Transmission of Tuberculosis from Patients with Typical Versus Atypical Chest Radiographs: Implications for Automated Systems

by

Angela Shin Tung Lau

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Department of Medicine
University of Alberta

ABSTRACT

Automated detection of "typical" pulmonary tuberculosis (PTB) on chest radiograph (CXR) is warranted if it can be shown that patients with "typical" (vs "atypical") CXRs are responsible for most public health consequences.

Patient demographics and mycobacteriology of all adults (age >14 years) diagnosed with smear-positive PTB in Alberta between January 1, 2006 to December 31, 2008 was abstracted. Pre-treatment CXRs were scored by 3 independent readers as "typical" (having an upper lung zone infiltrate, with or without cavitation, but no discernable adenopathy) or "atypical".

A total of 97 smear-positive PTB cases were identified, of whom 69 (71.1 %) had a "typical" CXR. Patients with 'typical' CXRs had larger bacillary burdens and more metabolically active bacteria (larger semi-quantitative smears; shorter times-to-culture-positivity) than patients with "atypical" CXRs. Significantly, they are responsible for 78% of TST conversion and 95% of secondary cases.

PTB patients with "typical" CXRs are responsible for most public health consequences. Accordingly, the development of an automated TB detection system is warranted.

Key words: Tuberculosis, chest radiography, computer-aided detection systems, conventional epidemiology, molecular epidemiology

PREFACE

This thesis is a final work submitted in partial fulfillment of the requirements for a Master of Science in the Department of Medicine at the University of Alberta. This thesis focuses on the transmission of tuberculosis from patients with features typical for adult-type PTB on chest radiography, and discusses the implications for computer-aided detection systems for pulmonary tuberculosis. No part of this thesis has been previously published. Study approval was obtained from the University of Alberta Health Research Ethics Board (HREB). Retrospective analysis of anonymous and routinely collected surveillance data did not require direct patient contact; therefore the need for patient's informed consent was waived by HREB. Statistical analyses were performed using SPSS version 17 and reviewed with a statistician.

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List of Abbreviations and Symbols

CAD – Computer-aided Detection

CBA – Canadian-born Aboriginal

CBNA – Canadian-born non Aboriginal

CI – Confidence Interval

CXR – Chest Radiograph

DOT – Directly Observed Therapy

FB – Foreign-born

FSA – Forward Sortation Area

LTBI – Latent TB Infection

Mycobacterium.tuberculosis – M.tuberculosis

p – Significant Level

PTB – Pulmonary TB

TB – Tuberculosis

TST – Tuberculin Skin Test

WHO – World Health Organization

Chapter 1: Introduction

This chapter provides the rationale of the study, the research objectives, the methods and results, researchers involved in the study, and a general organization of the thesis.

1.1 Rationale

The timely diagnosis and treatment of infectious (smear-positive) pulmonary tuberculosis (PTB) is critical to the interruption of transmission and patient outcome. In middle-to-high income, medium-to-low TB incidence countries a patient may present with symptoms and signs referable to the respiratory system and undergo a plain chest radiograph without any clinical suspicion of PTB. Radiograph requisitions, may not often invite the radiologist to consider PTB. Ideally, the presence of "typical" radiographic features - i.e. typical for adult-type PTB (a predominantly upper lung zone infiltrate, with or without cavitation, but no discernable intrathoracic adenopathy) should, along with selected pieces of clinical information such as community or country-of-birth, symptomatology, and co-morbidities prompt consideration of PTB. Unfortunately, this is often not the case, with responsibility for failing to consider PTB shared between the clinician and the radiologist. Were it possible in this age of digital radiographics and electronic information systems, to automate this process, infectious PTB might be diagnosed earlier, transmission reduced and patