency virus
INH	Isoniazid
IUATLD	International Union Against Tuberculosis and Lung Disease
LTBI	Latent tuberculosis infection
MADO	Maladies à déclaration obligatoires
MCI	Montreal Chest Institute
MDR	Multi-drug resistance
PZA	Pyrazinamide
RFLP	Restriction fragment length polymorphism
RMP	Rifampin
SM	Streptomycin
TB	Tuberculosis
TST	Tuberculin skin test
WHO	World Health Organization

1. INTRODUCTION

The epidemiology of tuberculosis (TB) in Canada has changed considerably in the past 25 years, particularly with respect to the origin of reported cases. Although the overall incidence of the disease has remained stable (6-7 cases per 100,000 persons), the proportion of TB cases accounted for by persons born outside of Canada has nearly doubled – in 2001, 65% of all cases were in foreign-born individuals, compared to only 35% in 1980. [1,2] This trend coincides with an observable increase in the arrival of immigrants and refugees from countries in Asia, Africa, and Latin America – regions where both the incidence and prevalence of *Mycobacterium tuberculosis* is very high. In fact, of the more than 200,000 immigrants and refugees received by Canada each year, an estimated 85% arrive from countries where TB is endemic (i.e., annual TB incidence of >100 cases per 100,000 population). [3] Consequently, the annual risk of infection for persons arriving from such countries is very high, and as a result many new arrivals have likely already been exposed to and infected with the TB bacilli prior to arrival and may be carrying latent TB infection (LTBI) with them at time of immigration. [4]

Foreign-born individuals with LTBI are at increased risk of developing active disease compared to the Canadian-born population - several studies estimate the risk to be 5 to 20 times higher. [1,5-8] Although this increased risk appears to be highest in the first five years after immigration, it may persist for several years; in some countries, TB rates in the foreign-born may exceed that of the native population even 20 years after arrival. [1,5-11] Because of the potential risk for transmission of the disease to the Canadian-born

population, all prospective immigrants aged 11 years and older are required to undergo radiographic screening for TB prior to being granted permanent residence. [12]

The goal of radiographic screening is two-fold: 1) detect cases of active (i.e., contagious) disease and provide curative treatment prior to immigration, and 2) identify individuals with LTBI so that they may be referred for medical surveillance upon arrival to Canada. [12] The effectiveness of radiographic screening may be limited, however, by the following factors: the yield of active TB cases detected through chest x-ray screening is quite low (0.05%-0.15% in overall immigrant population, 0.45%-0.8% in refugees and those from high incidence countries) [13-19]; high cost – estimates range from $4,000 to $10,000 (Cdn) per person screened [20]; and, as a diagnostic tool for TB, the chest x-ray (CXR) has both low sensitivity (60%-80%) and low specificity (60%-70%) and very poor reproducibility. [21,22] Despite these limitations, the chest x-ray continues to be used as a screening tool for TB in immigrants to Canada making the need for further evaluation more pressing.

2. STUDY OBJECTIVES

The objective of this study was to evaluate the ability of chest radiographic screening to detect prevalent active TB and predict future incident disease in immigrants to Canada. More specifically, the study objectives were:

1. To measure the extent of agreement between physicians when interpreting screening chest x-rays, with respect to TB, using a standardized x-ray categorization scheme developed by Citizenship and Immigration Canada (CIC). (see Observer Agreement Study)

2. To determine the incidence of active disease in a cohort of immigrants previously screened for TB at the Montreal Chest Institute (MCI) between May 1995 and December 1998 and identify potential "failures" of the screening process. (see Prospective Cohort Study)

3. To estimate the prevalence and subsequent incidence of active TB by specific radiographic finding among immigrants undergoing radiographic screening for the disease. (see Prospective Cohort Study)

3. REVIEW OF THE LITERATURE

3.1 Natural History of Tuberculosis (TB)

3.1.1 Infectious Agent

TB is caused by three closely related species of tuberculous mycobacteria commonly referred to as the *Mycobacterium tuberculosis* complex. In humans, the disease results primarily from infection with *M. tuberculosis* or *M. africanum,* however, in regions where the disease remains uncontrolled in cattle, infection with *M. bovis* may occur following ingestion of raw milk and milk products. [23] Occasionally, atypical mycobacteria such as *M. avium* complex produce disease that is clinically indistinguishable from TB and identifiable only by culture. TB bacilli are slender, non-motile, aerobic rods with a high lipid-containing cell wall making staining difficult; acid and alcohol solutions are unable to remove the stain, hence mycobacteria are often called acid-fast bacilli (AFB). [24]

3.1.2 Transmission

TB bacilli are spread by airborne droplet nuclei that are generated when a person with TB of the respiratory tract (i.e., pulmonary or laryngeal TB) expels the bacteria during expiratory efforts such as coughing, sneezing, speaking, or singing. Larger particles generally settle on external surfaces, however, smaller droplets (1-5 microns in diameter) can remain suspended in the air for several hours and enter the lungs upon inhalation, eventually reaching the alveoli. [25,26] Close contacts of the infected individual have the highest risk of becoming infected, but the likelihood of transmission depends on several factors: the infectiousness of the person with TB (i.e., the number of organisms expelled

into the air – depends on the bacterial load and symptoms of the case); the virulence of the organism; the ventilation, including humidity in the air and exposure to sunlight; the environment in which the exposure took place; and, the duration of the exposure. In general, given the low concentration of airborne bacteria, the length of the exposure needs to be prolonged for transmission to occur. [24]

3.1.3 Pathogenesis

Upon inhalation, the *M. tuberculosis* bacilli are engulfed by alveolar macrophages and transported to the hilar lymph nodes. During the first few weeks of infection, at which time the body's cell-mediated immunity (CMI) is primed, the bacteria disseminate uniformly in the bloodstream and thus have the potential to cause disease anywhere in the body. In approximately 5% of infected individuals, however, the TB bacilli may at this time cause a brief, often sub-clinical disease in the middle and lower lobes of the lung known as primary pulmonary TB. [25,26]

3.1.4 Latent TB Infection

For the remaining 95% of infected persons, the bacilli eventually lodge in areas of high oxygen tension, such as the lung apices. At this time, a component of CMI known as delayed-type hypersensitivity allows host tissue to form tubercles that imprison the TB bacilli, rendering them dormant but viable indefinitely. [25] Because the mycobacteria are now considered inactive, this state is referred to as latent TB infection (LTBI). Individuals with LTBI are completely asymptomatic and are unable to spread the bacteria to others (i.e., non-contagious), however, they have a 10% lifetime cumulative risk of

developing active disease, half within the first 2-3 years of becoming infected. [24] Certain factors, such as immunosuppression (i.e., HIV/AIDS, transplantation, cancer), alcoholism/IV drug use, and malnutrition may increase the likelihood of progression from LTBI to active disease. [7,24]

LTBI may be diagnosed by means of the tuberculin skin test (TST); this involves injecting a small amount of purified protein derived from the *M. tuberculosis* bacilli intradermally. Within 48-72 hours, individuals who have been infected with the TB bacilli will display localized swelling and induration at the injection site. Depending on several factors – including the population being tested and the experience and technique of the person administering the test – the validity of the TST may be questionable with high proportions of both false positive and false negative reactions; as such, the TST can neither confirm nor rule out the presence of LTBI. [24]

3.1.5 Active TB Disease

Active disease occurs when the balance between the encased TB bacilli and the host's immunity is broken and the previously dormant bacteria begin to escape and multiply. [25,26] Although TB disease may occur in virtually any organ, approximately 60%-80% of active cases occur in the lungs (i.e., pulmonary TB). [24,27] As the TB bacilli are spread by means of airborne droplet nuclei, only individuals with active respiratory disease (i.e., pulmonary or laryngeal TB) are considered to be contagious. Individuals with respiratory disease may experience symptoms such as fever, night sweats, cough lasting > 3 weeks, anorexia, weight loss, and general malaise. [27] Extrapulmonary TB

occurs with greater frequency in the foreign-born population, and in those infected with HIV/AIDS. The most common sites of extrapulmonary TB are peripheral lymph nodes, pleura, bones and joints, genitourinary system, abdomen, and central nervous system. [24, 27]

3.1.6 Diagnosis of TB

A diagnosis of active TB may be made following physical examination and history, chest x-ray, as well as smear microscopy and mycobacterial cultures of sputum and/or other bacteriological specimens.

3.1.6.1 Chest X-ray (CXR)

In non-immunocompromised individuals with active pulmonary TB, the CXR is almost always abnormal. [27] Radiographic findings associated with active disease vary, but may range from small fibronodular shadows to extensive infiltrates and large cavities (some form of cavitation is visible in approximately 40% of patients). [24] As a diagnostic tool for active TB, however, the CXR has several limitations including poor reproducibility, low sensitivity and specificity; when used as a screening tool for TB, the CXR also has relatively low yield in detecting prevalent disease (these limitations will be described in greater detail in section 3.10.3). Therefore, in order to confirm the presence of active disease, bacteriological testing of sputum and/or other specimens (e.g., bronchial washings obtained through bronchoscopy or tissue biopsy samples) is required; the 2 most commonly performed tests are smear microscopy and mycobacterial culture.

3.1.6.2 Smear Microscopy

Direct smear of concentrated sputum for AFB is a rapid, inexpensive test that has high (89%-100%) specificity for mycobacteria, however, it is important to remember that because all mycobacteria are AFB positive, the direct smear does not distinguish between tuberculous and non-tuberculous bacilli. [24,28] The overall sensitivity of the direct AFB smear varies from 22% to 80%; the sensitivity may be improved, however, if multiple sputum specimens are examined. [24,26-28]

3.1.6.3 Mycobacterial Culture

Culture for *M. tuberculosis* is considered the gold standard in the diagnosis of TB. [24-28] The sensitivity of culture is much higher than smear microscopy – a single positive culture, in general, is considered to define active disease – and exceeds 90% when 3 or more sputums are collected. [22,24] Culture is also necessary to isolate specific species of *M. tuberculosis* and for performing drug susceptibility testing. The major drawback of mycobacterial culture, however, is the length of time required to obtain results. In most instances, it takes up to 3-8 weeks to obtain culture and drug susceptibility results. [27]

3.1.7 Treatment of TB

There are 4 1st-line drugs – referred to as "quadruple therapy" – that are routinely used in the treatment of individuals with active TB disease: isoniazid (INH), rifampin (RMP), pyrazinamide (PZA), and ethambutol (EMB). [24] Although streptomycin (SM) was once commonly used, its route of administration (intramuscular injection) raised concerns amidst the ongoing HIV epidemic and is no longer routinely prescribed. Treatment

usually begins with both INH and RIF, taken in combination with either PZA, EMB, or both, for 2 months (intensive phase). In the continuation phase, depending on the initial regimen used in the intensive phase, INH and RMP are typically taken for an additional 4-7 months for a total of 6-9 months of chemotherapy. Each of the antituberculous drugs has several adverse effects, including hepatitis, paresthesia, arthralgia, flu-like illness, neuritis, and elevated uric acid levels; considering the length of time required for curative treatment, patient compliance may not be optimal. [24]

3.2 Global Burden of TB

The global prevalence of *M. tuberculosis* infection is estimated by the World Health Organization (WHO) to be 1.86 billion or 32% of the world's population – in other words, 1 in 3 people worldwide are believed to be infected with the TB bacillus. [28] Each year, approximately 8.7 million new cases of TB are diagnosed and 2 million deaths occur as a result of the disease, making TB the leading cause of death due to an infectious disease worldwide. A 3% global increase in TB cases has been reported annually, although in regions of the world already burdened by the HIV epidemic, this percentage is much higher. For example, in some African countries, TB rates have increased by as much as 10% each year. With the number of new cases of TB expected to reach over 12 million by the year 2020, it is increasingly evident that TB remains a "global emergency" as previously declared by the WHO in 1993. [28]

In 2000, more than 3.6 million incident cases of TB were reported to the WHO, however, this represents only 42% of the estimated 8.7 million cases believed to have developed

worldwide. Table 3.1 illustrates the number of cases and incidence rates by WHO world region (see Appendix 1: Member States of the World Health Organization for a list of countries in each WHO region). South-East Asia reported the largest number of cases (n=1,397,389 or 38.1% of total), followed by Western Pacific (21.9%), and Africa (19.8%); together, these 3 regions accounted for close to 80% of the world's TB cases. The African region, however, had the highest incidence rate (118 per 100,000) of all 6 world regions. [29]

Table 3.1: Number of reported cases and incidence rates by World Health Organization (WHO) region, 2000

WHO Region	Population	Number (%) of Cases	Incidence Rate (per 100,000)
Africa	616,441,115	728,565 (19.8)	118
Americas	831,779,757	233,556 (6.4)	28
Eastern Mediterranean	484,845,673	137,996 (3.8)	28
Europe	873,574,716	369,935 (10.1)	42
South-East Asia	1,535,634,061	1,397,389 (38.1)	91
Western Pacific	1,688,064,926	804,532 (21.9)	48
Total	**6,030,340,248**	**3,671,973 (100.0)**	**61**

Source: Reference 29

3.2.1 High-Burden Countries

According to the WHO, there are 22 "high-burden" countries that contribute close to 80% of the world's estimated 8.7 million TB cases – even though together they account for only 62.5% of the global population. In 2000, these 22 countries (in descending order of number of cases) included: India, China, Indonesia, Nigeria, Bangladesh, Ethiopia, Philippines, Pakistan, South Africa, Russian Federation, Democratic Republic of Congo, Kenya, Tanzania, Brazil, Thailand, Uganda, Myanmar, Mozambique, Cambodia, Zimbabwe, and Afghanistan. [29]

South-East Asia contained 3 of the 5 highest-burden countries - India, Indonesia, and Bangladesh; together, these countries accounted for 31.9% of the world's TB cases. China alone attributed to 15.6% of the global TB burden. Although these "high burden" countries represented all 6 WHO world regions, 7 of the 10 countries with the highest TB incidence rates were found in Africa (Table 3.2). Ethiopia had the world's highest incidence rate (584 cases per 100,000 population), followed closely by Cambodia (572 per 100,000) and South Africa (526 per 100,000). [29]

Table 3.2: 10 countries with highest TB incidence rates, 2000

Country (WHO Region)	Population	Number of Cases	Incidence Rate (per 100,000)
Zimbabwe (Africa)	12,627,000	74,000	584
Cambodia (Western Pacific)	13,104,000	75,000	572
South Africa (Africa)	43,309,000	228,000	526
Kenya (Africa)	30,669,000	149,000	484
Mozambique (Africa)	18,292,000	79,000	433
Ethiopia (Africa)	62,908,000	249,000	397
Tanzania (Africa)	35,119,000	126,000	359
Uganda (Africa)	23,300,000	82,000	351
Philippines (Western Pacific)	75,653,000	249,000	330
Afghanistan (Eastern Mediterranean)	21,765,000	70,000	321

Source: Reference 30

3.3 TB in Developing Countries

It is estimated that close to 95% of the 8.7 million new cases developing each year and approximately 98% of all deaths due to TB occur in developing nations; despite these staggering statistics, TB control receives only 2 cents of every $10 spent on health. [30-32] The spread of TB in the developing world has been hastened by several factors including the ongoing HIV epidemic, and the spread of drug resistant strains.

3.3.1 HIV and TB

In 1997, the worldwide prevalence of co-infection with HIV and TB was reported as 0.18% and approximately 640,000 incident cases (8% of total) had HIV infection. [33] Infection with HIV weakens the immune system and for those with LTBI, increases the risk of progression to active disease by an estimated 113 times (compared to individuals with no known risk factors); for persons with AIDS, the risk of progression to active disease is estimated to be 170 times higher. [24] As the result of the spread of HIV, an estimated 1.4 million cases of active TB are expected to occur annually in people co-infected with HIV worldwide. [33]

3.3.2 Drug Resistance

In most developing countries, the high cost and limited availability of anti-tuberculous medications makes completion of adequate treatment regimens difficult. The irregular, inadequate, and often inappropriate treatment that results, in addition to patient non-compliance, makes acquired drug resistance (i.e., initially drug susceptible but because of aforementioned factors later develops resistance) an important issue in the developing world. A study conducted by the WHO and the IUATLD between 1994 and 1997, determined that of the participating countries, acquired resistance to any of the four 1st-line drugs used to treat TB was present in 12.6% of all TB cases. This ranged from 2.3% in the Czech Republic to 42.4% in the Dominican Republic. Acquired multi-drug resistance (MDR), i.e., resistance to at least both INH and RIF, occurred in approximately 2.2% of all TB cases, ranging from 0% in Kenya to 22.1% in Latvia. [34]

3.3.3 Impact on the Developed World

Although the greatest burden of the TB epidemic continues to be experienced by the world's developing nations, many industrialized countries are currently experiencing a resurgence of the disease. After declining steadily for several decades, TB incidence rates in many low-incidence countries have leveled off or slowly increased. As with the developing world, the HIV epidemic and the spread of drug resistance have also been implicated as reasons for this resurgence. However, the most significant factor responsible for the resurgence of TB in the developed world is the increase in the immigration of persons from TB endemic areas.

3.4 History of Migration and TB

Although there is evidence to suggest that mycobacterial diseases similar to TB may have existed in the pre-Columbian Americas, the disease first reached epidemic proportions in Western Europe during the 17th and 18th centuries. [35,36] Sub-standard living conditions, worsened by explosive population growth and overcrowding, created the ideal circumstances for the spread of this airborne disease – so ideal in fact that by the 18th and early 19th centuries, TB was the leading cause of death in Western Europe. [35] At the same time, massive numbers of Europeans began to migrate to regions of Asia, Africa, and the Americas. [4,37] Consequently, these migrants likely carryied with them latent TB infection or in some cases, active pulmonary disease. As such, they undoubtedly exposed the highly susceptible, indigenous populations to the disease, creating devastating epidemics in these developing nations. [38]

Soon after the discovery of the causative organism and the advent of anti-microbial therapy, morbidity and mortality rates in Western Europe began to decline, due also in part to improvements in public health sanitation and overall living standards. Ironically, what was once the epicenter of the global TB crisis soon had one of the lowest incidence rates in the world; in much of the developing world, however, the epidemic was just beginning. In a reversal of circumstances, global migration patterns have shifted in the past 50 years – movement is now predominantly taking place from regions of high TB prevalence such as Asia, Latin America, and Africa into low-incidence regions including Western Europe, Australia, New Zealand, the United States of America (USA), and Canada. This trend of increased migration from high-prevalence countries has consequently reversed the global migration of the TB bacilli as well, with many previously low-incidence countries now beginning to experience a resurgence of the disease.

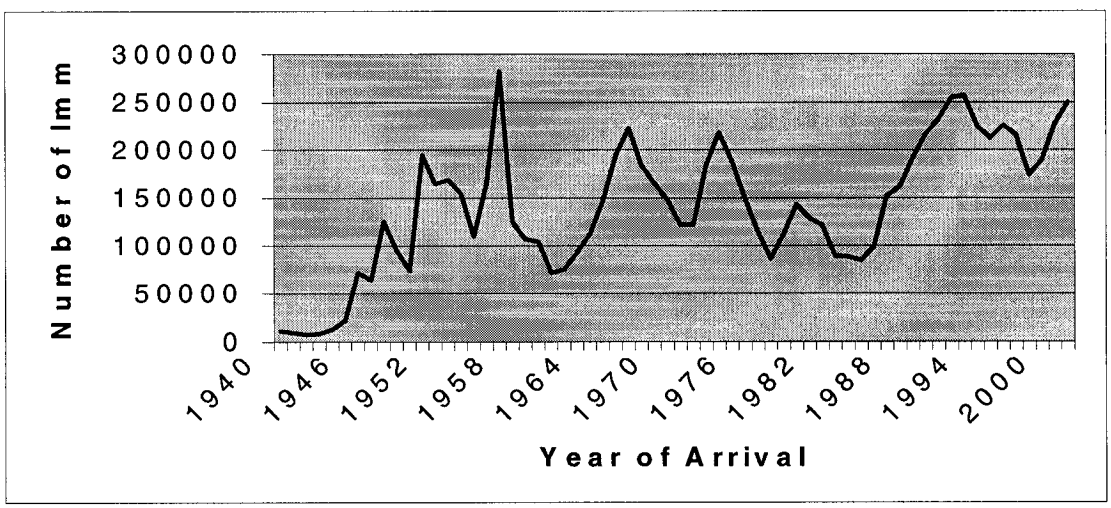
This reversal in immigration patterns has serious ramifications for the receiving countries. Given the high prevalence and incidence of disease in the source countries, most adult migrants have already been exposed to the TB bacilli prior to arrival and may in fact have active disease at the time of immigration or LTBI which may reactivate post-landing. [4] The implications for low-incidence countries become even more apparent given the fact that compared to native-born populations, immigrants are at increased risk of developing TB disease – some studies estimate this risk to be 5 to 20 times higher. [1,5-8] This risk varies by region of origin – in a recent Canadian study, compared to established market economies, the odds of developing disease post-arrival ranged from

1.8 for immigrants from former socialist countries of Europe, to 25.0 and 67.7 for persons from Vietnam and Somalia, respectively. [39]

3.4.1 History of Canadian Immigration

Historically, the number of immigrants arriving in Canada peaked in the early 1900's, reaching an all-time high of 400,870 in 1913. Following both World War I and World War II, however, immigration slowly declined; in 1942 only 7,576 foreign-born persons entered the country. [3] Figure 3.1 illustrates the trend in Canadian immigration observed between 1940 and 2001. Although the number of persons arriving in Canada has fluctuated from year to year, in each of the last 10 years, an average of 220,000 immigrants entered the country; in 2001, the number surpassed 250,000. [3]

Figure 3.1: Number of immigrants and refugees arriving in Canada each year, 1940-2001



Source: Reference 3

The origin of immigrants to Canada has changed considerably in the past 50-60 years. During the period before 1960, immigrants came almost exclusively from European countries experiencing incidence rates of TB very similar to those observed in Canada [40]. More recently, however, the majority of Canadian immigrants have arrived from countries in Asia, Africa, and Latin America – regions where both the prevalence of TB infection and incidence of TB disease are reported to be as much as 50 times higher than experienced in Canada. In fact, in 2001, the percentage of foreign-born persons arriving from these regions was as follows: Asia and Pacific (53.0%), Africa and the Middle East (19.2%), and South and Central America (8.0%). In contrast, only 19.5% entered the country from Europe, the United Kingdom (UK), and the USA. [3]

In 2001, the 10 leading source countries for immigrants to Canada included: China, India, Pakistan, Philippines, Republic of Korea, USA, Iran, Romania, Sri Lanka, and the UK. These 10 countries accounted for 53.4% of all immigration to Canada in 2001. [3] Most of these countries (with the exception of USA and the UK) report very high rates of TB; in fact, 4 of the top 10 source countries – China, India, Pakistan, and Philippines – were among the world's 22 highest burden countries in 2000 (according to the WHO). [29]

3.5 Factors Influencing TB in Immigrants in Low-Incidence Countries

The development of active TB disease among immigrants in low-incidence countries is dependent on several factors, including cumulative lifetime risk of infection, length of time in host country, return travel to country of origin, and status at time of immigration.

3.5.1 Cumulative Lifetime Risk of Infection

The likelihood that a foreign-born person has been exposed to *M. tuberculosis* and carrying LTBI at time of immigration is dependent on both the incidence of disease in the country of origin (i.e., annual risk of infection) and the age at immigration (i.e., number of years of exposure). [4] Thus, the longer an immigrant has lived in a high-incident country, the greater the likelihood that they will be infected. [41] It follows then, that persons who migrated to a low prevalence country at a young age tend to have TB rates more comparable to those of their new country than persons of the same age who migrated later in life. [42] In fact, several studies demonstrate that TB rates among foreign-born populations in low-incidence countries tend to parallel rates in their countries of origin, and tend to be higher in individuals who were older at time of immigration. [9,40,42]

3.5.2 Length of Time in Host Country

Numerous studies indicate that immigrants and refugees with LTBI are at highest risk of developing active disease within the first 5 years of arrival, and that the risk of TB tends to decline with the number of years after immigration. In several Canadian studies, approximately 37% - 56% of foreign-born persons with TB were diagnosed within 5 years of arriving in Canada [1,5-7] Similar proportions were reported in the USA and Australia where roughly 40%-55%, and 65% of all immigrants were diagnosed with TB within 5 years, respectively. [9,10,19,43,45] In the USA, TB rates were 3-5 times higher in the first 5 years compared to more than 5 years after arrival; in Denmark, the annual

incidence of TB declined only gradually during first 7 years (from an initial 2,000 per 100,000 to 700 per 100,000) in a sub-population of Somali refugees. [9,44]

It has been hypothesized that the greater likelihood of being diagnosed within the first 5 years may be an artefact of pre-immigration screening strategies targeting new arrivals, or even the results of increased access to healthcare in the receiving country. [41] It is more likely, however, the result of recent exposure (i.e., within last 2 years) to the TB bacilli in the immigrant's country of origin. Given that the annual risk of infection is 100-200 times greater in countries of high TB incidence compared to low-incidence countries, it is reasonable to conclude that most immigrants from high-incidence countries arriving in low-incidence countries with LTBI acquired the infection in their own country of origin, i.e., prior to arrival. [3,9] Considering that relative to persons with no known risk factors, the risk of developing active disease is 15 times higher for persons infected within the last 2 years, and that 50% of individuals with LTBI will progress to active disease within the first 2-3 years after infection, it follows that many immigrants, particularly those infected just prior to their departure, will develop active TB within the first 2-5 years following arrival. [24]

3.5.3 Return Travel to Country of Origin

Return travel to the immigrant's country of origin for prolonged periods of time has been identified as a risk factor for the development of active disease among foreign-born persons in low incidence countries. [46,47] In a British study, for example, 88 (41.9%) of the 210 Asian immigrants diagnosed with TB within 10 years of arrival had re-visited

their countries of origin since entering the UK. [46] Similarly, Weis and colleagues found that 23% of all foreign-born individuals diagnosed with TB in Tarrant County, Texas had traveled to regions with a high incidence of TB for a median length of 6 weeks in the previous 2 years. [47]

3.5.4 Status at Immigration

The WHO reports that more than 85% of refugees originate from regions of the world with high TB rates. [48] Refugee claimants have often faced additional challenges and experiences (e.g., impeded access to healthcare due to war, conflict, or natural disasters) that differentially affect the incidence and prevalence of TB. [49] For example, in some African refugee camps TB rates have been reported to be as much as 4 times the rate observed in local populations. [48] Consequently, on arrival to low-incidence countries, individuals claiming refugee status may have much higher rates of active disease than other migrant populations. [49]

3.6 Impact of TB in Immigrants in Low-Incidence Countries

Despite the fact that many low-incidence countries have experienced an overall decline or stabilization of TB rates over the last 50 years, the proportion of cases accounted for by the foreign-born population - as a direct result of increased immigration from high prevalence countries - has increased considerably. In Canada, for example, 65% of all TB cases reported in 2000 were in persons born outside of the country, compared to only 35% in 1980. [1] Similar statistics have been reported in the USA, where between 1986 and 2000, the proportion of TB cases accounted for by the foreign-born increased from

22% to 46%. [19,50] These foreign-born cases have a substantial impact on the health-care system of the receiving country, both in terms of the cost associated with screening, diagnosis, and treatment, as well as the risk of disease transmission among native populations.

3.6.1 Healthcare Costs

A comprehensive study of healthcare expenditures for TB in the US estimated the total costs associated with the diagnosis, treatment, and prevention of the disease in 1991 was $703 million. Of this, $606.1 million (86%) was spent on treating active cases, both inpatient and outpatient; $72.1 million (10%) was directed towards screening activities, while prevention efforts received only $17.9 million (3%). [51] Based on these total expenditures, each case of active TB treated in the US in 1991 cost an estimated $26,700 (range $19,500-$35,500); accordingly, cases of disease in the foreign-born population cost approximately $210 million (given that in 1991, close to 30% of all TB cases were among the foreign-born). Globally, therefore, healthcare expenditures for foreign-born TB in low-incidence countries likely exceed $500 million. [4]

3.6.2 Risk of Transmission

Each case of infectious TB is believed to have 5-20 close contacts, of whom 0.8%-12.7% develop active disease. [52] Furthermore, it has been demonstrated that those at highest risk of acquiring TB infection from an infectious source are those living in closest proximity – in fact, within the first year of developing active TB, each case is estimated to transmit TB infection to 40% - 50% of household contacts, and secondary active

disease to 2% - 4%. [53,54] With respect to TB in immigrants to low-incidence countries, the greatest potential public health threat is that foreign-born persons with active disease will transmit TB to the highly susceptible native-born population. Several studies have been conducted - using both tuberculin skin testing and DNA fingerprinting – to assess the risk of transmission of disease from immigrants to native-born populations of low-incidence countries. [55-58]

A cross-sectional study was conducted in Montreal to test the hypothesis that among children and young adults who were born in Canada, the prevalence of tuberculin reactivity (i.e., TST > 10mm) was associated with indicators of exposure to active TB among foreign-born persons, both household and non-household contact. After adjusting for significant factors (age, population group, and household contact), positive tuberculin reactions were not associated with any indices of potential contact, including incidence of reported cases of TB among foreign-born. [55]

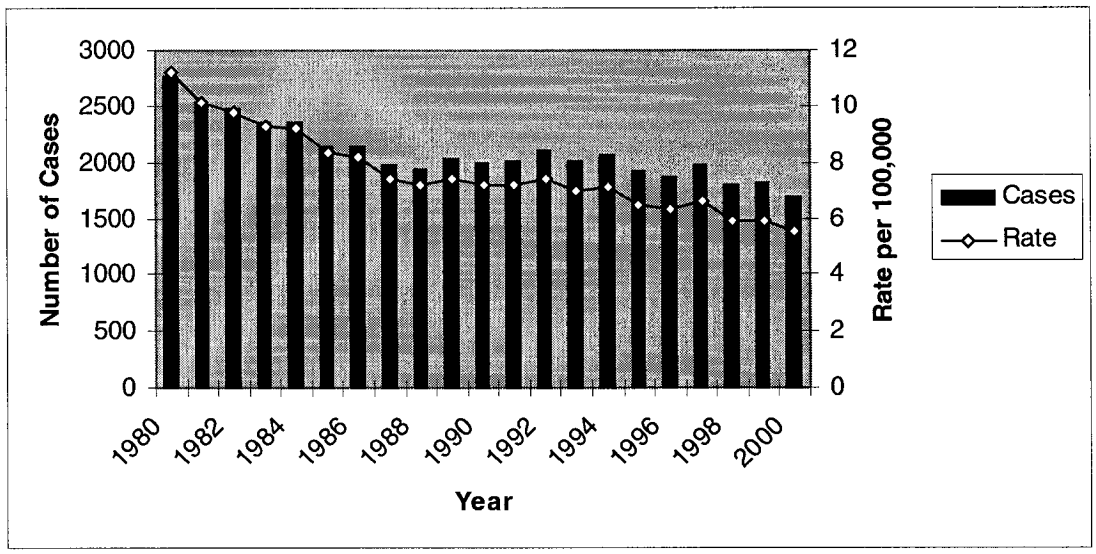
Transmission of TB from foreign-born to native-born populations has also been assessed, in 3 separate studies, by means of DNA fingerprinting (i.e., restriction fragment length polymorphism or RFLP). In San Francisco, only 2% of all US-born cases could be attributed to transmission from foreign-born sources; in Montreal, however, 11% of all cases in Canadians 18-49 years of age could be attributed to foreign-born transmission. [56,57] The highest proportion was observed in the Netherlands, where as many as 17% of Dutch-born cases occurred in clusters, indicating possible transmission from foreign-born individuals with active disease. [58]

3.7 Epidemiology of TB in Canada

At the turn of the 19th century, as many as 1 in 5 Canadians had TB in their lifetime. [7] Incidence rates peaked in the mid-1940's, reaching a high of approximately 120 cases per 100,000 population in 1945, but following the advent of antimicrobial therapy and overall improvements in living and sanitary conditions, morbidity and mortality due to TB rapidly began to decline. [24] Over the past 25 years, however, incidence rates have slowly begun to level off to a current annual rate of approximately 6 cases per 100,000 population – one of the lowest reported incidence rates in the world. [23] Although the overall incidence of TB remains relatively stable, the epidemiology of the disease in Canada has changed significantly.

In 2000, a total of 1,694 cases of TB were reported to the Canadian Tuberculosis Reporting System; the corresponding incidence rate was 5.5 per 100,000. [1] This represents both the lowest number of cases and the lowest incidence rate ever reported in Canada – in fact, in the last 10 years alone the number of reported cases has declined by 19.6%; incidence rates by 25.6%. Figure 3.2 presents the number of TB cases and corresponding incidence rates reported in Canada between 1980 and 2000. Since 1980, the number of cases and the incidence of TB have declined annually. Beginning in the late 1980's, however, while the rate of disease began to level off, there was a resurgence of TB cases. This trend was similarly observed in many industrialized countries during the same time period.

Figure 3.2: Reported TB cases and incidence rates (per 100,000) in Canada, 1980-2000



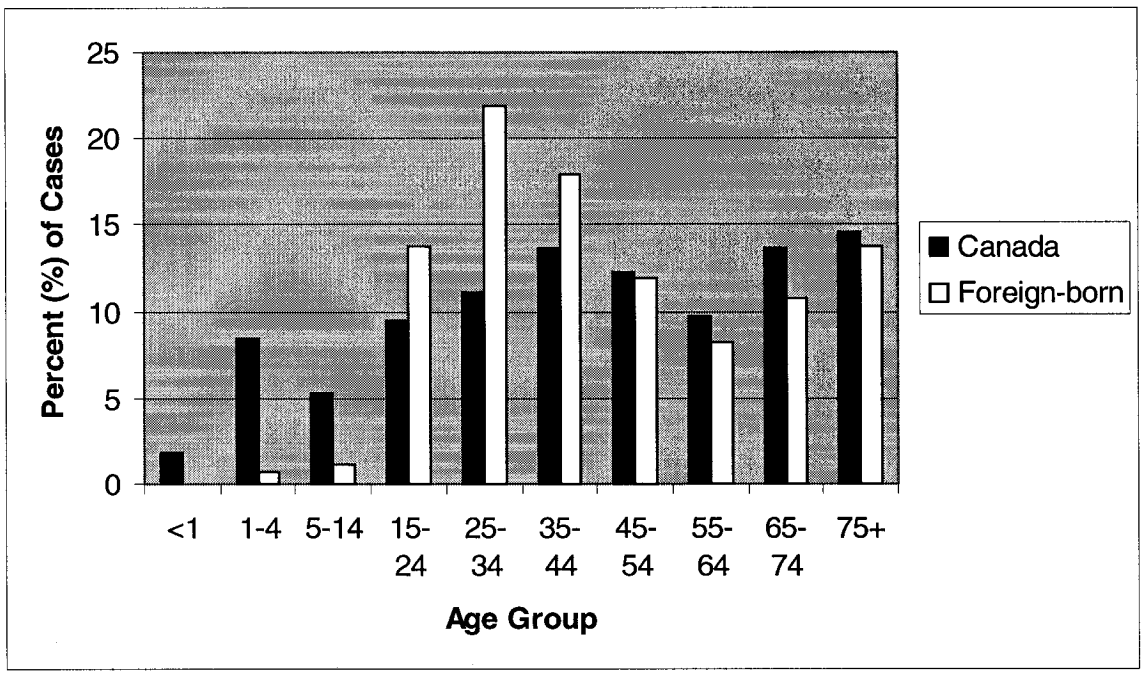
Source: References 1, 2

Of the 1,694 TB cases reported in Canada in 2000, 670 (39.5%) were reported in Ontario, 318 (18.8%) were in Quebec, and 285 (16.8%) were from British Columbia; together, these 3 provinces reported 75% of all TB in Canada. The highest incidence rate, however, was reported in Northern Canada (61.1 cases per 100,000), followed by Saskatchewan (10.1 per 100,000) and Manitoba (8.5 per 100,000). The Atlantic provinces (Nova Scotia, Newfoundland and Labrador, New Brunswick, and Prince Edward Island) contributed the lowest number of cases, collectively reporting only 25 (1.5%) new or relapsed cases – they also had the lowest incidence rate (1.0 case per 100,000). [1]

Figure 3.3 presents the age distribution of all TB cases reported in Canada in 2000, by birthplace (i.e., Canadian vs. foreign-born). Canadian-born individuals diagnosed with TB were much older than their foreign-born counterparts. For example, Canadians aged 65 and older accounted for 28.4% of all reported cases in 2000, whereas only14.6% of

foreign-born cases were among this age group. [1] The majority (53.6%) of foreign-born cases were between 15 and 44 years of age, compared to just 34.5% of Canadian cases.

Figure 3.3: Age distribution of TB cases reported in Canada in 2000, by birthplace (Canada vs. foreign-born)



Source: Reference 1

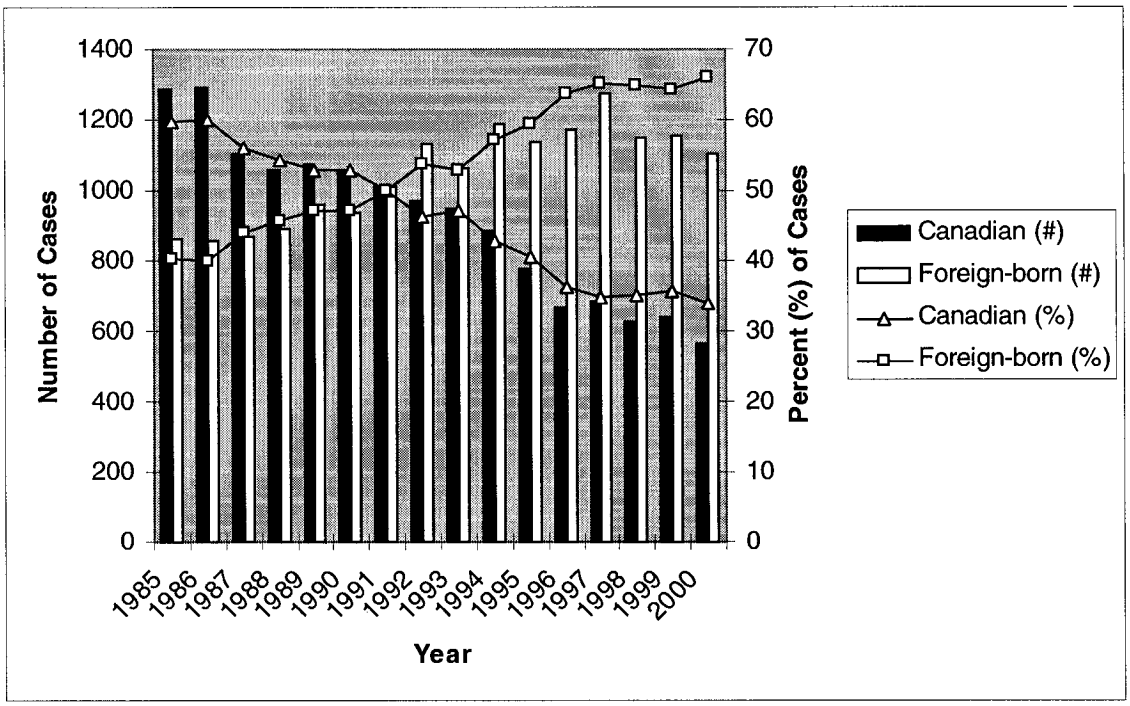
By diagnostic site, respiratory disease (i.e., pulmonary with or without silicosis, pleurisy, and laryngeal respiratory sites) was most frequently reported, representing 67.1% (n=1,138) of all reported cases. Peripheral lymph node TB was the second most common disease site and accounted for 15.0% (n=254) of all TB. Interestingly, individuals from the WHO's Western Pacific region – representing 28% of all TB cases in Canada – were responsible for 38% (n=97) of all lymph node disease. Other sites, including abdominal, bones and joints, genitourinary, and other non-respiratory, accounted for 8.5% of all cases (n=144). Finally, 101 (6.%) cases of primary TB were reported in 2000 – of these,

more than 55% occurred in aboriginal Canadians (i.e., status Indian, non-status Indian/Métis, Inuit). [1]

Although the overall incidence of TB in Canada has remained steady (at approximately 6-7 cases per 100,000) for the past 15 years, significant changes have occurred in the epidemiology of the disease, particularly with respect to the origin of reported cases. Persons born outside of Canada account for an increasing proportion of all TB cases reported in the country. This trend clearly coincides with the previously described immigration patterns whereby the majority of new immigrants are now arriving from regions of the world with high rates of TB.

For example, in 1985, the majority (59.8%) of TB cases occurred in persons born in Canada; the remainder (40.2%) were diagnosed in the foreign-born population, who at the time originated predominantly from low-incidence countries in Western Europe and the USA. [24] In just 15 years, these proportions have completely reversed – in 2000, foreign-born individuals – now predominantly from TB endemic regions such as Asia, Africa – accounted for 66% of all reported cases in Canada, while the Canadian-born population was responsible for only 34%. [1] Both the number and the proportion of all TB cases accounted for by Canadian-born and foreign-born populations reported between 1985 and 2000 are illustrated in Figure 3.4.

Figure 3.4: Number and percentage of all TB cases reported in Canada between 1985 and 2000, by birthplace (Canada vs. foreign-born)



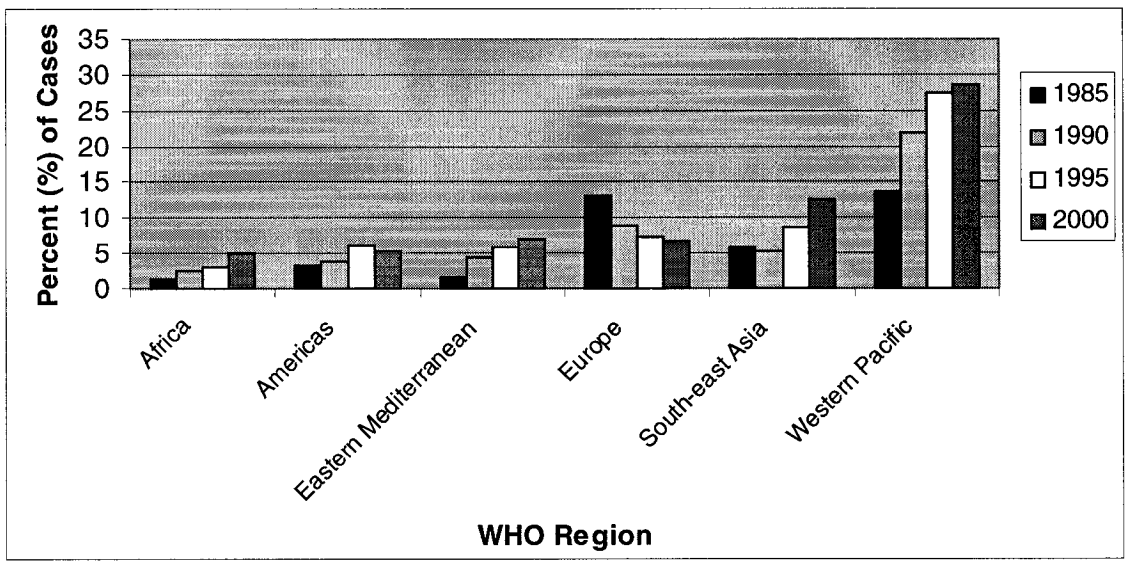
Source: References 1, 2

The changing pattern of immigration to Canada is reflected not only by the increased proportion of TB cases accounted for by the foreign-born population, but also by the regional breakdown of reported cases. In 2000, 28% of cases of TB in Canada were accounted for by individuals arriving from the WHO's Western Pacific region (n=468 or 28%) – this population represented 42.4% of all cases in the foreign-born. (see Appendix A: Member States of the World Health Organization for a list of countries in each WHO region) Persons entering Canada from countries in South-East Asia contributed 12.2% of all TB cases (19.2% of all foreign-born cases) and reported the highest regional incidence rate (53.5 per 100,000). Although accounting for only 4.9% of all TB cases in Canada, individuals from Africa reported the second highest incidence rate (46.4 per 100,000), followed by the Western Pacific (39.7 per 100,000) and Eastern

Mediterranean (32.5 per 100,000) regions. Not surprisingly, Europeans and persons from the WHO's region of the Americas had the lowest incidence rates (4.2 and 9.2, respectively) and together accounted for 11.7% of all TB cases in Canada. [1]

Consistent with the changing trend in the source of immigrants to Canada, the regional breakdown of TB cases has also changed significantly over the past 15 years – this phenomenon is illustrated in Figure 3.5, which shows the proportion of all TB cases reported in Canada between 1985 and 2000, by WHO region of origin. Of the 6 world regions, the European region was the only one to have shown a decline in the proportion of TB cases during these 15 years. Each of the other regions – most notably South-east Asia and Western Pacific – have demonstrated a steady increase in the number of cases reported in Canada..

Figure 3.5: Proportion of all TB cases in Canada by WHO Region, 1985 – 2000



Source: References 1, 2

3.7.1 Summary of the Canadian Experience of Immigration and TB

Over the last 50 years, Canada has experienced a substantial increase in immigration from TB endemic countries in regions such as Asia, Africa, and Latin America. Given the high prevalence of TB in these source countries, the likelihood that immigrants arriving from such countries have already been exposed to the TB bacilli and have active disease or LTBI at time of arrival is very high. As described previously, immigrants and refugees entering Canada with LTBI face an increased risk of developing active disease soon after their arrival. Consequently, the increased migration of persons from high-prevalence countries to Canada has resulted in a concurrent rise in the proportion of TB cases accounted for by the foreign-born population.

Because of the high financial burden associated with the treatment and diagnosis of TB in the foreign-born, as well as the elevated risk of transmission of active disease to the native-born population, the prompt identification and treatment of immigrants with infectious TB prior to settlement in Canada is a priority for the prevention and control of the disease. For this reason, all prospective immigrants to Canada must undergo radiographic screening for TB before being granted permanent residency.

3.8 Screening for TB in Immigrants to Canada

3.8.1 General Principles of Screening

Screening refers to the, "...application of a test to people who are as yet asymptomatic for the purpose of classifying them with respect to their likelihood of having a particular disease". [59] The screening procedure itself, however, does not diagnose disease – it

simply identifies persons for whom subsequent evaluation and diagnostic testing would be justified. The goal of screening is to discover conditions suitable for early intervention; individuals with such conditions are often asymptomatic and may not seek out medical assistance on their own. [24]

In order to be appropriate for screening, it has been suggested that the disease or condition under investigation should meet the following 4 requirements: 1) have a known natural history; 2) be amenable to a definitive intervention; 3) have agreed upon diagnostic criteria; and, 4) be sufficiently prevalent for screening process to be cost-effective. [24,54,59]

3.8.2 Rationale for Screening for TB

To determine the appropriateness of TB as a disease suitable for medical screening, it is necessary to measure the disease against each of the 4 requirements mentioned above.

3.8.2.1 Known Natural History

The natural history of TB is well-known and has been described in earlier in this chapter.

3.8.2.2 Amenable to Definitive Intervention

As described earlier in this chapter, both LTBI and active TB disease can be treated. Treatment for LTBI usually involves a 9 month course of INH and has been demonstrated to be 90% efficacious. [24,60] Curing active disease, however, is much more complicated. Treatment usually begins with both INH, rifampin (RMP), ethambutol

(EMB) and pyrazinamide (PZA) for a minimum of 2 months. Following this intensive phase of chemotherapy, the EMB and PZA are discontinued, and INH and RMP are prescribed for at least another 4 months. [24]

3.8.2.3 Diagnostic Criteria

For individuals in Canada with no known risk factors for TB, a TST with induration measuring 10 mm or more is diagnostic of LTBI. For persons with HIV infection, an abnormal CXR with fibronodular disease, or those who are close contacts of a contagious cases, a reaction of 5mm or greater is considered diagnostic of LTBI. Severely immunosuppressed persons who have additional risk factors (e.g., immigrant from TB endemic country, close contact of contagious case, or abnormal radiograph) may be considered to have LTBI even if the TST reaction measures < 5 mm. [24]

The CXR is often used as the first step in establishing the presence of active disease, however, no radiographic pattern is considered diagnostic of TB. [22] Many diseases of the lung have a similar radiographic appearance and can easily mimic TB; similarly, lesions of pulmonary TB can take almost any form on a radiographic picture. [21] Consequently, although the CXR may be useful in localizing abnormalities in the lung, microbiological testing (i.e., AFB smear and mycobacterial culture) of sputum and other specimens obtained, for example, through bronchoscopy and tissue biopsy, is necessary to establish the etiological nature of the radiographic findings. [22]

3.8.2.4 Cost-effectiveness

For populations with a low prevalence of the disease, studies have demonstrated that any TB screening program will provide minimal health benefits and be extremely costly. [20,59] For populations at higher risk of carrying TB infection or disease, the cost-effectiveness varies depending on the screening tool being used - when the objective is the identification of undiagnosed active cases of infectious pulmonary TB, the CXR is the primary tool; for the detection of LTBI, the tuberculin skin test (TST) could be considered. [24] In high-prevalence populations, the CXR is more cost-effective than the TST because it identifies persons with potentially active pulmonary disease and also detects individuals with radiographic abnormalities who are at significantly higher risk of reactivation, and would benefit the most from INH prophylaxis. [60] Although the TST may also be successful in preventing additional cases by identifying persons with LTBI for whom preventive treatment would be beneficial, its consistently higher expense when compared to CXR screening makes its routine use difficult to justify. [60]

To summarize, TB has a known natural history, both LTBI and active disease are amenable to therapeutic intervention and have agreed upon diagnostic criteria, and in certain high-risk populations, TB is sufficiently prevalent to ensure the cost-effectiveness of the screening process. Therefore, as TB meets each of the 4 previously described requirements, it is reasonable to conclude that TB is indeed a disease suitable for medical screening.

3.8.3 Targeted Screening of Immigrants

At the peak of the TB epidemic in the mid-20th century, many countries began to employ population-based radiographic screening in an effort to control the spread of the disease. These mass screening campaigns were extremely time-consuming, expensive to carry out, and generally detected only a small number of cases. [18,62] In Canada, for example, the 1st formal mass community surveys were conducted in Saskatchewan in the 1940s; approximately 96% of the population underwent radiography. The detection rate for active cases of TB fell from 1.0 per 1,000 screened, to 0.6 per 1,000 by the end of 1945. [62] By the1960's, the incidence rate of TB in Canada was too low to justify the continuation of mass screening campaigns. [62] In Denmark, the case detection rate for mass radiographic screening was only 0.2 per 1,000 adults tested in 1972. [18]

Given the low yield of active cases detected by mass screening, it has been recommended that TB screening activities focus on groups known to be at high risk for TB. [24] In most low-incidence countries, immigrants and refugees arriving from high-prevalence countries have the highest risk of developing active disease – for this reason, the WHO has advocated for the screening of immigrants on arrival to low-incidence countries as part of increased global infection control measures. [54]

3.9 Immigration Medical Screening of Immigrants to Canada

As early as 1899, concern about the magnitude of TB among immigrants was raised in the House of Commons, however, mandatory screening was not implemented until following World War II. [63,64] Subsequently, since the mid-1940's, all prospective

immigrants to Canada (e.g., immigrant applicants, refugees, certain types of visitors) have been required to undergo an immigration medical evaluation in order to "identify those who may pose a risk to public health, risk to public safety, or may place excessive demands on Canadian health and social services". [12] Depending on where the individual makes their application for residency, this evaluation may be conducted either overseas in the applicant's country of origin, or within Canada - in both instances, however, it may only be performed by physicians authorized to do so by Citizenship and Immigration Canada.

The immigration medical evaluation consists of a detailed medical history, physical examination, and 4 age-related routine tests: urinalysis (>= 5 years); chest radiograph (>= 11 years), syphilis and HIV serology (>= 15 years). At the discretion of the examining physician, additional tests may be ordered if there is sufficient evidence of an underlying medical condition. With respect to TB, applicants with abnormal chest films, as well as those presenting with history or symptoms indicative of active disease, may be requested to provide sputum samples for smear microscopy and culture, or undergo additional testing such as bronchoscopy, tissue biopsy or CT scan. [12]

Applicants undergoing medical screening overseas who are subsequently identified as having active TB are denied entry to Canada until they have completed a satisfactory course of treatment and are reassessed. Individuals who present with inactive TB at time of screening and those with a past history of TB are placed under medical surveillance as a condition of entry and subsequently must report to a public health authority in the

province/territory of destination within 30 days of entry. Refugee claimants and individuals making their application for immigration or other changes of status (i.e., visitor extension beyond 6 month stay) from within Canada are also obligated to undergo pre-immigration screening by an authorized physician. Applicants identified with active TB are reported to public health authorities in the responsible province/territory and are required to undergo appropriate treatment. Individuals judged to have inactive TB or those reporting a history of previous TB are placed under medical surveillance and investigated in the same manner as those placed on surveillance after being evaluated overseas. [12]

Guidelines for the investigation and follow-up of immigrants placed on medical surveillance have been developed by the Immigration Subcommittee of the Canadian Tuberculosis Committee (CTC) and have been approved by both the CTC and the Canadian Thoracic Society. At the initial appointment, the immigrant will be re-evaluated to rule out active disease; this usually involves obtaining a comprehensive history, repeat CXR, sputum specimens, and any other medical tests deemed necessary by the evaluating physician. Depending on the outcome of this investigation, individuals may be referred to a specialist for treatment of active disease, placed on prophylaxis for treatment of latent TB infection, or if prophylaxis is refused or not tolerated, counseled with regards to the signs and symptoms of active disease and the need for continued medical surveillance. [12]

3.10 Evaluation of Radiographic Screening Process

As discussed previously, the goal of pre-immigration radiographic screening for TB is to prevent the spread of the potentially communicable disease among the native-born population by: 1) detecting individuals with active disease (i.e., those who are contagious) and providing curative treatment before allowing the individual to enter or reside in Canada, and 2) identifying persons with latent or inactive TB and offering preventive chemotherapy to halt the progression to active disease. The ability of a screening test to meet these goals may be evaluated by measuring its yield in detection of active cases and the effectiveness of medical surveillance for LTBI – both of which may be seriously influenced by the recognized limitations of the CXR as a screening tool for TB.

3.10.1 Yield of Radiographic Screening

The yield of prevalent active cases detected as a result of pre-immigration radiographic screening has been documented in several studies and has been shown to vary depending on the population being evaluated. [15-17,65-67] In Switzerland, for example, 69 cases of active disease requiring curative treatment were detected among 43,803 foreign-born workers screened for the disease on arrival; the corresponding yield of prevalent cases detected was 0.16%. Among the 4,512 refugees screened at the same time, however, active TB was discovered in 0.93% (n=42). [15] In 2 additional studies, involving immigrants screened at Heathrow airport [17] and illegal aliens applying for adjustment of immigration status in Denver [65], both populations had a case detection rate of 5 per 10,000 or 0.05% (51 of 96,638 and 4 of 7,573 persons screened, respectively).

When the proportion of immigrants from TB endemic countries is high among those being screened, the yield of prevalent cases is increased, as demonstrated by Ormerod in 2 separate studies conducted between 1983-1988 and 1990-1994 in the United Kingdom. [66,67] In the first study, a total of 1,691 immigrants underwent radiographic screening on arrival; the overwhelming majority (85.9%) were from India and Pakistan, countries with a high incidence of TB. Consequently, the yield of active cases detected was 0.65% (n=11). [66] In the second study, a total of 10 prevalent cases of TB were detected among 2,242 immigrants – also mainly (86.4%) from India and Pakistan – for a yield of 0.45%. [67]

Finally, the yield of detected prevalent cases is higher among refugee populations, who for reasons discussed previously (i.e., geo-political and social conflict, natural disasters, and limited access to medical care) have a greater likelihood of arriving in low-incidence countries with LTBI or even active disease. [49] Recall that in Switzerland, the yield of active cases detected among refugees undergoing radiographic screening on arrival was 0.93%. In a similar study involving 9,328 south-east Asian refugees arriving in the U.S., 78 (0.84%) were diagnosed with TB as a result of the immigration medical evaluation. [16]

3.10.2 Effectiveness of Medical Surveillance

Studies have demonstrated that between 2% - 5% of all immigrants undergoing medical screening for TB will present with radiographic abnormalities or clinical histories suggestive of LTBI. [13,14] Those referred for post-landing medical surveillance for

LTBI have an increased risk of developing active disease after arrival. This risk is particularly high for individuals with screening chest films indicative of apical fibronodular disease, who relative to persons with no known risk factors and a normal chest x-ray are 6-19 times more likely to progress to active disease. [24]

Several Canadian studies have demonstrated that immigrants referred for surveillance are 4-5 times more likely to develop active disease than those not placed on surveillance. [13,14,68] In Manitoba, for instance, 7 cases of TB developed among immigrants on surveillance (3.2 per 1,000 person-years) whereas only 67 cases (0.7 per 1,000 person-years) were diagnosed among those with normal pre-immigration evaluations (RR 4.5, 95% CI 2.1, 8.8). [13] In a study conducted in Ontario, 12.8% of TB cases and 2.7% of controls had been referred for medical surveillance (OR 3.8, 95% CI 2.6,6.0). [39]

For many immigrants referred for medical surveillance for LTBI, the risk of developing active disease is so high that in the relatively short interval between pre-immigration screening and arrival in Canada (usually < 1 year), a small proportion will have already progressed to active disease and will be diagnosed with TB at the first post-landing investigation. This has been demonstrated in 2 Canadian studies. Of 1,173 Asian immigrants referred for surveillance upon arrival in B.C., 14 (1.5%) of the 932 who presented for evaluation were diagnosed with active disease. [13] Similarly, in Manitoba active TB was detected in 12 (2.8%) of the 429 immigrants investigated for surveillance of LTBI. [14] Similar percentages have been reported in the U.S. where 0.4% - 3.8% of

all immigrants identified as having inactive TB (i.e., B2 notification) were diagnosed with active disease on arrival. [19]

In a study measuring the effectiveness of the immigration medical surveillance program for TB in Ontario, researchers determined that the surveillance process identified only 14% of immigrants subsequently diagnosed with TB. [68] An even lower proportion of TB cases in southern Alberta (10%) were detected as a result of surveillance. [5] Poor compliance with the requirements of medical surveillance (both immigrants and healthcare providers) partially explains the low overall effectiveness of the surveillance program. For example, of immigrants referred for medical surveillance on the basis of the overseas evaluation, only 20%-70% ever present for evaluation after arriving in Canada. [13,14,68] Another possible explanation is the fact that many immigrants and refugees who subsequently develop TB post-immigration were assessed as having a normal CXR during pre-immigration evaluation even though they may have had active disease or recently acquired LTBI that was either radiographically undetectable at the time or misinterpreted by the evaluating physician.

3.10.3 Limitations of Chest X-ray as Screening Tool for TB

The usefulness of the CXR as a screening tool for TB in immigrants may be evaluated in terms of validity (i.e., its ability to correctly categorize persons with disease as test-positive and those without disease as test-negative) and reliability (i.e., the consistency of results when repeat examinations are performed on the same person under the same conditions. [59]

3.10.3.1 Validity

The validity of a screening tool is determined by its sensitivity and specificity. Sensitivity is defined as, "the probability of testing positive if the disease is truly present"; specificity is, "the probability of screening negative if the disease is truly absent". [59] With high sensitivity, there is less likelihood that individuals who truly have the disease will be misclassified as being test-negative – i.e., the number of false-negatives will be low. Similarly, the number of persons incorrectly classified as being test-positive (i.e., false positive) will decrease with increasing specificity. In terms of TB control, it would be preferable to have a screening test with high sensitivity at the risk of lower specificity because given the infectiousness of the disease, it would be more important to limit the number of persons incorrectly determined to be free of disease – such individuals may subsequently go untreated and transmit the TB bacilli to others.

According to Toman [22], chest radiographs will have a sensitivity of only 70% to 80% for the diagnosis of active TB and specificity is even lower (60% to 70%). In a study of immigrant screening for TB conducted in the U.K., for example, the sensitivity of the CXR was 63.6% (i.e., of 44 individuals with positive cultures, only 28 had screening x-rays suggestive of active disease) and the specificity was 62.8% (i.e., of the 140 culture-negative immigrants, 88 had radiographs that were not indicative of active disease). [17] The validity of the CXR in screening for TB is markedly improved if used in symptomatic populations. For instance, in a study conducted in India the sensitivity and specificity of the CXR in screening 2,229 symptomatic patients (e.g., cough, chest pain

with or without fever for 4 weeks, or hemoptysis) was 87.7% (95% CI 82.5, 92.7) and 95.9% (95% CI 95.0, 96.7), respectively. [69]

3.10.3.2 Reliability

Reliability refers to the consistency (i.e., reproducibility) of results when repeat examinations are performed on the same person under the same conditions. [58] The reproducibility of a screening test may affected by 4 sources: 1) biological/subject variation; 2) measurement variation; 3) intra-observer variability (i.e., differences in repeated measurements by same screener); and, 4) inter-observer variability (i.e., inconsistencies attributable to differences in the way different screeners apply or interpret test results). The latter 2 sources are commonly referred to as observer error and may be measured by means of the kappa coefficient. [59]

3.10.4 Kappa Statistics

First proposed by Cohen in 1960, the kappa coefficient approaches the measure of reliability by estimating the amount of agreement that exists between 2 or more raters, and has been shown to be directly analogous to the intraclass correlation coefficient. [68,69] More specifically, the kappa statistic reflects the extent to which the observed proportion of agreement between readers exceeds that expected by chance alone and is based on the assumption that when 2 or more observers independently classify a radiograph, there is a random chance that their classifications will be the same. This correction for chance agreement is the main reason why the kappa coefficient as a measure of reliability is advantageous over other comparable statistics. [70-75]

The kappa coefficient (κ) is calculated using the following formula,

$$\kappa = P_o - P_e / (1 - P_e)$$

where P_o represents the total proportion of observations on which there is agreement and P_e is the proportion of observations on which there is agreement which would be expected by chance alone, assuming the statistical independence of the readers. In other words, kappa is the ratio of observed nonchance agreement to possible nonchance agreement. [70-75] The calculation of the kappa statistic will be discussed in greater detail in section 4.1.9.

The kappa statistic will be positive only when the observed agreement exceeds the expected chance agreement and normally ranges between 0 and +1. A kappa value of 0 indicates no agreement above that expected by chance, while a value of +1 corresponds to perfect agreement. Negative values are possible, however, the only meaningful interpretation is that the level of disagreement is worse than what would be expected by chance. [70-75] The suggested interpretation of agreement for different values of the kappa statistic are presented in Table 3.3.

Observer error in the interpretation of CXR has been studied extensively over the past 50 years; much of the early work in evaluating the reliability of chest radiographs, conducted by Yerushalmy, focused on screening or survey procedures using chest radiographs to detect TB and lung cancer. [72] In mass screening for TB, the CXR had an inter-observer agreement of 70.0% and an intra-observer agreement of 78.5%. [76]

Table 3.3: Suggested interpretation of agreement for different values of the kappa statistic

Value of Kappa (K)	Relative Strength of Agreement
< 0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good
> 0.81	Excellent

Source: Reference 73

In perhaps the most definitive study on observer error in the reading and interpretation of chest radiographs, a sample of 1100 films was randomly selected from among those taken during a mass screening campaign of adults in Norway. Organized by the International Union Against Lung Disease and Tuberculosis (IUATLD), the ultimate goal of the study was to arrive at a uniform nomenclature and interpretation of x-ray findings that could serve as the basis for an international classification of chest radiographs. [77,78] The 1100 x-rays were read by 90 experienced physicians (radiologists and chest specialists) who answered a series of questions (most requiring yes or no answers) designed primarily to measure the extent of agreement or disagreement between readers. [79]

Overall, the worst agreement was observed for the question, "Is there an abnormality in the lymph nodes?" – for which there was only 40% agreement; whereas, the best agreement (72%) was for the question, "Is there a cavity present?". There was moderate agreement for the following 2 questions, "Is the abnormality probably tuberculous?", and "Is there calcification in the lung?" – 55% and 58%, respectively. Finally, the questions "Is the film abnormal?", and "Is there a need for medical action?" both had good agreement (66% and 69%, respectively). [79]

In a more recent study, CXRs were obtained for 973 individuals evaluated at the Montreal Chest Institute (MCI) for the purposes of pre-immigration screening, surveillance of LTBI, investigation of close contacts, and clinical evaluation of suspect pulmonary TB cases. [80] Each of the 973 films were read twice by each of the 3 chest radiology specialists at the MCI and were grouped into 5 broad categories: 1) normal or minor findings (unrelated to TB); 2) granulomas with or without calcification considered likely to be related to remote (but latent) tuberculosis infection; 3) apical fibronodular disease or multiple non-calcified nodules; 4) pleural disease or a mass in the parenchyma, hilum, or mediastinum; and, 5) parenchymal lung infiltrates with or without cavitation – the latter 3 findings were considered consistent with possible active TB. [80]

The overall agreement was moderate, with kappas coefficients ranging from 0.439 for inter-reader agreement to 0.621 for intra-reader agreement (overall kappa = 0.51). The best agreement was for the question of whether or not the film was normal with an overall kappa value of 0.623 (0.561 and 0.722 for inter- and intra-reader agreement, respectively) and was worst for the diagnosis of a mass or pleural disease (category 4), however, only 0.3% of the total readings were assigned to this category. [80]

3.11 Summary of the Review of the Literature

Globally, TB remains a leading cause of morbidity and mortality with close to 8 million new cases and 2 million deaths reported annually. In addition, one-third of the world's population is estimated to be infected with the *Mycobacterium tuberculosis* bacteria. [33] Increased immigration from regions of the world where both the prevalence and

incidence of TB is high (e.g., Africa, Asia, and Eastern Europe) has led to a resurgence of the disease in many industrialized countries. [35-38]

Canada receives more than 200,000 immigrants and refugees each year; the majority (~85%) arrive from countries with a very high annual risk of TB infection. [3] Consequently, many new immigrants have likely already been exposed to and infected with the TB bacteria and may be carrying LTBI with them which may reactivate post-arrival. [1,4-11] Furthermore, some prospective immigrants may have already progressed to active disease by the time they enter the country. Because of the possible risk of transmission to the Canadian-born population, all foreign-born individuals applying for permanent residence in Canada must undergo pre-immigration radiographic screening for TB. [12]

The primary objective of the radiographic screening process is to detect individuals with active pulmonary TB (i.e., those who are contagious) and provide curative treatment before permanent residency is granted. [12] Although most non-immunocompromised individuals with active disease will present with an abnormal CXR [27], as a screening tool for TB the CXR has several important limitations: 1) the yield of case detection varies from 0.05% to 0.15% in the overall immigrant population and is only slightly higher (0.45% to 0.8%) for refugees and persons from high incidence countries [13-19], 2) radiographic screening is expensive – estimates range from $4,000 to $10,000 (Cdn) per person screened [20], 3) the CXR has low sensitivity (60%-80%) and low specificity (60%-70%) in diagnosing TB [21,22], and 4) observer agreement (reliability) is very low

– even for questions such as "is this x-ray normal or abnormal?" and "is this suggestive of active TB?"[22]. In spite of these limitations, the CXR continues to be used by many countries, including Canada, to screen potential immigrants for TB disease.

With respect to the immigration screening process currently employed in Canada, few studies have been conducted to evaluate the yield of prevalent cases detected by CXR. Also, given that the incidence of TB among the foreign-born in Canada remains high among those previously screened for the disease, the ability of the radiographic screening process to predict and prevent future cases of disease has also not been fully assessed. This study aims to address these gaps in knowledge by evaluating both the prevalence and incidence of active TB disease among a cohort of immigrant applicants undergoing radiographic screening in Montreal. The second aim is to assess the extent of agreement between physicians when interpreting screening chest films and determine how the reliability of the CXR as a screening tool for TB may subsequently influence both the prevalence and incidence of TB among immigrants to Canada.

4. METHODS

4.1 Review of the Immigration Medical Screening of Immigrants to Canada

As described earlier in section 3.9, all foreign-born persons applying for permanent residence in Canada must undergo an immigration medical evaluation consisting of a detailed medical history, physical examination, and 3 age-related tests. With respect to TB, persons 11 years of age and older must have a chest x-ray performed in order to detect those with prevalent active TB as well as to identify persons with LTBI. Immigrant applicants diagnosed with active disease are required to complete curative treatment prior to being granted permanent residence; persons found to have LTBI are referred for medical surveillance and may be offered preventive chemotherapy to halt the progression to active disease. [12] Depending on where the application for permanent residence was made, the immigration medical evaluation may take place either overseas (i.e., in the immigrant applicant's country of origin) or within Canada for those already holding visas).

4.2 Evaluating the Chest X-ray as a Screening Tool for TB

As discussed in section 3.10, as a screening tool for TB, the chest x-ray is limited by several factors including poor reliability (i.e., low intra- and inter-observer agreement), low yield in detecting prevalent active cases of disease, and both low sensitivity and low specificity. These factors are closely inter-related – for example, low observer agreement may lead to misclassification with respect to the category and clinical significance of the screening chest x-ray, which in turn influences both the prevalence and incidence of disease among those screened. In order to evaluate the usefulness of the chest x-ray as a

screening tool for TB in immigrants to Canada, particularly with respect to these limitations, 2 separate studies were conducted for the purposes of this thesis. In the first study (see Observer Agreement Study), the extent of agreement between physicians interpreting immigration screening chest films was measured using Citizenship and Immigration Canada's x-ray categorization scheme. The second study (see Prospective Cohort Study) involved a cohort of immigrant applicants screened for TB at the Montreal Chest Institute and calculated both the yield of prevalent active cases detected at the time of screening as well as the incidence of active disease diagnosed post-screening in order to identify potential limitations of the radiographic screening process.

4.3 Observer Agreement Study

4.3.1 Selection and Preparation of Chest X-rays

Postero-anterior chest x-rays performed for immigration medical examination purposes were obtained from recent immigrant applicants who had undergone pre-immigration medical examination overseas and were referred to one of 4 Canadian centres (Vancouver, Edmonton, Calgary, and Montreal) for medical surveillance of latent TB infection. Both pre-immigration (i.e., performed overseas) and post-landing (i.e., performed in Canada) chest films were collected; to be eligible for the study individuals were required to have a complete set (i.e., 1 of each) available for review. From each referral centre, 50 consecutive immigrants with a complete set of screening x-rays were selected, thus a total of 100 chest films (50 overseas and 50 Canadian) were obtained from each of the 4 sites.

In order to prepare the films for the study, the x-rays from each centre (n=100) were packaged and shipped to the Montreal Chest Institute (MCI). Any identifying information (e.g., name, date of birth, x-ray site etc.) was either removed or covered up and a random 8-digit study identification number was assigned to each film. The study numbers indicated to the investigator the location where the x-ray was performed (i.e., overseas or Canada) as well as the specific referral centre the films originated from yet provided no additional information to the physicians interpreting the x-rays. The films from each centre were then placed in random order and merged together to form a final set of 400 chest x-rays (200 obtained overseas and 200 obtained in Canada).

4.3.2 Reading of Chest X-rays

Each of the 400 chest films were independently read and interpreted by 12 physicians from locations across Canada. The study participants had varying years of experience in interpreting chest x-rays and represented several different specialty areas including infectious diseases, radiology, and respiratory medicine. Each reader was blinded to the patient's identity and subsequent diagnosis, as well as to the location where the x-ray was performed (i.e., overseas or specific Canadian centre). The entire set of films was delivered to one reader at a time and was accompanied by a 2-page questionnaire to be completed for each of the 400 chest films. The readers were asked to interpret each x-ray using Citizenship and Immigration Canada's (CIC) current chest x-ray categorization scheme as well as answer an additional set of questions regarding the clinical findings and technical quality of the films. (see Appendix B: CIC Chest X-ray Categorization

Scheme and Study Questionnaire) The completed questionnaires were returned directly to the MCI to ensure independent results.

4.3.3 Citizenship and Immigration Canada's Chest X-ray Categorization Scheme

The CIC categorization scheme used to interpret immigration screening chest x-rays was designed to provide clinicians with a tool for determining the clinical significance of a chest x-ray with respect to tuberculosis (TB). It is comprised of 5 major categories that are coded from 0 to 4: 0) normal; 1) non-pulmonary problems; 2) pulmonary problems – of no clinical significance; 3) pulmonary problems – minimal, may be due to old TB infection; and, 4) pulmonary problems – potentially active disease (active TB or other conditions). Categories 1 through 4 are further broken down into 22 sub-categories – in general, the higher the category, the greater the likelihood that the chest x-ray represents active TB. Without instruction or guidance, the 12 readers were asked to interpret each x-ray and, using the CIC categorization scheme, indicate which category or categories best described the film. If more than 1 category was assigned, the highest rating was used in the analysis.

4.3.4 Clinical and Technical Findings

In addition to assigning an appropriate category to each film, the study participants were asked to estimate the percent of lung parenchyma involved (0%, 1-4%, 5-9%, 10-24%, 25% or more) and indicate whether or not, in their opinion, the chest x-ray was representative of active pulmonary disease (yes or no).

Using the questionnaire provided, readers were also asked to evaluate the technical quality of the screening chest films by rating each with respect to the following 4 characteristics: penetration (ideal, over, or under); presence of artefacts (yes, no, or unsure); visibility of entire lung field (yes or no); and, overall quality of the film (excellent, good, sub-optimal, poor, or terrible).

4.3.5 Data Management

Before the study began, each of the 12 physicians was assigned an identification number (1-12) to be used on all questionnaires and other correspondence in order to guarantee anonymity. As the completed questionnaires were returned to the MCI, each reader's results were coded and entered manually into a database managed using Microsoft Access ®. Upon completion of data entry, any questionable results were verified against the original data and the master list of study identification numbers, and either corrected or discarded. Forms with missing or incomplete study identification numbers were also excluded from the analysis. In the case where results were missing for only 1 or 2 questions but the study identification number was valid, the available responses were included in the analysis. In preparation for analysis, the cleaned data was exported from Microsoft Access ® into SAS statistical software (SAS Institute, Cary, NC, USA).

4.3.6 Descriptive Statistics

To evaluate potential differences in the technical quality of the x-rays performed overseas and those performed in Canada, the frequency (%) of films assigned to each category of technical findings (i.e., penetration, artefacts, lung field visibility, and overall quality) for

both sets of films was compared. The 200 Canadian x-rays were also further examined to determine if notable differences existed in the technical quality of films performed in the 4 centres (Vancouver, Edmonton, Calgary, and Montreal).

4.3.7 Assessment of Reliability

As a statistical measure of reliability, the kappa coefficient (κ) was used to calculate the level of agreement between the readers with respect to the findings observed on the screening chest films. Intra-observer reliability (i.e., the extent to which an individual's multiple readings on a single subject agree) and inter-observer reliability (i.e., the extent of agreement between 2 readers' interpretations for the same subject) was determined for all clinical and technical findings by generating kappa coefficients using SAS statistical software and the methods described below. To determine the amount of agreement between all 12 readers (i.e., multi-observer reliability), data was transferred to Microsoft Excel ® worksheets and kappa statistics were calculated using methods described by Fleiss [75].

4.3.8 Calculation of the Kappa Coefficient

As described in section 3.10.4, the kappa coefficient (κ) reflects the extent to which the observed proportion of agreement exceeds that expected by chance alone and is calculated using the following formula: $\kappa = P_o - P_e / (1 - P_e)$. P_o represents the total proportion of observations on which there is agreement and P_e is the proportion of observations on which there is agreement which would be expected by chance alone, assuming the statistical independence of the readers. [70-75]

4.3.8.1 Example 1: Intra- and Inter-observer Agreement

To illustrate the methods used for calculating both intra- and inter-observer kappa coefficients, consider the following 2 x 2 table where 2 readers, A and B, have both independently read and classified 100 chest x-rays with respect to the presence or absence of pneumonia:

	Reader B		
Reader A	Present	Absent	Total
Present	50	15	**65**
Absent	15	20	**35**
Total	**65**	**35**	**100**

The observed agreement (P_o) is calculated by summing together the proportion of all observations where both readers observed the pneumonia to be either present (50/100 = 0.50) or absent (20/100 = 0.20); thus, in this example, $P_o = 0.50 + 0.20 = 0.70$. To determine the proportion of expected agreement, the numbers in the margins (i.e., totals) are used. If reader A found pneumonia to be present in 65 of the 100 chest x-rays (0.65) and reader B also discovered the presence of pneumonia in 65 of the 100 films (0.65), then the expected agreement for the presence of the disease – assuming the statistical independence of the 2 readers – is calculated as: 0.65 x 0.65 = 0.4225. Similarly, if both reader A and reader B determined that pneumonia was absent in 0.35 of the 100 chest films, the expected agreement for the absence of pneumonia is 0.35 x 0.35 = 0.1225; therefore, the total proportion of expected agreement (P_e) is: 0.4225 + 0.1225 = 0.545. Finally, to determine the extent of agreement between readers A and B the above values are substituted into the equation for calculating kappa statistics: $\kappa = P_o - P_e / (1 - P_e) = 0.70 - 0.545 / (1 - 0.545) = 0.34$. Thus, when interpreting chest x-rays for the presence or absence of pneumonia, readers A and B agreed with each other only 34% of the time.

According to the rating scale earlier (see Table 3.3) this result corresponds to "fair" agreement.

4.3.8.2 Example 2: Multi-observer Agreement

Fleiss [75] has described methods for calculating kappa coefficients in situations involving multiple readers and/or multiple categories (i.e., situations where a 2 x 2 table is not applicable). For instance, consider the following example where 4 readers must independently classify each of 4 subjects with respect to one of 4 categories (e.g., none, mild, moderate, and severe). The combined results are presented below:

	None	**Mild**	**Moderate**	**Severe**	**Total**
Subject 1	2	0	1	1	4
Subject 2	0	0	0	4	4
Subject 3	1	2	1	0	4
Subject 4	0	3	0	1	4
Total	3	5	2	6	16

According to methods developed by Fleiss [75], the overall proportion of observed agreement (P_o) may be determined by calculating the proportion of agreeing pairs out of all the n(n-1) possible pairs of assignments for each subject. For example, the proportion of observed agreement for subject 1 is calculated as: 2(2-1) + 0(0-1) + 1(1-1) + 1(1-1) / 4(4-1) = 2/12 = 0.17. Similarly, for subject 2, the observed agreement is: 0(0-1) + 0(0-1) + 0(0-1) + 4(4-1) / 4(4-1) = 12/12 = 1.0. In other words, there was perfect observed agreement for subject 2 as each of the 4 readers classified the subject as "severe". For subjects 3 and 4, the observed agreement was 0.5 and 0.17, respectively. To obtain the overall observed agreement for the entire sample, the proportion of observed agreements for each subject are summed together and then averaged by dividing by the total number

of subjects. In this example, the sum of observed agreement = 0.17 + 1.0 + 0.17 + 0.50 = 1.84, thus the overall proportion of observed agreement, $P_o = 1.84/4 = 0.46$.

The proportion of expected agreement (P_e) is determined by squaring the proportion of all readings (i.e., number of readers times the number of subjects – in this case, 4 x 4 = 16). assigned to each category and summing the results. For example, since 3 of the 16 readings were classified as "none", the proportion of expected agreement for this category is $(3/16)^2 = 0.035$. Similarly, the proportion of expected agreement for the category of "mild" is $(5/16)^2$ or 0.098. The overall proportion of expected agreement is calculated by summing the results for each category – for this example, $P_e = 0.29$. Given that $P_o = 0.46$ and $P_e = 0.29$, these values can now be substituted into the general equation for the calculation of the kappa coefficient: $\kappa = P_o - P_e / (1 - P_e)$. Thus, for this example, the kappa statistic is: 0.46 – 0.29 / (1 – 0.29) = 0.24. In other words, the 4 readers agreed on the classification of the 4 subjects only 24% of the time.

4.3.9 Intra-observer Agreement

For each of the 12 physicians, kappa statistics were calculated to determine the extent of intrapersonal agreement when interpreting 2 chest x-rays from the same individual (i.e., 1 performed overseas and 1 performed in Canada). Using the Proc Freq function in SAS, kappa coefficients were generated for each of the following clinical findings, based on the categories found on the CIC categorization scheme: general category (0-4); normal vs. abnormal (0 vs. 1-4); normal vs. minor vs. possible active (0 vs. 1-3 vs. 4); no TB vs. TB infection/disease (0-2 vs. 3-4); and, no active disease vs. possible active disease (0-3

vs. 4). Agreement was also measured for the question of whether or not the film was suggestive of active TB (yes or no) and the extent of lung parenchyma involved (0%, 1-4%, 5-9%, 10-24%, and, 25% or more). Intra-observer kappa coefficients were not calculated for the technical findings of penetration and overall quality as it was predicted that the x-rays performed overseas and in Canada would differ substantially in technical quality and thus intra-observer agreement for such measures would not have been meaningful.

4.3.10 Inter-observer Agreement

To determine how well each of the 12 physicians agreed with the interpretation of the other 11 physicians when reading the same chest x-ray, inter-observer kappa statistics were generated using methods illustrated earlier (Example 1) and SAS statistical software (Proc Freq function). For each of the clinical categories described above, as well as for the technical findings (i.e., penetration, presence of artefacts, visibility of entire lung field, and overall quality), the agreement between one reader and each of the 11 others were calculated separately and then averaged to obtain a single inter-observer kappa statistic for each reader (i.e., kappas were obtained for reader 1 vs. reader 2, reader 1 vs. reader 3...reader 1 vs. reader 12 and then averaged). Results were computed independently for films performed in Canada and those performed overseas in order to examine whether the general quality of the x-rays influenced the agreement between readers, given the hypothesis that the 2 sets of films would differ substantially in technical quality.

4.3.11 Multi-observer Agreement

Using methods described by Fleiss [75] outlined earlier, the extent of agreement between all 12 of the raters combined was evaluated for each of the previously described clinical categories and technical findings using worksheets in Microsoft Excel ®. Again, to examine the potential differences in agreement depending on the location the x-rays were taken (i.e., location as a proxy for quality) the multi-observer kappa statistics were calculated separately for overseas and Canadian films.

4.4 Prospective Cohort Study

4.4.1 Study Design

A prospective cohort study was designed to determine the prevalence and subsequent incidence of active TB among immigrants undergoing radiographic screening for the disease prior to being granted permanent residence in Canada. The dependent variable was the rating of the initial screening chest x-ray as interpreted by the evaluating physician using Citizenship and Immigration Canada's categorization scheme (see Appendix B). Other variables of interest included: sex, age at time of screening, length of time between screening and diagnosis (months of follow-up), country and continent of origin, incidence of TB in country of origin (>100 per 100,000, 25 – 99 per 100,000, or <25 per 100,000), and status at time of screening (visa holder or refugee claimant).

4.4.2 Study Setting

The Montreal Chest Institute (MCI) is a tertiary care facility that specializes in the diagnosis and treatment of respiratory diseases. The MCI has been designated by CIC as

a Medical Centre responsible for pre-immigration screening for TB of individuals making their application for permanent residence from within the greater Montreal area. The public health department for the island of Montreal has also independently designated the MCI as a centre for the evaluation and treatment of individuals referred for medical surveillance. Contact tracing (i.e., investigation and follow-up of persons identified as close contacts to an active case of TB) for all new cases of TB reported to the public health department for the island of Montreal is also the responsibility of the MCI.

4.4.3 Study Population

All foreign-born individuals who applied for permanent residence in Canada from within the greater Montreal area (i.e., island of Montreal, Laval, and the region of Monterégie) and who underwent pre-immigration medical screening at the MCI between May 1995 and December 1998 were eligible for the study. Individuals were excluded if they were diagnosed with TB in Canada prior to undergoing immigration screening (i.e., they were passively detected on the basis of symptoms and sought medical attention prior to screening), were under 11 years of age at time of the evaluation, or if chest x-ray examination was medically contraindicated or otherwise not performed.

This project (and the preceding Chest X-ray observer agreement study) was considered and approved by the Montreal Chest Institute Research Ethics Committee. This project was also approved by the Research Ethics Boards of the Directions de Sante Publique of Laval, Monteregie, and Montreal Centre, plus the Commission d'Acces a l'Information of the Government of Quebec.

4.4.4 Montreal Chest Institute (MCI) Records

For all individuals undergoing pre-immigration screening at the MCI, demographic characteristics such as the applicant's name, date of birth, date of medical evaluation, sex, country of origin, immigration number and status at time of application were recorded in the hospital's computerized database. Following the initial assessment, the evaluating physician's interpretation of the screening chest film (i.e., the specific x-ray category determined using the CIC categorization scheme) was also captured in the database. Individuals with chest x-rays consistent with active pulmonary disease (Category 4) were contacted and asked to return to the MCI for a follow-up evaluation with a medical specialist. The results of this evaluation, which often included a repeat chest x-ray, a tuberculin skin test (TST), and bacteriological examination (i.e., AFB smear microscopy and mycobacterial culture) of sputum or other specimens collected at the discretion of the evaluating physician, were also recorded in the MCI database.

4.4.5 Public Health Records

All individuals diagnosed with TB in Canada, either on the basis of bacteriologic evidence or other clinical findings, are reported to the responsible public health units. In the province of Quebec, all reportable diseases, including pulmonary and extrapulmonary TB, are captured in the Maladies à déclaration obligatories (MADO) database. This database contains the following fields: name, date of birth, sex, country of birth, year of arrival in Canada (if applicable), date of TB diagnosis, disease site (i.e., pulmonary or extrapulmonary), the public health region reporting the case and the date it was transmitted to MADO. To determine the number of individuals screened for the disease at the MCI who were subsequently diagnosed with TB, MADO records were obtained for

all foreign-born individuals (i.e., country of birth not Canada) 11 years of age and older who were living in the greater Montreal area (i.e., island of Montreal, Laval, and the region of Monterégie) and were reported to MADO with a diagnosis of TB between June 1995 and December 1999. Given that the study cohort included individuals screened between 1995 and 1998, the selection of December 1999 as the end of the MADO reporting period guaranteed that individuals screened in December of 1998 would be followed for a full 12 months. The selected records were then extracted from the MADO database and exported into SAS for further analysis.

4.4.6 Matching of MCI and Maladies à Déclaration Obligatoires (MADO)Records

The records obtained from the MCI and the MADO database contained several variables (e.g., last name, first name, sex, date of birth, and country of origin) that were common to both datasets and could thus be used to search for matching records among the 2 datasets. Using different combinations of these variables (e.g., last name and first name; last name, first name and date of birth; date of birth, sex, and country of origin etc.), the MCI and MADO data was merged together in SAS in an attempt to obtain the maximum number of duplicate records (i.e., individuals who were screened for TB at the MCI during the study period who were subsequently diagnosed with the disease and reported to MADO).

After matching the data in SAS and manually verifying the results, the records for those individuals found in both the MCI and MADO datasets were carefully reviewed and merged together to form the most complete dataset possible. The MADO records for those individuals not captured in the MCI dataset (i.e., not screened at the MCI between May 1995 and December 1998) were discarded. With the additional information available from the MADO records, a variable was created to examine the length of time

between radiographic screening and the diagnosis of TB (i.e., months follow-up) by subtracting the date of the chest x-ray from the date the diagnosis of TB was reported to MADO. For those individuals screened at the MCI but who were not subsequently diagnosed, the last date of the study period (i.e., December 31, 1999) was used to obtain the total months of follow-up. Finally, individuals with a diagnosis of TB reported prior to the date they were screened at the MCI were excluded from further analysis as their cases were detected passively and not as a result of the screening process.

4.4.7 Preparation of Data for Analysis

In preparation for data analysis, the records of all foreign-born individuals 11 years of age or older who underwent radiographic screening for TB between May 1995 and December 1998 were extracted from the MCI database and exported into SAS statistical software (SAS Institute, Cary, NC, USA). Duplicate entries were deleted, as were the records of individuals who were missing a value for the dependent variable (i.e., screening chest x-ray category). Variables were created for age at time of screening (both as a continuous variable and by 10-year age groups) by subtracting the date of birth from the date of the initial screening chest x-ray. Countries of origin were grouped into 3 categories of incidence (<25, 25 – 99, and > 100 cases per 100,000) in order to examine the possible association between TB incidence in the immigrant's country of origin with the subsequent risk of developing the disease upon arrival in Canada.

Using SAS univariate analysis, the demographic characteristics (e.g., sex, age, continent of origin, incidence in country of origin, and status at screening) of the study cohort were

examined. Individuals were further categorized with respect to the CIC category assigned to each film. In order to determine which factors, if any, were associated with having an x-ray suggestive of active disease at time of screening, the demographic characteristics of those with category 4 chest films were compared to the remainder of the study cohort and analyzed with multivariate logistic regression techniques using SAS statistical software. Knowing that the variables "continent of origin" and "incidence in country of origin" would be strongly correlated, 2 separate logistic regression models were created; the first model included the variables sex, age, continent of origin, and status at screening, and the second model included sex, age, incidence in country of origin, and status at screening. The 2 models were then compared in order to determine which model had stronger statistical significance.

4.4.8 Chart Review

In order to determine if the foreign-born individuals captured in both datasets were prevalent or incident cases, the medical charts for each were retrieved from the MCI records department and carefully reviewed. If it was apparent that the diagnosis of active TB disease was made on the basis of clinical and/or bacteriologic examinations prompted by the results of the initial screening chest x-ray (i.e., case was detected as a direct result of the radiographic screening process), then the individual was classified as having prevalent disease. Conversely, if active disease was not discovered during the course of the pre-immigration screening evaluation, yet the immigrant was subsequently diagnosed with active TB (i.e., months or years following screening) then the individual was classified as having incident disease.

4.4.9 Prevalent Cases

In an attempt to uncover factors that may be associated with having prevalent disease detected at time of screening, the demographic characteristics of the prevalent cases were compared to 2 study populations: 1) the remainder of the study cohort (i.e., those screened but not diagnosed with prevalent disease, regardless of chest x-ray category), and 2) those screened and found to have a category 4 chest x-ray (i.e., suggestive of active disease) but who were not diagnosed with prevalent disease. For each study variable, univariate analysis yielded crude odds ratios (and 95% confidence intervals) which were later adjusted using multivariate logistic regression. Again, 2 separate regression models were created in order to account for the strong correlation between continent of origin and incidence in country of origin.

In addition to univariate and multivariate analysis, the overall yield of prevalent cases for each category and sub-category of the initial screening chest x-ray (using CIC categorization scheme) was calculated to determine which sub-categories were most likely to lead to a diagnosis of active prevalent TB. Crude prevalence rates (per 100,000) were also generated for each country represented among those with prevalent disease for comparison with current TB prevalence rates in their respective countries of origin.

4.4.10 Incident Cases

Each incident case of TB arising in a cohort of foreign-born individuals screened for the disease prior to immigration represents a possible failure of the radiographic screening

process; for this reason, the medical charts of persons categorized as having incident disease were carefully scrutinized in order to determine if active disease was missed by the initial screening process and thus could have been prevented.

Excluding those individuals diagnosed with active prevalent disease at time of screening, the crude incidence rate of active disease was determined for the cohort of immigrants screened for the disease at the MCI over the study period. To account for the varying lengths of follow-up contributed to the study by each member of the cohort, the total number of person-months accrued during the study period was calculated; using this total, the overall crude incidence density rate of TB was determined (i.e., cases per 100,000 person-months of follow-up) for the cohort.

To identify possible factors associated with the development of incident disease, crude incidence density rates and incidence density rate ratios (with 95% confidence intervals) were calculated for each of the study variables (i.e., sex, age, continent of origin, incidence in country of origin, and status at screening). Furthermore, incidence density rates were also determined for each sub-category of the CIC categorization scheme (i.e., 0 – 4) in order to assess whether specific immigration screening x-ray categories were predictive of future incident disease.

5. RESULTS

5.1 Observer Agreement Study

5.1.1 Study Chest Films

Each of the 12 study participants independently read and categorized the 400 chest x-rays obtained from recent immigrants to 4 Canadian centres providing a total of 4,800 readings for analysis. Because of missing or illegible responses and/or incomplete or incorrect study identification numbers, 27 (0.6%) readings were discarded entirely. If forms were missing responses to only 1 or 2 questions, the remaining results were included in the analysis in order to utilize as much of the collected information as possible. Of the 4,773 readings available for analysis, 2,388 (50.0%) were for films performed in Canada, and 2,385 (50.0%) were for those performed overseas.

5.1.2 Clinical Findings

In total, 1,345 (28.2%) of the readings were judged to be completely normal (Category 0 CIC's current x-ray categorization scheme. The next most frequently assigned category was apical fibronodular/fibrocalcific lesions or apical microcalcifications (Category 4.1: 12.3%). Less than 10% (n=448) of the 4,773 readings were interpreted as being compatible with active TB disease (i.e., requiring urgent investigation and consideration for initiation of treatment while awaiting results).

The clinical findings for chest x-rays performed in Canada compared to those performed overseas are presented in Table 5.1. No notable differences were observed between the 2 sets of films with respect to these findings.

Table 5.1: Clinical findings on screening chest x-rays performed in Canada compared to those performed overseas

Clinical Finding	No. (%) of Canadian Films (n=2,388)	No. (%) of Overseas Films (n=2,385)
CIC X-Ray Category (Description)		
0 (Normal)	668 (27.9)	677 (28.3)
0.1 (Skeletal/soft tissue abnormalities)	35 (1.5)	20 (0.8)
0.2 (Abnormal great vessel/heart shadows)	33 (1.4)	23 (1.0)
0.3 (Abnormal hemi-diaphragms)	17 (0.7)	12 (0.5)
1.1 (Fibrous streak/band/scar)	69 (2.9)	56 (2.3)
1.2 (Bony islets)	10 (0.4)	17 (0.7)
2.1 (Pleural capping-smooth inferior border)	43 (1.8)	30 (1.3)
2.2 (Costophrenic angle blunting-below)	65 (2.7)	64 (2.6)
2.3 (Calcified nodules-hilum/mediastinum)	65 (2.7)	74 (3.1)
3.1 (Granuloma-unremarkable hilum)	215 (9.0)	255 (10.7)
3.2 (Granuloma-calc./enlarged hilar nodes)	45 (1.9)	78 (3.3)
3.3 (Calcified nodules-distinct borders)	170 (7.1)	197 (8.3)
3.4 (Calcified pleural lesions)	17 (0.7)	24 (1.0)
3.5 (Costophrenic angle blunting-above)	15 (0.6)	29 (1.2)
3.6 (Pleural capping-rough inferior border)	79 (3.3)	64 (2.7)
4.1 (Apical fibronodular/calcific lesions)	324 (13.6)	263 (11.0)
4.21 (Well-defined non-calcified nodules)	68 (2.8)	86 (3.6)
4.22 (Poorly-defined nodules/micronodules)	98 (4.1)	92 (3.9)
4.3 (Hilar or mediastinal mass/adenopathy)	27 (1.1)	26 (1.1)
4.4 (Lung mass or masses > 1 cm)	78 (3.3)	82 (3.4)
4.5 (Pleural fibrosis and/or effusion)	59 (2.5)	43 (1.8)
4.6 (Fibrosis/parenchymal lung disease)	156 (2.5)	140 (5.9)
4.7 (Any cavitating lesion)	32 (1.3)	36 (1.5)
Likely Active TB?*		
Yes	233 (9.8)	215 (9.1)
No	2133 (90.2)	2141 (90.9)

* responses may not add up to total because of missing responses to certain items on the study questionnaire

5.1.3 Technical Quality

As shown in Table 5.2, screening x-rays performed in Canada and those completed overseas were found to be similar with respect to the presence of artefacts and the visibility of the entire lung field. Significant differences existed, however, in the penetration and overall quality of the films. The majority (84.2%) of films performed in Canada were judged to have been ideally penetrated – the proportion of overseas x-rays with this finding, however, was only 48.3%. Similarly, 84.3% (n=2,005) of Canadian x-

rays were rated as being of excellent or good quality; less than half (46.8% or 1,112) of the films performed overseas received such a rating. In fact, 49.8% of overseas chest x-rays were judged to be of sub-optimal or poor quality, compared to only 15.5% of Canadian films. Of the 85 films rated as terrible, 79 (92.9%) were obtained overseas.

Table 5.2: Technical findings on screening chest x-rays performed in Canada compared to those performed overseas

Technical Finding*	No. (%) of Canadian Films (n=2,388)	No. (%) of Overseas Films (n=2,385)
Artefacts Present?		
Yes	364 (15.3)	295 (12.4)
No	2016 (84.6)	2066 (86.7)
Unsure	4 (0.2)	21 (0.9)
Entire Lung Field Visible?		
Yes	2328 (97.8)	2311 (97.1)
No	52 (2.2)	70 (2.9)
Penetration of X-Ray#		
Ideal	2005 (84.2)	1143 (48.3)
Over	192 (8.1)	280 (11.8)
Under	185 (7.8)	945 (39.9)
Quality of X-Ray#		
Excellent	421 (17.7)	194 (8.2)
Good	1584 (66.6)	918 (38.6)
Sub-optimal	325 (13.7)	894 (37.6)
Poor	42 (1.8)	291 (12.2)
Terrible	6 (0.3)	79 (3.3)

* responses may not add up to total because of missing responses to certain items on the study questionnaire

\# differences in ratings between Canadian vs. Overseas films significant; $p < 0.0001$

Although chest x-rays performed in Canada received higher ratings for penetration and quality than those taken overseas, considerable differences existed in the technical quality of films obtained from the 4 Canadian study centres. As illustrated in Table 5.3, the number of readings available for each centre ranged from 591 to 599 due to missing or incomplete responses. The proportion of x-rays rated as being of excellent or good quality was lowest in Calgary (71.7%) and highest in Montreal (90.5%).

Table 5.3: Comparison of technical findings on screening chest x-rays performed in 4 Canadian study centres

Technical Finding*	No. (%) of X-Rays by Canadian Centre			
	Montreal (n=597)	Calgary (n=591)	Edmonton (n=599)	Vancouver (n=597)
Artefacts Present?				
Yes	73 (12.2)	97 (16.4)	112 (18.7)	82 (13.7)
No	523 (87.6)	492 (83.2)	486 (81.1)	515 (86.3)
Unsure	1 (0.2)	2 (0.3)	1 (0.2)	0 (0)
Entire Field Visible?				
Yes	590 (99.0)	582 (98.5)	584 (97.7)	572 (96.1)
No	6 (1.0)	9 (1.5)	14 (2.3)	23 (3.9)
Penetration of X-Ray				
Ideal	520 (87.4)	436 (73.8)	534 (89.1)	515 (86.3)
Over	64 (10.8)	69 (11.7)	37 (6.2)	22 (3.7)
Under	11 (1.8)	86 (14.6)	28 (4.7)	60 (10.1)
Quality of X-Ray				
Excellent	130 (21.8)	86 (14.6)	101 (16.9)	104 (17.4)
Good	409 (68.7)	337 (57.1)	433 (72.5)	405 (68.0)
Sub-optimal	53 (8.9)	135 (22.9)	58 (9.7)	79 (13.3)
Poor	3 (0.5)	26 (4.4)	5 (0.8)	8 (1.3)
Terrible	0 (0)	6 (1.0)	0 (0)	0 (0)

* responses may not add up to total because of missing responses to certain items on the study questionnaire

5.1.4 Intra-observer Agreement

The kappa coefficients for intra-observer agreement are presented in Table 5.4. On average, the intra-observer agreement for each reader was in the fair to moderate range, however, the kappa values were considerably worse for some readers compared to others. There was no significant correlation between years of experience interpreting chest x-rays and intra-observer reliability, but with respect to medical specialty, radiologists had the highest agreement. Interestingly, the intra-observer agreement increased consistently with increasing clinical significance of the film – i.e., kappa coefficients were lowest when simply asked if the x-ray was normal or abnormal and highest for the question of whether or not the film was suggestive of active disease.

Table 5.4: Kappa coefficients for intra-observer agreement for clinical findings on Canadian and overseas screening chest x-rays

Clinical Findings on X-ray (CIC Categories)	Kappa Coefficients for Individual Readers												Average Kappas
	1	2	3	4	5	6	7	8	9	10	11	12	
General Category (0 – 4)	0.46	0.58	0.38	0.31	0.42	0.46	0.55	0.49	0.33	0.36	0.48	0.37	**0.43**
Normal vs. Abnormal (0 vs. 1 – 4)	0.49	0.50	0.34	0.22	0.37	0.42	0.55	0.50	0.20	0.37	0.47	0.35	**0.39**
Normal vs. Minor vs. Possible Active (0 vs. 1 – 3 vs. 4)	0.46	0.54	0.35	0.31	0.42	0.47	0.54	0.51	0.31	0.32	0.47	0.42	**0.43**
No TB vs. TB Infection/Disease (0 – 2 vs. 3 – 4)	0.49	0.63	0.40	0.32	0.41	0.46	0.58	0.48	0.42	0.38	0.49	0.36	**0.45**
No Active Disease vs. Possible Active (0 – 3 vs. 4)	0.42	0.65	0.39	0.39	0.52	0.58	0.49	0.56	0.42	0.30	0.48	0.46	**0.47**
Likely Active TB? (Yes/No)	0.65	0.71	0.57	0.42	0.73	0.40	0.66	0.65	0.47	0.19	0.41	0.54	**0.53**
Extent of Lung Involvement	0.41	0.68	0.55	0.56	0.51	0.28	0.59	0.65	0.37	0.23	0.54	0.48	**0.49**

Table 5.5: Kappa coefficients for inter-observer agreement for clinical and technical findings on Canadian and overseas screening chest x-rays

Clinical Findings on X-ray (CIC Categories)	Kappa Coefficients for Individual Readers												Average Kappas
	1	2	3	4	5	6	7	8	9	10	11	12	
Canadian X-rays (n=2,385)													
Technical Quality	0.18	0.16	0.14	0.07	0.16	0.16	0.11	0.16	0.18	0.11	0.09	0.02	**0.13**
Penetration of Film	0.26	0.28	0.16	0.19	0.23	0.17	0.20	0.26	0.25	0.19	0.23	0.24	**0.22**
General Category (0 – 4)	0.44	0.48	0.35	0.29	0.43	0.42	0.43	0.45	0.35	0.42	0.42	0.49	**0.42**
Normal vs. Abnormal (0 vs. 1 – 4)	0.49	0.52	0.33	0.28	0.46	0.42	0.43	0.49	0.36	0.43	0.41	0.49	**0.43**
Normal vs. Minor vs. Possible Active (0 vs. 1 – 3 vs. 4)	0.41	0.43	0.31	0.29	0.43	0.46	0.47	0.47	0.38	0.40	0.48	0.52	**0.38**
No TB vs. TB Infection/Disease (0 – 2 vs. 3 – 4)	0.44	0.49	0.37	0.28	0.44	0.45	0.43	0.45	0.39	0.41	0.48	0.46	**0.43**
No Active Disease vs. Possible Active (0 – 3 vs. 4)	0.37	0.39	0.32	0.35	0.46	0.36	0.36	0.38	0.32	0.40	0.37	0.45	**0.38**
Likely Active TB? (Yes/No)	0.40	0.41	0.28	0.28	0.37	0.09	0.15	0.40	0.31	0.20	0.29	0.35	**0.29**
Extent of Lung Involvement	0.32	0.42	0.39	0.41	0.42	0.35	0.38	0.37	0.33	0.32	0.36	0.39	**0.37**
Overseas X-rays (n=2,388)													
Technical Quality	0.12	0.14	0.03	0.12	0.21	0.19	0.19	0.20	0.22	0.12	0.10	0.01	**0.13**
Penetration of Film	0.31	0.33	0.18	0.33	0.33	0.31	0.38	0.28	0.33	0.18	0.23	0.23	**0.28**
General Category	0.44	0.48	0.41	0.40	0.46	0.44	0.42	0.43	0.38	0.41	0.44	0.41	**0.43**
Normal vs. Abnormal (0 vs. 1 – 4)	0.47	0.50	0.42	0.39	0.49	0.44	0.45	0.46	0.35	0.45	0.39	0.36	**0.43**
Normal vs. Minor vs. Possible Active (0 vs. 1 – 3 vs. 4)	0.41	0.43	0.38	0.36	0.42	0.42	0.38	0.44	0.34	0.39	0.44	0.39	**0.40**
No TB vs. TB Infection/Disease (0 – 2 vs. 3 – 4)	0.45	0.51	0.41	0.40	0.44	0.46	0.44	0.40	0.40	0.42	0.48	0.47	**0.44**
No Active Disease vs. Possible Active (0 – 3 vs. 4)	0.39	0.39	0.37	0.41	0.39	0.42	0.31	0.44	0.39	0.37	0.46	0.40	**0.40**
Likely Active TB? (Yes/No)	0.47	0.44	0.38	0.39	0.44	0.32	0.36	0.42	0.39	0.31	0.30	0.38	**0.38**
Extent of Lung Involvement	0.33	0.42	0.38	0.45	0.44	0.35	0.41	0.40	0.35	0.34	0.38	0.32	**0.38**

5.1.5 Inter-observer Agreement

The average kappa values for inter-observer agreement are presented in Table 5.5. Interestingly, the inter-observer agreement for clinical and technical findings on the overseas screening x-rays was somewhat higher than for films obtained in Canada, suggesting that the technical quality of the films did not affect the observer agreement.

For both Canadian and overseas films, the inter-observer agreement was best for the questions concerning the CIC category and clinical significance of the x-ray, however, the average kappa values were only in the fair to moderate range. Although the intra-observer agreement was highest for this question, the kappa coefficients for inter-observer agreement on both sets of films was only fair when asked "Is this likely active TB?". The 2 questions regarding the technical quality of the films (i.e., overall quality and penetration of the films) had the lowest inter-observer agreement for both sets of film. Average kappa values for both intra- and inter-observer agreement for all 12 readers are presented in Table 5.6.

Table 5.6: Average kappa coefficients for intra- and inter-observer agreement

Findings on Chest X-Ray (CIC Rating Scheme Categories)	**Intra-observer Agreement**	**Inter-observer Agreement**	
		Canadian Films (n=2,388)	**Overseas Films (n=2,385)**
Technical Quality of Film	n/a	0.129	0.128
Penetration of Film	n/a	0.222	0.284
General Category (0 – 4)	0.433	0.415	0.427
Normal vs. Abnormal (0 vs. 1 – 4)	0.399	0.426	0.432
Normal vs. Minor vs. Possible Active (0 vs. 1 – 3 vs. 4)	0.428	0.384	0.401
No TB vs. TB Infection/Disease (0 – 2 vs. 3 – 4)	0.451	0.433	0.440
No Active Disease vs. Possible Active (0 – 3 vs. 4)	0.472	0.377	0.396
Likely Active TB? (Yes/No)	0.533	0.292	0.375
Extent of Lung Involvement	0.487	0.370	0.382

5.1.6 Multi-observer Agreement

Similar to the results obtained for inter-observer agreement, there was notably higher agreement between all 12 readers for findings on the overseas x-rays when compared to those performed in Canada. The kappa coefficients for multi-observer agreement are presented in Table 5.7.

Table 5.7: Multi-observer agreement for clinical and technical findings on Canadian and overseas screening chest x-rays

Findings on Chest X-Ray (CIC Rating Scheme Categories)	Canadian Films (n=2,388)	Overseas Films (n=2,385)
Technical Quality of Film	0.059	0.077
Penetration of Film	0.204	0.260
General Category (0 – 4)	0.361	0.404
Normal vs. Abnormal (0 vs. 1 – 4)	0.431	0.438
Normal vs. Minor vs. Possible Active (0 vs. 1 – 3 vs. 4)	0.373	0.407
No TB vs. TB Infection/Disease (0 – 2 vs. 3 – 4)	0.464	0.467
No Active Disease vs. Possible Active (0 – 3 vs. 4)	0.405	0.442
Likely Active TB? (Yes/No)	0.301	0.361
Extent of Lung Involvement	0.272	0.279

There was fair to moderate multi-observer agreement for the clinical findings on both the Canadian and overseas screening x-rays. The kappa coefficients were highest for the comparison of normal vs. abnormal films and when asked whether or not the x-ray was suggestive of TB infection/active disease. On average, the 12 readers agreed with each other as a whole only 33% of the time (corrected for chance) when asked if the screening film was likely representative of active disease.

5.2 Prospective Cohort Study

5.2.1 Montreal Chest Institute (MCI) Records

Between May 1995 and December 1998, a total of 40,110 foreign-born individuals underwent chest x-ray screening for TB at the MCI. Of these, 3,677 (9.2%) were excluded from the study for the following reasons: duplicate records (n=1,491); missing chest x-ray results (n=929); initially screened prior to May 1995 (n=744); and under age 11 at the time of screening (n=513). As a result, immigration records for a total of 36,433 foreign-born persons screened during the study period were available for analysis.

5.2.2 Characteristics of the Study Cohort

Of the 36,433 foreign-born individuals screened at the MCI during the study period, 56.1% were male and 67.2% were less than 35 years of age at the time of screening (mean: 32.3 years, 95% CI 32.1, 32.4). A total of 887,038 person-months of follow-up were contributed by the cohort between May 1995 and December 1999 (mean: 24.3 months, 95% CI 24.2, 24.4). The majority (55.5%) of those screened were from high incidence countries. Of those for whom status at time of screening was known (n=24,037), 63.6% were refugee claimants while the remainder were visa holders.

Approximately one-third (33.8%) of the screened individuals arrived from Asia; in fact, close to 20% of the entire cohort was represented by only 5 Asian countries: Pakistan, Bangladesh, India, Sri Lanka, and China. Another 20% (n=6,622) entered Canada from countries on the European continent, and 19.2% (n=5,915) were from Africa. A total of 179 countries were represented among the screening cohort, however, the 10 leading

source countries were: China, Russia, Sri Lanka, Democratic Republic of Congo, Algeria, India, Mexico, Pakistan, Bangladesh, and France. Together, these countries accounted for 45.6% (n=14,823) of all immigrant applicants screened for TB at the MCI during the study period.

5.2.3 Clinical Findings on Screening Chest X-rays

The results of the screening chest films – as interpreted using the CIC's x-ray categorization scheme – for the 36,433 foreign-born individuals evaluated at the MCI during the study period are presented in Table 5.8.

Table 5.8: Clinical findings on screening chest x-rays of foreign-born individuals (n=36,433) screened for TB at the Montreal Chest Institute between May 1995 and December 1998

Clinical Significance of X-Ray	General Categories		Specific Categories	
	Category	No. (%)	Category	No. (%)
Normal	0	31211 (85.7)	0	31211 (85.7)
Non-Pulmonary Problems (Skeletal/ soft tissue abnormalities, abnormal great vessel, heart shadows, hemi-diaphragms)	1	515 (1.4)	0.1	187 (0.5)
			0.2	78 (0.2)
			0.3	250 (0.7)
Minor Findings (Fibrous streak/band/ scar, bony islets, apical pleural capping with smooth inferior border, costophrenic angle blunting below horizontal, calcified hilar/mediastinal nodules)	2	1725 (4.7)	1.1	82 (0.2)
			1.2	7 (0.02)
			2.1	464 (1.3)
			2.2	420 (1.2)
			2.3	752 (2.1)
Possible TB Infection (Granulomas with unremarkable hilum/calcified or enlarged hilar lymph nodes, calcified pulmonary nodules with distinct borders, calcified pleural lesions, costophrenic angle blunting below horizontal, apical pleural capping with rough inf. border)	3	919 (2.5)	3.1	516 (1.4)
			3.2	193 (0.5)
			3.3	165 (0.4)
			3.4	3 (0.01)
			3.5	16 (0.04)
			3.6	26 (0.07)
Possible TB Disease (Apical fibronodular/fibrocalcific lesions, well-defined non-calcified nodules, poorly-defined nodules, hilar or mediastinal mass/lymphadenopathy, lung mass > 1cm, pleural fibrosis/effusion, interstitial fibrosis/parenchymal lung disease/acute pulmonary disease, any cavitating lesion)	4	2064 (5.7)	4.1	1228 (3.4)
			4.21	144 (0.4)
			4.22	48 (0.1)
			4.3	128 (0.4)
			4.4	88 (0.2)
			4.5	70 (0.2)
			4.6	319 (0.9)
			4.7	39 (0.1)

5.2.4 Category 4 Screening Chest X-rays

The characteristics of the individuals with category 4 screening chest films, compared to those judged as having an x-ray incompatible with active disease (i.e., Categories 0-3) are illustrated in Table 5.9.

Table 5.9: Demographic characteristics of individuals with screening x-rays suggestive of active disease (Category 4) compared to those with Category 0-3 x-rays

Characteristic*	Category 4 (n=2,064)	Category 0-3 (n-34,369)	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex				
Male	1246	19197	1.20 (1.10, 1.32)	1.43 (1.30, 1.58)
Female	818	15172	1	1
Age				
< 15	37	1481	0.53 (0.38, 0.73)	0.55 (0.39, 0.77)
15 – 24	177	7503	0.50 (0.42, 0.59)	0.50 (0.42, 0.59)
25 – 34	695	14588	1	1
35 – 44	487	6635	1.54 (1.37, 1.74)	1.55 (1.38, 1.75)
45 – 54	218	2178	2.10 (1.79, 2.47)	2.19 (1.87, 2.57)
55 – 64	200	1111	3.78 (3.20, 4.48)	4.19 (3.52, 4.97)
65 +	250	873	6.02 (5.13, 7.06)	6.89 (5,84, 8.12)
Continent				
Asia	772	10211	1	1
Africa	378	5537	0.90 (0.80, 1.02)	1.07 (0.94, 1.21)
Europe	373	6250	0.79 (0.69, 0.89)	0.75 (0.66, 0.85)
North America	24	565	0.56 (0.37, 0.85)	0.66 (0.43, 1.00)
Central America	264	2776	0.78 (0.66, 0.93)	0.93 (0.78, 1.11)
South America	208	3293	0.84 (0.71, 0.98)	1.05 (0.89, 1.25)
Caribbean	107	1826	0.78 (0.63, 0.95)	0.84 (0.68, 1.04)
Oceania	2	43	0.62 (0.15, 2.54)	0.75 (0.18, 3.12)
Incidence in Country of Origin#				
Low	196	4116	0.73 (0.62, 0.86)	0.75 (0.63, 0.89)
Intermediate	618	9562	1	1
High	1214	16824	1.12 (1.01, 1.23)	1.07 (0.97, 1.19)
Status at Screening				
Visa Holder	521	8224	1	1
Refugee Claimant	1009	14283	1.12 (1.00, 1.25)	1.15 (1.02, 1.30)

* results may not add up to total because of missing values for continent (n=3,904), incidence (n=3,904), and status at screening (n=12,396)

\# Incidence rates: Low (<24 cases per 100,000); Intermediate (25-99 per 100,000), and High (>100 per 100,000) based on 1999 estimates by the WHO

On multivariate analysis using logistic regression, sex, age, and status at immigration were significantly associated with having a category 4 screening chest x-ray. Being of European or North American origin, however, was not associated with having a chest film suggestive of active disease compared to persons from Asia.

5.2.5 Maladies à Déclarations Obligatoires (MADO) Records

A total of 883 cases of TB were diagnosed between June 1995 and December 1999 among foreign-born individuals living in Montreal, Laval, and the region of Monterégie; these individuals were subsequently reported to local public health authorities and entered into MADO (reportable disease database for the province of Québec). Of these, 151 (17.1%) had been diagnosed prior to the study commencement date and were thus excluded from the study; one duplicate entry was also deleted. In total, the records of 731 foreign-born persons diagnosed with TB during the study period were available to be matched to the dataset of individuals who underwent chest x-ray screening at the MCI.

5.2.6 Matching of Records from the MCI and MADO Databases

In total, 75 foreign-born individuals radiographically screened for TB at the MCI between May 1995 and December 1998 were identified in the MADO database of TB cases reported between June 1995 and December 1999. Upon performing a manual re-check of the data, an additional three matches were discovered for a total of 78 matches. After verifying the available information, six of the matched individuals were discovered to have been diagnosed prior to their respective immigration screening evaluations and were thus excluded from the study (i.e., diagnosis resulted from passive case detection

prior to the individuals undergoing their immigration medical exam). Therefore, a total of 72 individuals screened for TB at the MCI were subsequently diagnosed with the disease.

5.2.7 Determination of Prevalent or Incident TB Cases

After reviewing the medical charts of the 72 individuals diagnosed with active TB disease, 53 (73.6%) were determined to have been prevalent cases – i.e., the diagnosis came as the direct result of medical investigations prompted by the initial screening examination. 19 individuals (26.4%) were diagnosed with the disease between 6 and 30 months following their initial screening evaluation and were thus classified as incident cases.

5.2.8 Prevalent Cases – Entire Screening Cohort

The demographic characteristics of those individuals diagnosed with prevalent TB compared to those who were screened but not found to have active disease are presented in Table 5.10. Individuals diagnosed with prevalent TB were significantly older (mean: 37.7 years, 95% CI 33.1, 42.4) than the remainder of the cohort (mean: 32.3 years, 95% CI 32.1, 32.4) even though the majority (60.4%) were under 35 years of age at the time of screening.

In multivariate logistic regression, the variables sex, age, and incidence in country of origin were significantly associated with a diagnosis of prevalent disease at time of screening compared to the remainder of the screening cohort. Males, immigrants arriving

from high incidence countries, and older adults were more likely to be diagnosed with TB as a result of the immigration screening process.

Table 5.10: Demographic characteristics of individuals diagnosed with prevalent active TB at time of screening compared to those screened but not found to have active disease

Characteristic	Prevalent TB (n=53)	All Screened (n=36,380)	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex				
Male	38	20405	1.98 (1.09, 3.61)	2.01 (1.08, 3.73)
Female	15	15975	1	1
Age				
< 15	0	1518	-	-
15 – 24	10	7670	0.90 (0.43, 1.91)	0.89 (0.42, 1.87)
25 – 34	22	15261	1	1
35 – 44	7	7115	0.68 (0.29, 1.60)	0.67 (0.29, 1.57)
45 – 54	4	2392	1.16 (0.40, 3.37)	1.21 (0.42, 3.53)
55 – 64	5	1306	2.66 (1.00, 7.02)	3.15 (1.17, 8.46)
65 +	5	1118	3.10 (1.17, 8.21)	4.51 (1.66, 12.2)
Continent				
Asia	21	10962	1	1
Africa	15	5900	1.32 (0.68, 2.58)	1.38 (0.70, 2.71)
Europe	9	6613	0.71 (0.33, 1.55)	0.90 (0.41, 1.98)
North America	0	589	-	-
Central America	3	2938	0.53 (0.16, 1.79)	0.61 (0.18, 2.07)
South America	2	3499	0.30 (0.07, 1.27)	0.90 (0.21, 3.85)
Caribbean	3	1930	0.81 (0.24, 2.72)	1.22 (0.36, 4.13)
Oceania	0	45	-	-
Incidence in Country of Origin*				
Low	0	4311	-	-
Intermediate	8	10173	1	1
High	45	17993	3.18 (1.49, 6.74)	2.61 (1.23, 5.54)
Status at Screening				
Visa Holder	10	8734	1	1
Refugee Claimant	43	15250	2.46 (1.24, 4,90)	1.85 (0.91, 3.74)

* Incidence rates: Low (<24 cases per 100,000); Intermediate (25-99 per 100,000), and High (>100 per 100,000) based on 1999 estimates by the WHO

5.2.9 Percent Yield of Prevalent Cases by Chest X-ray Category

Table 5.11 presents the percent yield of prevalent cases observed for each category 4 sub-category.

Table 5.11: Percent (%) yield of prevalent active TB cases for persons with Category 4 screening chest x-rays

Specific Category	Description	No. (%) of Category 4 (n=2,064)	No. (%) of Prevalent Cases (n=53)	Percent (%) Yield
4.1	Apical fibronodular/calcific lesions or microcalcifications	1228 (59.5)	2 (3.8)	0.16
4.21	Well-defined non-calcified nodules or micronodules	144 (7.0)	3 (5.7)	2.1
4.22	Poorly-defined non-calcified nodules or micronodules	48 (2.3)	0 (0)	0
4.3	Hilar or mediastinal mass or lymphadenopathy	128 (6.2)	2 (3.8)	1.6
4.4	Lung mass < 1 cm	88 (4.3)	7 (13.2)	8.0
4.5	Poorly or non-calcified pleural fibrosis and/or effusion	70 (3.4)	1 (1.9)	1.4
4.6	Interstitial fibrosis, parenchymal lung disease, acute pulmonary disease	319 (15.5)	28 (52.8)	8.8
4.7	Any cavitating lesion	39 (1.9)	9 (17.0)	23.1
Total		2064 (100.0)	53 (100.0)	2.6

Although only 39 (1.9%) of the 2,064 immigrant applicants with screening films suggestive of active disease were described as having "any cavitating lesion", this sub-category provided the greatest yield of prevalent cases. Despite being the most common clinical finding, only 2 of the 1,228 (0.16%) individuals with a category 4.1 screening chest film were subsequently diagnosed with prevalent active disease upon further investigation.

As shown in Table 5.12, the 53 individuals with prevalent active TB, compared to those with category 4 screening chest films but without prevalent active disease, were more likely to be from countries with a high incidence of TB.

Table 5.12: Demographic characteristics of individuals diagnosed with prevalent active TB at time of screening compared to those with category 4 x-rays but not diagnosed with active TB

Characteristic	Prevalent TB (n=53)	Category 4 X-Ray (n=2,064)	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex				
Male	38	1207	1.69 (0.92, 3.09)	1.42 (0.75, 2.71)
Female	15	804	1	1
Age				
< 15	0	37	-	-
15 – 24	10	168	1.82 (0.84, 3.91)	1.64 (0.75, 3.59)
25 – 34	22	672	1	1
35 – 44	7	480	0.45 (0.19, 1.05)	0.45 (0.19, 1.08)
45 – 54	4	214	0.57 (0.19, 1.68)	0.59 (0.20, 1.76)
55 – 64	5	195	0.78 (0.29, 2.10)	0.86 (0.31, 2.40)
65 +	5	245	0.62 (0.23, 1.66)	0.84 (0.30, 2.35)
Continent				
Asia	21	751	1	1
Africa	15	364	1.47 (0.75, 2.89)	1.23 (0.62, 2.45)
Europe	9	363	0.89 (0.40, 1.96)	1.18 (0.53, 2.66)
North America	0	24	-	-
Central America	3	161	0.67 (0.20, 2.26)	0.64 (0.19, 2.19)
South America	2	206	0.35 (0.08, 1.49)	0.87 (0.19, 3.82)
Caribbean	3	104	1.03 (0.30, 3.52)	1.51 (0.43, 5.30)
Oceania	0	2	-	-
Incidence in Country of Origin*				
Low	0	195	-	-
Intermediate	8	610	1	1
High	45	1170	2.93 (1.37, 6.26)	2.56 (1.19, 5.50)
Status at Screening				
Visa Holder	10	510	1	1
Refugee Claimant	43	967	2.27 (1.13, 4.55)	1.73 (0.84, 8.57)

* Incidence rates: Low (<24 cases per 100,000); Intermediate (25-99 per 100,000), and High (>100 per 100,000) based on 1999 estimates by the WHO

5.2.10 Prevalence and Country of Origin

Individuals from a total of 28 countries were diagnosed with prevalent active TB. Close to one-third of all prevalent cases were from only 3 countries: Democratic Republic of Congo (11.3%), Pakistan (11.3%), and India (7.5%); additionally, 3 active cases were detected among persons from each of the following 4 countries: Haiti, Russian Federation, Somalia, and Ukraine.

5.2.11 Incident Cases

Over the course of the 4 ½ year study period, an additional 19 cases of active TB developed among the cohort of applicants previously screened at the MCI between May 1995 and December 1998. These incident cases were judged to be free of the disease at the time of radiographic screening and potentially represent failures of the immigration screening process.

After accounting for the 53 individuals diagnosed with prevalent active disease at time of screening, the remainder of the cohort (n=36,380) contributed a total of 884,494 person-months of follow-up (mean: 13.3 months, 95% CI 8.9, 17.8). The corresponding incidence density rate for foreign-born persons previously screened for TB at the MCI between May 1995 and December 1998 was 25.7 cases per 100,000 person-years of follow-up.

Table 5.13 shows the demographic characteristics and corresponding incidence density rates and rate ratios for the 19 individuals diagnosed with incident TB disease.

Table 5.13: Incidence density rates (per 100,000 person-years of follow-up) and incidence rate ratios for selected demographic characteristics

Characteristic	No. Incident Cases (n=19)	Person Years of Follow-up At Risk (n=73,707)	Incidence Density Rate (per 100,000 person-years)	Incidence Rate Ratio (95% CI)
Sex				
Male	11	41441	26.5	1.07 (0.43, 2.66)
Female	8	32266	24.8	1
Age				
< 15	0	3162	-	-
15 – 24	5	15389	32.5	1.11 (0.37, 3.20)
25 – 34	9	30805	29.2	1
35 – 44	4	14546	27.5	0.94 (0.29, 3.06)
45 – 54	0	4887	-	-
55 – 64	0	2655	-	-
65 +	1	2265	44.2	1.51 (0.19, 11.91)
Continent				
Asia	9	19874	45.3	1
Africa	7	10588	66.1	1.46 (0.54, 3.91)
Europe	1	12441	8.0	0.18 (0.02, 1.40)
North America	0	1102	-	-
Central America	1	5223	19.1	0.42 (0.05, 3.33)
South America	0	8240	-	-
Caribbean	1	3601	27.8	0.61 (0.08, 4.84)
Oceania	0	76	-	-
Incidence in Country of Origin*				
Low	0	7739	-	-
Intermediate	4	20136	19.9	1
High	15	33289	45.1	2.27 (1.16, 3.37)
Status at Screening				
Visa Holder	3	14113	21.3	1
Refugee Claimant	16	23516	68.0	3.20 (1.94, 4.45)

* Incidence rates: Low (<25 per 100,000), Intermediate (25 – 99 per 100,000), and High (>100 per 100,000) based on 1999 estimates by the WHO

On average, the 19 incident cases were younger (mean: 31 years, 95% CI 25.5, 36.5) than the 53 prevalent cases (mean: 37.7 years, 95% CI 33.1, 42.4). Although close to half (47.4%) of the incident cases were diagnosed in persons aged 25 – 34 years, the age-

specific incidence density rate was highest among individuals 65 year and older (44.2 cases per 100,000 person-years of follow-up "at-risk").

5.2.12 Incident Cases by Screening Chest X-ray Category

Of the 19 cases of incident TB disease diagnosed among the cohort of foreign-born individuals applying for permanent residence in Canada, 15 (78.9%) had been classified as having a completely normal pre-immigration chest radiograph; 4 (21.1%) had a screening x-ray suggestive of active disease (i.e., Category 4) but were not diagnosed with TB. The specific radiographic findings on the screening chest x-rays of the 19 incident cases are presented in Table 5.14.

Table 5.14: Findings on the screening chest x-rays for immigrant applicants subsequently diagnosed with incident TB disease

Screening Chest X-Ray Findings	No. (%) of Cases	Person -years of follow-up	Incidence Density Rate (per 100,000 person-years)	Incidence Rate Ratio (IRR) (95% CI)
General Category				
0 (Normal)	15 (78.9)	63589	23.6	1
4 (Potential Active Disease)	4 (21.1)	3684	108.5	4.60 (3.60, 5.60)
Specific Category				
0 (Normal)	15 (78.9)	63589	23.6	1
4.1 (Apical fibronodular lesions)	1 (5.3)	2321	43.1	1.83 (0.24, 13.8)
4.21 (Well-defined non-calcified nodules)	1 (5.3)	264	379.6	16.09 (2.13, 121.9)
4.4 (Lung mass/es > 1 cm)	1 (5.3)	139	722.0	31.36 (4.14, 237.6)
4.6 (Fibrosis/parenchymal disease)	1 (5.3)	509	196.6	8.34 (1.10, 63.1)

Although the majority (78.9%) of individuals diagnosed with incident TB disease had completely normal screening chest x-rays, the incidence density rate was almost 5 times

higher (IRR 4.60, 95% CI 3.60, 5.60) for foreign-born persons found to have a screening film suggestive of active disease.

5.2.13 Possible Failures of the Radiographic Screening Process

The underlying assumption of the pre-immigration radiographic screening process is that non-immunocompromised persons with active pulmonary TB at time of screening (i.e., prevalent disease) will almost always present with an abnormal chest x-ray. [26] Accordingly, only foreign-born persons with a screening film suggestive of either active disease or TB infection will be further investigated, and if prevalent active disease or latent TB infection is confirmed, appropriate treatment and follow-up is recommended. A detailed examination of each of the 19 incident cases' radiographic screening results and subsequent investigation and/or follow-up was conducted to determine whether or not TB disease was indeed present at the time of screening and should have, in theory, been detected and treated upon arrival.

Of the 19 incident cases that developed after screening, 15 (78.9%) had been screened as having a completely normal pre-immigration chest x-ray and thus would not have undergone further medical examination. 4 (21.1%) of the 19 incident cases, however, presented at the time of screening with chest x-rays suggestive of active TB but were not at that time diagnosed with disease; the demographic and clinical characteristics of these 4 individuals are found in Table 5.15.

Table 5.15: Demographic and clinical characteristics of immigrant applicants with a screening chest x-ray suggestive of active disease who were subsequently diagnosed with TB

Case	Age/ Sex	Continent of Origin	Status at Screening	X-Ray Category	Smear (+/-)	Culture (+/-)	INH or F/U by MD?	INH or F/U by Case?
1	31/F	Asia	Visa Holder	4.1	-	-	No	No
2	69/M	Europe	Refugee	4.21	-	-	No	No
3	39/F	Asia	Refugee	4.4	-	-	Yes	Refused
4	33/F	Caribbean	Visa Holder	4.6	-	-	Yes	Refused

The mean age of the 4 incident cases who had abnormal screening chest x-rays was 43 years (median: 33 years); 3 were female, and all were from high incidence countries. A mean of 18.3 months (range: 12 to 30 months) elapsed between the initial screening x-ray and the clinical diagnosis of TB. At the time of the medical evaluation, each of the 4 had sputum specimens collected for purposes of smear microscopy and bacteriological culture, however, none of the specimens from the 4 patients were positive for AFB and none grew *Mycobacterium tuberculosis* on culture.

Information on the clinical impression and subsequent follow-up and treatment recommendations made by the evaluating physicians at the MCI for each of these 4 incident cases was obtained from the patients' medical charts. Although the clinical notes indicated that a diagnosis of LTBI or old, healed TB was suspected for each of these 4 cases, only 2 of the 4 individuals were prescribed INH treatment – neither of the 2 complied with these recommendations.

The other 2 incident cases, however, were not prescribed treatment for LTBI by the evaluating physician. In one case, although the clinical notes clearly stated, "...could

benefit from INH prophylaxis", the individual did not begin treatment nor did she return for the recommended follow-up. The most probable explanation for her non-compliance, and consequently his progression to active disease, would be that she could not afford to pay for such services because she did not have health insurance. The second individual was not prescribed INH treatment likely because of his advanced age (69 yrs).

In theory, each of the 4 incident cases of TB that developed among those previously screened for the disease could have been prevented if the individuals had been compliant with the prescribed treatment and/or recommended follow-up and if health insurance was readily available, thus, they do not necessarily indicate failure of the immigration screening program but rather highlight failures in the follow-up mechanisms.

6. DISCUSSION

6.1 Summary of Findings

Chest radiographs performed overseas for the purposes of pre-immigration screening were rated by the study participants as being of significantly poorer technical quality than those obtained in Canada post-arrival, however, significant variation existed in the technical quality of the post-landing chest films performed in the 4 Canadian study centres. In general, x-rays obtained in Montreal rated the best in terms of overall quality, while those from Calgary were interpreted as being of the poorest overall quality.

There was moderate intra-observer agreement for clinical findings on the Canadian and overseas screening chest x-rays. Interestingly, the technical quality of the screening x-rays did not appear to influence the kappa coefficients for inter-observer agreement although they were lower than those for intra-observer agreement. Overall, agreement was worst for technical quality, extent of lung involvement, and the question of whether or not the film was suggestive of active TB. The best agreement was for the clinical significance of the x-rays (i.e., the major diagnostic classification).

Of the 36,433 foreign-born individuals who underwent pre-immigration radiographic screening at the MCI between May 1995 and December 1998, 53 (0.145%) were diagnosed with prevalent active TB. Compared to persons screened but not found to have active disease, the odds of being diagnosed with prevalent TB were significantly increased for males, immigrants arriving from countries with a high incidence of TB, and persons 55 years of age and older.

19 incident cases of TB were diagnosed among the cohort post-screening. A total of 73,708 person-years of follow-up were contributed by the cohort for an incidence density rate of 25.7 cases per 100,000 person-years. The incidence of TB was highest among refugees, individuals from Asia and Africa, persons from high incidence countries, and applicants with a screening x-ray suggestive of active disease (Category 4). However, 15 (78.9%) of those with incident TB had been classified as having a normal chest x-ray at the time of screening.

6.2 Study Limitations

The observer agreement study was limited by the fact that, in order to ensure independent results, the 12 study participants received no guidance or instructions before using the CIC x-ray categorization scheme. The degree of familiarity and experience in interpreting chest films using the CIC x-ray categorization scheme varied considerably among the study physicians and thus may have accounted for some of the disagreement between readers.

Sizeable losses to follow-up may have limited the results of the prospective cohort study. Many of the foreign-born who initially underwent radiographic screening at the MCI may have either moved to other regions of Quebec or Canada or had their applications for permanent residence rejected, forcing them to return to their countries of origin. If any of these individuals were later diagnosed with active TB, this information would have been reported to their respective health departments and thus not available for inclusion in this study – i.e., only cases reported to the public health units in Montreal, Laval, and the

region of Monterégie were extracted from the MADO database for the purposes of this study. As a result, the incidence of TB among the cohort of individuals screened at the MCI during the study period may have been underestimated. Also, the relatively short length of follow-up (1 – 4½ years) may not have allowed sufficient time for incident cases to have been detected given that the risk of progression to active disease may persist for several decades following infection with the TB bacilli. It has been well documented, however, that the risk of progressing to active disease is highest in the first 2 years following arrival in which case the long-term incidence of disease in this cohort may have in fact been overestimated. [1,5-11]

6.3 Study Strengths

Several strengths have been identified in both the observer agreement and prospective cohort studies. In measuring the reliability of the chest x-ray in screening immigrants for TB, the study participants represented a variety of medical specialties and had varying years of experience in interpreting chest films. This allowed the investigator to assess whether observer agreement was influenced by specialty training (e.g., radiology, infectious disease, respirology) and/or years of experience. The inclusion of both pre- and post-landing chest x-rays for each of the 200 prospective immigrants in the study also provided for the opportunity to evaluate the effect of technical quality of screening films on the extent of observer agreement. Finally, the design of the study ensured that the readings were done independently, and that participants were blinded to the immigrant's subsequent diagnosis as well as the location (i.e., overseas, Canadian) where the x-ray was done.

As a single-centre prospective cohort study, it was possible to directly calculate the incidence of active TB among foreign-born persons previously screened for the disease at the MCI between May 1995 and December 1998. As well, the large number of individuals included in the study (n=36,433) ensured a high degree of statistical confidence in the results. Information for both the dependent and independent variables was retrieved from the MCI database and the public health department's reportable disease database (MADO), eliminating the potential for information bias and guaranteeing the completeness of the data. Finally, the study population was heterogeneous, and very closely resembled the target population of foreign-born individuals applying for permanent residence in Canada ensuring the generalizability of the results.

6.4 Interpretation of Findings

6.4.1 Observer Agreement of Immigration Screening Chest X-Rays

In mass screening conducted by Yerushalmy over 30 years ago, intra-observer agreement was 78.5% for the diagnosis of active pulmonary TB. [76] More recent studies have focused on the observer agreement in interpreting chest films taken for the purposes of pre- and post-immigration screening. In work published by Graham et al., for example, the kappa coefficient for overall intra-observer agreement was 0.621 and ranged from 0.588 for the question of whether or not the screening x-ray was suggestive of active disease, to 0.722 for the comparison of whether the chest film was normal or abnormal. [80] The current study, involving 12 physicians reading 400 pre- and post-immigration chest x-rays taken both overseas and in Canada, found considerably lower intra-observer

agreement – kappa coefficients ranged from 0.399 for the question of whether or not the screening x-ray was normal or abnormal to a high of only 0.533 for the question, "Is this likely active TB".

In each of the studies described above, the kappa coefficients for inter-observer agreement were notably lower than those obtained for intra-observer agreement. For example, in Yerushalmy's evaluation, the inter-observer agreement was 70.0% compared to 78.5% for intra-observer agreement. [76] Similarly, in Graham et al.'s study, the inter-reader kappa values ranged from 0.439 for overall agreement to 0.561 for the question of whether or not the screening x-ray was normal or abnormal (recall that intra-observer values ranged from 0.588 to 0.621). [80] Consistent with the results of both of these studies, the extent of inter-observer agreement in interpreting the pre- and post-immigration screening films of the current study was considerably lower than the intra-observer agreement – kappa statistics ranged from 0.292 to 0.433 for the Canadian films and from 0.375 to 0.440 for the x-rays obtained overseas (compared to 0.399 to 0.533 for intra-observer agreement).

There was fair to moderate multi-observer agreement when judging the clinical findings on both the Canadian and overseas screening x-rays in the current study. Kappa coefficients varied from 0.331 for the question, "Is this likely active TB?" to a high of 0.466 when asked whether the chest film was not clinically significant or suggestive of possible TB infection/disease. In comparison, the overall kappas for multi-observer agreement reported by Graham et al., were consistently higher, ranging from 0.510 for

overall agreement to 0.623 for the question of whether or not the screening x-ray was normal. [80]

One would not necessarily expect the results of the current study and those of Graham and colleagues to be comparable, however, mainly because the number of study participants involved in both studies differed considerably. In the current study, observer agreement was measured between 12 physicians from several locations across Canada, each of whom had varying experience in interpreting chest x-rays for the purposes of TB screening. Graham et al.'s study measured the agreement between only 3 physicians, each with specialized training in chest radiology. Given that each of the 3 radiologists in Graham et al.'s study were from the same institution, it is possible that they could have consulted with each other when interpreting the x-rays, even though they were read blindly, which could have theoretically increased the extent of agreement between them.

In perhaps the most definitive study on observer agreement with respect to TB, the IUATLD measured the extent of agreement between 90 experienced physicians interpreting chest x-rays taken for the purposes of mass screening in Norway. [77-79] The multi-observer agreement between the 90 physicians was moderate to good, with indices of agreement ranging from 40 when asked if the chest x-ray revealed any abnormality in the lymph nodes to 72 for the question, "Is there a cavity present?" [77-79] Interestingly, the extent of overall agreement between physicians was notably higher in the IUATLD study than in both the current study and the one conducted by Graham et al.

6.4.2 Yield of Prevalent TB Cases Detected Through Radiographic Screening

In this study, the yield of prevalent active TB cases detected as a result of pre-immigration medical screening was 0.145% (53/36,433). Similar results were obtained in a Swiss study where 69 active cases of TB were diagnosed among 43,803 foreign-born workers screened for the disease upon arrival (yield=0.16%). [15] A much lower yield, however, was detected in 2 additional studies – conducted in London, England and Denver, U.S. – where only 5 prevalent TB cases were detected per 10,000 screened persons. [17,65]

Several studies have demonstrated an increased yield of TB case-detection when the proportion of immigrants from TB endemic countries is high among those being screened. In 2 studies conducted by Ormerod, for instance, 85.9% and 86.4% of those undergoing radiographic screening on arrival to the U.K. were from countries with a high incidence of TB such as India and Pakistan. The corresponding yield of active cases detected as a result of immigration screening in both studies was 0.45% and 0.65%. [66,67] These percentages are much higher, however, than those obtained in the current study at the MCI – in this study, only 0.22% of the foreign-born individuals who arrived from high incidence countries (55.4% of the cohort) were diagnosed with prevalent active TB as a result of radiographic screening.

Several studies have also documented a high prevalence of active TB detected at the time of screening among refugee populations. For example, in the Swiss study discussed earlier, 42 of 4,512 (0.93%) of refugees radiographically screened for TB upon arrival

were diagnosed with prevalent disease. [15] Similarly, of 9,328 southeast Asian refugees who underwent x-ray screening for TB in Seattle between January 1980 and December 1981, 78 (0.84%) had active TB. [16] Although the yield of prevalent disease detected among refugees was relatively high in these 2 studies, the current study conducted at the MCI saw only 0.19% of refugees diagnosed with TB at the time of screening, however, it is important to note that the prevalence of active disease detected by the radiographic screening process was more than 2 times higher (OR 2.47, 95% CI 1.24, 4.91) for refugees than for visa holders.

6.4.3 Predicting Future Incident Cases of Active Disease

In this study, 19 incident cases of TB were diagnosed among the 36,380 foreign-born individuals who were previously screened for the disease at the MCI between May 1995 and December 1998 and who were not diagnosed with prevalent active TB. The corresponding crude annual incidence rate over the 4½ years of follow-up was 25.7 per 100,000 person years. Of the 19 incident cases, 15 (78.9%) had a completely normal screening film; 4 (21.1%) had a screening x-ray suggestive of active disease.

Other studies have also documented a persistently high incidence of TB among foreign-born persons previously screened for the disease in low incidence countries. In a historical cohort study conducted in Australia, for example, the crude annual incidence of TB among 24,610 predominantly Southeast Asian refugees was 74.9 per 100,000 person-years of follow-up. [45]

Similar studies have also demonstrated that a considerable proportion of individuals diagnosed with incident TB post-screening had presented with a completely normal chest x-ray. For example, in a Danish study involving 286,250 adult tuberculin reactors who were followed for 16-years after undergoing mass radiographic screening for TB, 1,133 incident cases of TB were diagnosed – of these, 867 (76.5%) had had a normal chest x-ray. [18] In another study conducted in Czechoslovakia, approximately 71% of those diagnosed with bacteriologically confirmed TB between 1965 and 1972 had a chest x-ray that, prior to the diagnosis of TB, had been considered as normal. [81] Finally, of 20,786 recent Asian immigrants to Canada with a normal screening x-ray, 30 were diagnosed with active pulmonary TB during the 4 years following arrival for an average annual incidence rate of 80 per 100,000 persons. [14]

Poor intra- and inter-observer agreement of the chest x-ray as a screening tool for TB may explain how an individual judged as having a normal screening film could subsequently be diagnosed with pulmonary TB. As demonstrated in the observer agreement studies discussed previously, significant variability exists in the interpretation of chest x-rays for the presence of TB. [76-80] For example, in the current x-ray reliability study involving 200 consecutive immigrants referred for medical surveillance upon arrival to Canada, the average intra-observer kappa coefficient for the question, "Is this likely active TB?" was only 0.533. Inter-observer agreement for the same question was even lower, with kappa values ranging from 0.292 for Canadian films to 0.375 for x-rays done overseas. Thus, it is entirely possible that an individual's chest film could be interpreted as normal by one physician, but if it had been read on a different day by either

the same physician or a different physician, may actually have been judged as a Category 4 chest x-ray, prompting further medical investigations and possibly yielding a diagnosis of prevalent active disease.

To further evaluate the potential impact of misclassification, consider the current prospective cohort study involving 36,433 immigrant applicants screened for TB at the MCI between May 1995 and June 1998. Of these, 31,211 (91.8%) were initially classified as having a completely normal screening x-ray (Category 0); only 2,064 (5.7%) were judged as having a screening film suggestive of active disease (Category 4). In the observer agreement study conducted earlier, approximately 21.3% of the films initially classified as Category 0 were subsequently judged to be Category 4 when read the second time (by either the same physician or a second physician). If these results were applied to the prospective cohort study, approximately 6,647 of the 31,211 immigrant applicants screened as having a normal chest x-ray may actually have been Category 4 if the x-ray had been read a second time or by a different physician. Given that the yield of prevalent active cases was 0.145%, an additional 10 cases of TB may have possibly been detected at the time of screening if these 6,647 individuals had not been misclassified.

The most plausible explanation for the diagnosis of active pulmonary TB in individuals previously screened as having a normal chest x-ray, particularly in the context of immigration screening, is the subsequent reactivation of remotely acquired latent TB infection. [9,84] It has been well documented that many foreign-born individuals arriving in low-incidence countries are carrying LTBI with them upon arrival that may reactivate

post-landing. [4] Although the risk of progressing to active disease is greatest in the first 2-5 years, it may persist for decades after arrival. [1,5-11]

As discussed previously, individuals with LTBI are asymptomatic and will, 80% to 90% of the time, present with a completely normal chest radiograph. [24] The presence of LTBI is detectable by means of the tuberculin skin test (TST), however, because of its questionable validity and low cost-effectiveness, the TST is not routinely included in the initial immigration medical evaluation. For this reason, most foreign-born persons carrying LTBI at the time of screening will go undetected and cannot, therefore, be given treatment to prevent the progression to active disease. [24,60] Consequently, foreign-born individuals with LTBI account for a large proportion of incident TB cases that arise among persons previously screened for the disease by means of chest x-ray alone.

Many studies have sought to determine whether or not including the TST in the initial pre-immigration screening evaluation would be effective in terms of cost-savings and prevention of future incident cases of TB. [20,42,61,82-84,86-88] For instance, a recent American study argued that, for new immigrants to the United States from developing nations, a strategy of detecting and treating latent tuberculosis infection would lead to substantial health and economic benefits and could potentially save $60 to $90 million (US) if implemented for just one year. [86]

Such success, however, is only achievable if individuals with a positive TST: a) undergo medical evaluation, and b) adhere to the prescribed treatment and follow-up

recommendations. Several studies have documented that both the prescription of INH for treatment of LTBI by physicians, and compliance with the recommended treatment on the part of the patient to be very low. [68] The inclusion of the TST as part of the initial immigration screening evaluation is further limited by several factors, including a high rate of false positive reactions due to prior vaccination with Bacille Calmette-Guerin (BCG) and the presence of non-tuberculous mycobacteria as well as the fact that 2 visits are required (i.e., one to plant the TST and a second, 48 – 72 hours later, to interpret the results). Finally, several studies have demonstrated that as a screening tool for TB, the TST is much less cost-effective than the CXR. [20,61] For these reasons, it has been concluded that outside of contact investigation, screening for LTBI is a high-cost, low-yield strategy for controlling TB in foreign-born individuals. [20,61,82,85]

Despite the fact that screening for LTBI may prevent future incident cases of active disease from developing, one must keep in mind that the management of active cases is the highest priority for TB control measures in industrialized countries. [87] Accordingly, the primary goal of immigration screening is to identify foreign-born persons with active pulmonary TB so that treatment may be completed prior to being granted permanent residence and subsequent transmission of disease to native-born populations may be diminished. [12] Therefore, the chest x-ray, not the TST, is included in the immigration screening evaluation because it alone has the ability to detect radiographic findings associated with active disease and identifies individuals for whom further microbiological testing (e.g., AFB smear microscopy and culture) may be warranted.

6.5 Future Direction and Recommendations

The extent of observer agreement in interpreting chest x-rays for the presence of TB has previously been studied in the context of mass population surveys and immigration screening. [76-80] Almost all such studies, including the current one involving the screening x-rays of immigrants referred for medical surveillance upon arrival to Canada, have found intra-observer agreement to be consistently higher than inter-observer agreement. [76-80]

Inter-observer reliability in interpreting screening chest x-rays could potentially be improved if a standardized radiographic classification scheme similar to the one created by the International Labour Organization (ILO) for pneumoconiosis was developed for TB. The ILO classification system, designed for the systematic recording of radiographic changes compatible with pneumonoconiosis, includes written text and a set of notes, as well as standard films for comparison with the film in question. [89] Improvement of the current CIC x-ray categorization scheme (i.e., reducing the number of categories and eliminating redundant or underused categories) as well as the development of a set of standard films to be used in the training of physicians could prove to be successful in improving inter-observer agreement in reading chest x-rays and should be further evaluated.

Numerous studies have demonstrated that although still relatively low, the percent yield of prevalent active TB cases detected at time of screening is considerably higher for refugees and persons arriving from high incidence countries (0.45% to 0.93%) than for

immigrants from low to intermediate incidence countries (0.05% to 0.16%). [15-17,65-67] With this in mind, several countries have begun to target only those immigrants arriving from countries with a TB incidence greater than 50 per 100,000, as well as all refugee claimants, for radiographic screening. [85] If such a policy were implemented in Canada, both the percent yield of prevalent active cases detected at time of screening and the cost-effectiveness of the immigration radiographic screening process may improve.

6.6 Conclusion

The extent of agreement between physicians in interpreting screening chest x-rays using Citizenship and Immigration Canada's current x-ray categorization scheme is poor to moderate, and does not appear to be influenced by the overall technical quality of the screening films. Immigration radiographic screening is moderately successful in detecting applicants with prevalent active disease at the time of screening, however, the yield could be considerably improved if screening was further targeted at foreign-born persons arriving from countries with a high incidence of TB or those entering the country as refugee claimants. The chest x-ray is limited in its ability to prevent future incident cases as many immigrant applicants carrying latent TB infection at the time of screening will be missed by the radiographic screening process and subsequently progress to active disease post-arrival.

Regardless of the effectiveness of immigration radiographic screening, efforts to control TB among the foreign-born population in Canada will be futile unless more aggressive measures are taken in controlling the global epidemic. As stated previously, close to one-

third of the world's population is believed to be infected with the TB bacilli and by the year 2020, the number of new active cases reported annually is expected to reach over 12 million worldwide. [28] Although the greatest burden of disease will continue to be experienced by the developing regions of Asia, Africa, and Latin America, the continuous influx of immigrants and refugees arriving from such regions will inevitably contribute to persistently high rates of TB among the foreign-born in many low-incidence countries, including Canada. Thus, in the absence of a concerted global effort towards the elimination of TB, pre-immigration radiographic screening alone will not significantly reduce the burden of disease among Canada's foreign-born population because as Grzybowski once said, "It should never be forgotten that Canada's borders are a sieve, not a seal". [62]

REFERENCES

1. Health Canada. Tuberculosis in Canada, 2000. Minister of Public Works and Government Services Canada, 2003.
2. Health Canada. Tuberculosis in Canada, 1985. Minister of Public Works and Government Services Canada, 1987.
3. Citizenship and Immigration Canada. Facts and Figures 2000. Minister of Public Works and Government Services Canada, 2001.
4. Menzies D. Tuberculosis crosses borders. *Int J Tuberc Lung Dis* 2000;4:S153-S159.
5. Cowie RL, Sharpe JW. Tuberculosis among immigrants: interval from arrival in Canada to diagnosis. *Can Med Assoc J* 1998;158:599-602.
6. Rivest P, Tannenbaum T, Bédard L. Epidemiology of tuberculosis in Montreal. *Can Med Assoc J* 1998;158:605-9.
7. Long R, Njoo H, Hershfield E. Tuberculosis:3. Epidemiology of the disease in Canada. *Can Med Assoc J* 1999;160:1185-90.
8. Gaudette LA, Ellis E. Tuberculosis in Canada: a focal disease requiring distinct control strategies for different risk groups. *Tuberc Lung Dis* 1993;74:244-53.
9. McKenna MT, McCray E, Onorato I. The epidemiology of tuberculosis among foreign-born persons in the United States, 1986 to 1993. *N Engl J Med* 1995;332:1071-6.
10. Zuber PLF, Knowles LS, Binkin NJ, Tipple MA, Davidson PT. Tuberculosis among foreign-born persons in Los Angeles County, 1992-1994. *Tuberc Lung Dis* 1996;77:524-30.

11. Zuber PLF, Binkin NJ, Ignacio AC, Marshall KL, Tribble SP, Tipple MA, Vogt RL. Tuberculosis screening for immigrants and refugees: Diagnostic outcomes in the state of Hawaii. *Am J Respir Crit Care Med* 1996;154:151-5.

12. Health Canada. Canadian guidelines for the investigation and follow-up of individuals under medical surveillance for tuberculosis after arrival in Canada. *Can Commun Dis Rep* 2001;27:157-65.

13. Orr PH, Manfreda J, Hershfield ES. Tuberculosis surveillance in immigrants to Manitoba. *Can Med Assoc J* 1990;142:453-8.

14. Wang JS, Allen EA, Enarson DA, Grzybowski S. Tuberculosis in recent Asian immigrants to British Columbia, Canada: 1982-1985. *Tubercle* 1991;72:277-83.

15. Bonvin L, Zellweger JP. Mass miniature x-ray screening for tuberculosis among immigrants entering Switzerland. *Tuberc Lung Dis* 1992;73:322-5.

16. Nolan C, Elarth AM. Tuberculosis in a cohort of southeast Asian refugees: A five-year surveillance study. *Am Rev Respir Dis* 1998;137:805-9.

17. Markey AC, Forster SM, Mitchell R, Larson E, Smith H. Suspected cases of pulmonary tuberculosis referred from port of entry into Great Britain, 1980-3. *Br Med J* 1986;292:378.

18. Horwitz O, Darrow MM. Principles and effects of mass screening: Danish experience in tuberculosis screening. *Public Health Rep* 1976;91:146-53.

19. Binkin NJ, Zuber PLF, Wells CD, Tipple MA, Castro KG. Overseas screening for tuberculosis in immigrants and refugees to the United States: Current status. *Clin Infect Dis* 1996;23:1226-32.

20. Dasgupta K, Schwartzman K, Marchand R, Tannenbaum TN, Brassard P, Menzies D. Comparison of cost-effectiveness of tuberculosis screening of close contacts and foreign-born populations. *Am J Respir Crit Care Med* 2000;162:2079-86.

21. Barnes PF, Verdegem TD, Vachon LA, Leedom JM, Overturf GD. Chest roentgenogram in pulmonary tuberculosis: New data on an old test. *Chest* 1988;94:316-20.

22. Toman K, Koppaka R, Bock N. 12: How reliable is chest x-ray? In: Frieden T, ed. *Toman's Tuberculosis: Case Detection, Treatment and Monitoring – Questions and Answers.* 2nd ed. Geneva: World Health Organization, 2002.

23. Benenson AS, Chin J. Tuberculosis. In: Benenson AS, Chin J, eds. *Control of Communicable Diseases Manual.* 16th ed. Washington, DC: American Public Health Association, 1995:488-97.

24. Long R, ed. *Canadian TB Standards.* 5th ed., 2002. Canadian Lung Association, Health Canada.

25. Leiner S, Mays M. Diagnosing latent and active pulmonary tuberculosis: A review for clinicians. *Nurse Pract* 1996;21:86-111.

26. Martin G, Lazarus A. Epidemiology and diagnosis of tuberculosis. *Postgrad Med* 2000;108:42-55.

27. Lobue PA, Perry S, Catanzaro A. Chapter 14: Diagnosis of tuberculosis. In: Davis AL, Reichman LB, Hershfield ES, eds. *Tuberculosis: a comprehensive international approach.* 2nd ed. New York: Marcel Dekker, Inc., 2000.

28. Nolte FS, Metchcock B. Mycobacterium. In: *Manual of clinical microbiology.* 6th ed. Washington, DC: American Society for Microbiology, 1995.

29. World Health Organization. Global Tuberculosis Control: Surveillance, planning, financing. *WHO Report 2002.* Geneva, 2002.

30. Fanning EA. Globalization of tuberculosis. *Can Med Assoc J* 1998;158:611-2.

31. Zumla A, Mwaba P, Squire SB, Grange JM. The tuberculosis pandemic – which way now? *J Infect* 1999;38:74-9.

32. World Health Organization. Press Release WHO/23, 20 March 1995.

33. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Global burden of tuberculosis: Estimated incidence, prevalence, and mortality by country. *JAMA* 1999;282:677-86.

34. Pablos-Mendez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, Cohn DL, Lambregts-van Weezenbeek CS, Kim SJ, Chaulet P, Nunn P. Global surveillance for antituberculosis drug resistance, 1994-1997. WHO-IUATLD Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med* 1998;338:1641-9.

35. Dubos RJ, Dubos J. *The white plague: tuberculosis, man, and society.* Boston: Little, Brown, and Company, 1957.

36. Stead WW. The origin and erratic global spread of tuberculosis: how the past explains the present and is the key to the future. *Clin Chest Med* 1997;18:65-77.

37. Daniel TM, Bates JH, Downes KA. History of tuberculosis. In: Bloom BR, ed. *Tuberculosis: Pathogenesis, Protection, and Control.* Washington, DC: ASM, 1994:13-25.

38. Bates JH, Stead WW. The history of tuberculosis as a global epidemic. *Med Clin North Am* 1993;77:1205-17.

39. Wobeser WL, Yuan L, Naus M, Corey P, Edelson J, Heywood N, Holness DL. Expanding the epidemiology profile: risk factors for active tuberculosis in people immigrating to Ontario. *Can Med Assoc J* 2000;163:823-8.

40. Enarson D, Ashley MJ, Grzybowski S. Tuberculosis in immigrants to Canada: A study of present-day patterns in relation to immigration trends and birthplace. *Am Rev Respir Dis* 1979;119:11-7.

41. Saraiya M, Binkin NJ. Chapter 25: Tuberculosis among immigrants. In: Davis Al, Reichman LB, Hershfield ES, eds. *Tuberculosis: a comprehensive international approach.* 2nd ed. New York: Marcel Dekker, Inc. 2000.

42. Zuber PL, McKenna MT, Binkin NJ, Onorato IM, Castro KG. Long-term risk of tuberculosis among foreign-born persons in the United States. *JAMA* 1997;278:304-7.

43. Talbot EA, Moore M, McCray E, Binkin NJ. Tuberculosis among foreign-born persons in the United States, 1993-1998. *JAMA* 2000;284:2894-2900.

44. Lillebaek T, Andersen AM, Dirksen A, Smith E, Skovgaard T, Kok-Jensen A. Persistent high incidence of tuberculosis in immigrants in a low-incidence country. *Emerg Infect Dis* 2002;8:679-84.

45. Marks GB, Bai J, Stewart GJ, Simpson SE, Sullivan EA. Effectiveness of post-migration screening in controlling tuberculosis among refugees: A historical cohort study, 1984-1998. *Am J Public Health* 2001;91:1797-9.

46. McCarthy OR. Asian immigrant tuberculosis – the effect of visiting Asia. *Br J Dis Chest* 1984;78:248-253.

47. Weis SE, Moonan PK, Pogoda JM, Turk L, King B, Freeman-Thompson S, Burgess G. Tuberculosis in the foreign-born population of Tarrant County, Texas by immigration status. *Am J Respir Crit Care Med* 2001;164:953-7.

48. World Health Organization. *Tuberculosis control in refugee situations*. Geneva; WHO. 1997.

49. Gushulak BD. Tuberculosis control in refugees – policy and practices. *Int J Tuberc Lung Dis* 1998;2:S87-S93.

50. Centers for Disease Control. Tuberculosis morbidity among US-born and foreign-born populations – United States, 2000. *MMWR* 2002;51:101-4.

51. Brown RE, Miller B, Taylor WR, Palmer C, Bosco L, Nicola RM, Zelinger J, Simpson K. Health-care expenditures for tuberculosis in the United States. *Arch Intern Med* 1995;155:1595-1600.

52. Research Committee of the British Thoracic Society. A study of standardised contact procedure in tuberculosis. *Tubercle* 1978;59:245-59.

53. Thomas RE, Gushulak B. Screening and treatment of immigrants and refugees to Canada for tuberculosis: Implications of the experience of Canada and other industrialized countries. *Can J Infect Dis* 1995;6:246-55.

54. Rieder HL, Zellweger JP, Raviglione MC, Keizer ST, Migliori GB. Tuberculosis control in Europe and international migration. *Eur Respir J* 1994;7:1545-53.

55. Menzies D, Chan CH, Vissandjée B. Impact of immigration on tuberculosis infection among Canadian-born schoolchildren and young adults in Montreal. *Am J Respir Crit Care Med* 1997;156:1915-21.

56. Chin DP, DeRiemer K, Small PM, Ponce de Leon A, Steinhart R, Schecter GF, Daley CL, Moss AR, Paz EA, Jasmer RM, Agasino CB, Hopewell PC. Differences in contributing factors to tuberculosis incidence in US-born and foreign-born persons. *Am J Respir Crit Care Med* 1998;158:1797-803.

57. Musana K, Menzies D, Tannenbaum T, Brassard P, Thibert L, Pollock S, FitzGerald JM, Kunimoto D, Schwartzman K. Molecular epidemiology of tuberculosis in 3 Canadian cities, 1995-1997 [abstract]. *Am J Respir Crit Care Med* 1999;159:A904.

58. Borgdorff NW, Nagelkerke N, van Soolingen D, de Haas PEW, Veen J, van Embden JDA. Analysis of tuberculosis transmission between nationalities in the Netherlands in the period 1993-1995 using DNA fingerprinting. *Am J Epidemiol* 1998;147:187-95.

59. Hennekens CH, Buring JE. Chapter 13: Screening. In: Mayrent SL, ed. *Epidemiology in Medicine*. Toronto: Little, Brown, and Company, 1987.

60. International Union Against TB Committee on Prophylaxis. Efficacy of various durations of INH preventive therapy for TB: 5 years of follow-up in the IUAT trial. *Bull World Health Organ* 1982;60:555-64.

61. Schwartzman K, Menzies D. Tuberculosis screening of immigrants to low-prevalence countries: A cost-effectiveness analysis. *Am J Respir Crit Care Med* 2000;161:780-9.

62. Grzybowski S, Allen EA. Tuberculosis: 2. History of the disease in Canada. *Can Med Assoc J* 1999;160:1025-8.

63. Wherrett GJ. *The Miracle of the Empty Beds: A History of Tuberculosis in Canada.* Toronto: University of Toronto Press, 1977.

64. Bennett CF. Tuberculosis in recent immigrants. *Can J Public Health* 1940;31:515-30.

65. Blum R, Polish LP, Tapy JM, Catlin BJ, Cohn DL. Results of screening for tuberculosis in foreign-born persons applying for adjustment of immigration status. *Chest* 1993;103:1670-4.

66. Ormerod LP. Tuberculosis screening and prevention in new immigrants 1983-88. *Respir Med* 1990;84:269-71.

67. Ormerod LP. Is new immigrant screening for tuberculosis still worthwhile? *J Infect* 1998;37:39-40.

68. Uppaluri A, Naus M, Heywood N, Brunton J, Kerbel D, Wobeser W. Effectiveness of the immigration medical surveillance program for tuberculosis in Ontario. *Can J Public Health* 2002;93:88-91.

69. Balasangameshwara VH, Charaborty AK. Validity of case-finding tools in a national tuberculosis programme. *Tuberc Lung Dis* 1993;74:52-8.

70. Ker M. Issues in the use of kappa. *Invest Radiol* 1991;26:78-83.

71. May SM. Modelling observer agreement – an alternative to kappa. *J Clin Epidemiol* 1994;47:1315-24.

72. Brennan P, Silman A. Statistical methods for assessing observer variability in clinical measures. *Br Med J* 1992;304:1491-4.

73. Tudor GR, Finlay D, Taub N. An assessment of inter-observer agreement and accuracy when reporting plain radiographs. *Clin Radiol* 1997;52:235-38.

74. Musch DC, Landis R, Higgins ITT, Gilson JC, Jones R. An application of kappa-type analyses to interobserver variation in classifying chest radiographs for pneumoconiosis. *Statist. Med* 1984;3:73-83.

75. Fleiss JL. Measuring nominal scale agreement among many raters. *Psychol Bull* 1971;76:378-82.

76. Yerushalmy J. The statistical assessment of the variability in observer perception and description of roentgenographic pulmonary shadows. *Radiol Clin North Am* 1969;7:381-92.

77. Springett VH. Results of the study on x-ray readings of the ad hoc Committee for the study of classification and terminology in tuberculosis. *Bull Int Union Tuberc Lung Dis* 1968;41:107-9.

78. Springett VH. Results of the international study on x-ray classification: Conclusions. *Bull Int Union Tuberc Lung Dis* 1968;41:125-9.

79. Waaler HT. Descriptions of the study material and organization of the study. *Bull Int Union Tuberc Lung Dis* 1968;41:110-14.

80. Graham S, Dasgupta K, Hidvegi RJ, Hanson R, Kosiuk J, Al Zahrani K, Menzies D. Chest radiograph abnormalities associated with tuberculosis: reproducibility and yield of active cases. *Int J Tuberc Lung Dis* 2002;6:137-42.

81. Krinkiva R, Drapela J, Kubik A, Dankova D, Krivanek J, Ruzha J, Mikova Z, Hejdova E. Epidemiological and clinical study of tuberculosis in the district of Kolin, Czechoslovakia: Second report (1965-1972). *Bull World Health Organ* 1974;51:59-69.

82. MacIntyre CR, Plant AJ, Yung A, Streeton JA. Missed opportunities for prevention of tuberculosis in Victoria, Australia. *Int J Tuberc Lung Dis* 1997;1:135-41.

83. Tattevin P, Casalino E, Fleury L, Engmann G, Ruel M, Bouvet E. The validity of medical history, classic symptoms, and chest radiographs in predicting pulmonary tuberculosis. *Chest* 1999;115:1248-53.

84. El-Hamad I, Casalini C, Matteelli A, Casari S, Bugiani M, Caputo M, Bombana E, Scolari C, Moioli R, Scarcella C, Carosi G. Screening for tuberculosis and latent tuberculosis infection among undocumented immigrants at an unspecialised health service unit. *Int J Tuberc Lung Dis* 2001;5:712-16.

85. Van den Bosch CA, Roberts JA. Tuberculosis screening of new entrants; how can it be made more effective? *J Public Health Med* 2000;22:220-23.

86. Khan K, Muennig P, Behta M, Graff Zivin J. Global drug-resistance patterns and the management of latent tuberculosis infection in immigrants to the United States. *N Engl J Med* 2002;347:1850-9.

87. Pang SC, Harrison RH, Brearley J, Jegathesan V, Clayton AS. Tuberculosis surveillance in immigrants through health undertakings in Western Australia. *Int J Tuberc Lung Dis* 2000;4:232-6.

88. Kendig EL Jr, Kirkpatrick BV, Carter WH, Hill FA, Caldwell K, Entwistle M. Underreading of the tuberculin skin test reaction. *Chest* 1988;113:1175-7.

89. Shipley RT. The 1980 ILO classification of the radiographs of the pneumonconioses. *Occupational Lung Dis* 1992;30:1135-45.

APPENDIX A: Member States of the World Health Organization

WHO Statistics -> WHO Member States -> WHO Member States

World Health Organization

Member States of the World Health Organization

(as of 21 October 2002)

This is the complete list of Member States of the World Health Organization as of 21 October 2002. There are 192 Member States.

WHO African Region	Population (1000's) (Source: UN estimates 1999)		
	Male	Female	Total
Algeria	14,916	14,557	29,473
Angola	5,715	5,855	11,570
Benin	2,811	2,909	5,720
Botswana	745	773	1,518
Burkina Faso	5,528	5,559	11,087
Burundi	3,122	3,276	6,398
Cameroon	6,923	7,014	13,937
Cape Verde	191	215	406
Central African Republic	1,654	1,762	3,416
Chad	3,310	3,392	6,702
Comoros	331	321	652
Congo	1,341	1,404	2,745
Côte d'Ivoire	7,291	7,008	14,299
Democratic Republic of the Congo	23,759	24,281	48,040
Equatorial Guinea	207	213	420
Eritrea	1,692	1,717	3,409
Ethiopia	30,257	29,891	60,148
Gabon	562	576	1,138
Gambia	577	591	1,168
Ghana	9,107	9,231	18,338
Guinea	3,828	3,786	7,614
Guinea-Bissau	547	565	1,112
Kenya	14,233	14,181	28,414
Lesotho	1,051	1,080	2,131
Liberia	1,243	1,225	2,468
Madagascar	7,892	7,953	15,845
Malawi	4,990	5,097	10,087
Mali	5,654	5,826	11,480
Mauritania	1,185	1,207	2,392
Mauritius	570	571	1,141
Mozambique	9,021	9,244	18,265
Namibia	803	810	1,613

Niger	4,838	4,949	9,787
Nigeria	58,695	59,674	118,369
Rwanda	2,902	2,981	5,883
Sao Tome and Principe	58	59	117
Senegal	4,386	4,376	8,762
Seychelles	38	38	76
Sierra Leone	2,171	2,257	4,428
South Africa	21,525	21,812	43,337
Swaziland	435	471	906
Togo	2,139	2,177	4,316
Uganda	10,330	10,461	20,791
United Republic of Tanzania	15,602	15,904	31,506
Zambia	4,177	4,301	8,478
Zimbabwe	5,798	5,884	11,682
WHO Region of the Americas	Population (1000's) (Source: UN estimates 1999)		
	Male	Female	Total
Antigua and Barbuda	37	40	77
Argentina	17,497	18,174	35,671
Bahamas	142	147	289
Barbados	127	135	262
Belize	113	111	224
Bolivia	3,863	3,911	7,774
Brazil	80,686	82,446	163,132
Canada	14,841	15,101	29,942
Chile	7,237	7,387	14,624
Colombia	18,394	18,673	37,067
Costa Rica	1,808	1,767	3,575
Cuba	5,550	5,518	11,068
Dominica	39	36	75
Dominican Republic	4,116	3,981	8,097
Ecuador	5,997	5,941	11,938
El Salvador	2,907	3,020	5,927
Grenada	43	46	89
Guatemala	5,674	5,567	11,241
Guyana	418	429	847
Haiti	3,630	3,765	7,395
Honduras	3,014	2,967	5,981
Jamaica	1,262	1,253	2,515
Mexico	46,703	47,577	94,280
Nicaragua	2,171	2,180	4,351
Panama	1,375	1,347	2,722
Paraguay	2,564	2,524	5,088
Peru	12,091	12,276	24,367
Saint Kitts and Nevis	20	21	41
Saint Lucia	66	70	136
Saint Vincent and the Grenadines	53	53	106
Suriname	217	220	437
Trinidad and Tobago	689	619	1,308
United States of America	133,855	137,793	271,648

Uruguay	1,570	1,652	3,222
Venezuela	11,467	11,310	22,777

WHO Eastern Mediterranean Region	Population (1000's) (Source: UN estimates 1999)		
	Male	Female	Total
Afghanistan	11,342	10,790	22,132
Bahrain	333	249	582
Cyprus	383	384	767
Djibouti	312	322	634
Egypt	32,721	31,745	64,466
Iran (Islamic Republic of)	36,373	35,145	71,518
Iraq	10,775	10,402	21,177
Jordan	2,954	2,820	5,774
Kuwait	889	842	1,731
Lebanon	1,535	1,609	3,144
Libyan Arab Jamahiriya	3,006	2,778	5,784
Morocco	13,776	13,742	27,518
Oman	1,276	1,125	2,401
Pakistan	74,330	69,501	143,831
Qatar	375	194	569
Saudi Arabia	10,833	8,661	19,494
Somalia	5,060	5,157	10,217
Sudan	13,998	13,900	27,898
Syrian Arab Republic	7,556	7,395	14,951
Tunisia	4,723	4,602	9,325
United Arab Emirates	1,473	835	2,308
Yemen	8,196	8,098	16,294

WHO European Region	Population (1000's) (Source: UN estimates 1999)		
	Male	Female	Total
Albania	1,751	1,671	3,422
Andorra	0	0	0
Armenia	1,770	1,872	3,642
Austria	4,015	4,146	8,161
Azerbaijan	3,753	3,902	7,655
Belarus	4,861	5,477	10,338
Belgium	4,993	5,195	10,188
Bosnia and Herzegovina	1,873	1,911	3,784
Bulgaria	4,115	4,313	8,428
Croatia	2,175	2,322	4,497
Czech Republic	5,004	5,234	10,238
Denmark	2,599	2,649	5,248
Estonia	684	771	1,455
Finland	2,507	2,635	5,142
France	28,517	30,026	58,543
Georgia	2,596	2,839	5,435
Germany	40,225	41,965	82,190
Greece	5,179	5,343	10,522
Hungary	4,775	5,214	9,989

Iceland	138	136	274
Ireland	1,777	1,782	3,559
Israel	2,871	2,910	5,781
Italy	27,833	29,407	57,240
Kazakhstan	8,185	8,647	16,832
Kyrgyzstan	2,196	2,284	4,480
Latvia	1,132	1,343	2,475
Lithuania	1,759	1,960	3,719
Luxembourg	207	210	417
Malta	184	187	371
Monaco	13	14	27
Netherlands	7,758	7,903	15,661
Norway	2,165	2,199	4,364
Poland	18,798	19,838	38,636
Portugal	4,721	5,082	9,803
Republic of Moldova	2,126	2,322	4,448
Romania	11,122	11,484	22,606
Russian Federation	69,136	78,573	147,709
San Marino	12	13	25
Slovakia	2,607	2,747	5,354
Slovenia	931	991	1,922
Spain	19,486	20,232	39,718
Sweden	4,375	4,469	8,844
Switzerland	3,608	3,669	7,277
Tajikistan	3,009	3,036	6,045
The former Yugoslav Republic of Macedonia	1,103	1,086	2,189
Turkey	31,742	31,032	62,774
Turkmenistan	2,095	2,140	4,235
Ukraine	23,898	27,526	51,424
United Kingdom	28,533	29,668	58,201
Uzbekistan	11,739	11,917	23,656
Yugoslavia	5,142	5,208	10,350

WHO South-East Asia Region	Population (1000's) (Source: UN estimates 1999)		
	Male	Female	Total
Bangladesh	62,622	59,391	122,013
Bhutan	936	926	1,862
Democratic People's Republic of Korea	11,441	11,396	22,837
Democratic Republic of Timor-Leste	0	0	0
India	495,862	464,316	960,178
Indonesia	101,510	101,969	203,479
Maldives	140	133	273
Myanmar	23,297	23,468	46,765
Nepal	11,438	11,154	22,592
Sri Lanka	9,063	9,210	18,273
Thailand	29,563	29,596	59,159

WHO Western Pacific Region	Population (1000's) (Source: UN estimates 1999)		
	Male	Female	Total

Australia	9,110	9,140	18,250
Brunei Darussalam	161	146	307
Cambodia	5,085	5,430	10,515
China	640,625	603,113	1,243,738
Cook Islands	10	9	19
Fiji	411	398	809
Japan	61,686	63,952	125,638
Kiribati	36	37	73
Lao People's Democratic Republic	2,566	2,629	5,195
Malaysia	10,606	10,412	21,018
Marshall Islands	31	30	61
Micronesia (Federated States of)	54	52	106
Mongolia	1,288	1,281	2,569
Nauru	0	0	0
New Zealand	1,801	1,840	3,641
Niue	0	0	0
Palau	8	7	15
Papua New Guinea	2,320	2,180	4,500
Philippines	35,613	35,111	70,724
Republic of Korea	23,041	22,676	45,717
Samoa	88	80	168
Singapore	1,733	1,706	3,439
Solomon Islands	208	196	404
Tonga	49	48	97
Tuvalu	0	0	0
Vanuatu	89	89	178
Viet Nam	37,743	38,805	76,548

APPENDIX B: Study Questionnaire and Citizenship and Immigration Canada's X-ray Categorization Scheme

Part 1: Identification and technical aspects

STUDY ID No._____ READER ID No. _____
ENTER THE NUMBER ON THE CXR FILM

Please judge the technical quality of the film relative to what you consider ideal and would be appropriate for x-rays performed in your centre.

1. What is the penetration of the chest x-ray?
   ☐ Under ☐ Ideal ☐ Over

2. Are there any overlying artefacts (hair, bony shadows) that could and should have been avoided?
   ☐ Yes ☐ No ☐ Unsure

3. Is the applicant's entire lung field visible on the PA chest film?
   ☐ Yes ☐ No

4. What is your rating of the overall quality of the film?
   ☐ Terrible ☐ Poor ☐ Sub-optimal ☐ Good ☐ Excellent

Part 2: Interpretation of the Chest X-ray findings using CIC scheme

☐ **THE FILM IS TOTALLY NORMAL**
CHECK THIS BOX IF NONE OF THE BELOW APPLY TO THIS CHEST X-RAY.

If the chest x-ray is NOT totally normal, check ONE category for the lesion(s) that has the most clinical importance. (Usually the highest category).

NON-PULMONARY PROBLEMS:

- ☐ 0.1 Significant skeletal and soft tissue abnormalities
- ☐ 0.2 Abnormal great vessel of heart shadows? (Contours suggestive of valvular/septal abnormalities, unfolding of the thoracic aorta, CT ratio > 50%)
- ☐ 0.3 Abnormalities of the hemi-diaphragms

PULMONARY PROBLEMS – OF NO CLINICAL SIGNIFICANCE:

- ☐ 1.1 Single fibrous streak/band/scar
- ☐ 1.2 Bony islets
- ☐ 2.1 Apical pleural capping with a smooth inferior border (< 1cm thick at all points)
- ☐ 2.2 Unilateral or bilateral costophrenic angle blunting (below the horizontal)
- ☐ 2.3 Calcified nodule(s) in the hilum/mediastinum with no pulmonary granulomas

PULMONARY PROBLEMS – MINIMAL, MAY BE DUE TO OLD TB INFECTION:

- ☐ 3.1 Solitary granuloma (< 1cm and of any lobe) with an unremarkable hilum
- ☐ 3.2 Solitary granuloma (< 1cm and of any lobe) with calcified/enlarged hilar lymph nodes
- ☐ 3.3 Single/multiple calcified pulmonary nodules/micronodules with distinct borders
- ☐ 3.4 Calcified pleural lesions
- ☐ 3.5 Costophrenic angle blunting (either side, above the horizontal)
- ☐ 3.6 Notable apical pleural capping (rough or ragged inferior border and/or > 1cm thick)

PULMONARY PROBLEMS – POTENTIALLY ACTIVE DISEASE (ACTIVE TB OR OTHER):

- ☐ 4.1 Apical fibronodular/fibrocalcific lesions or apical microcalcifications
- ☐ 4.2a Multiple/single <u>well-defined</u> non-calcified pulmonary nodules/micronodules
- ☐ 4.2b Multiple/single <u>poorly defined</u> pulmonary nodules/micronodules
- ☐ 4.3 Isolated hilar or mediastinal mass/lymphadenopathy (noncalcified)
- ☐ 4.4 Lung mass or masses > 1cm
- ☐ 4.5 Poorly calcified/non-calcified pleural fibrosis and/or effusion
- ☐ 4.6 Interstitial fibrosis/parenchymal lung disease/acute pulmonary disease
- ☐ 4.7 ANY cavitating lesion

What is the extent of the lung parenchyma affected? – estimate in percent of total lung area.
☐ 0% ☐ 1% – 4% ☐ 5% – 9% ☐ 10% – 24% ☐ 25% +

In your opinion, is it likely that this chest x-ray represents active TB? – *i.e., that requires urgent investigation and consideration of initiation of treatment while awaiting results?*
☐ No ☐ Yes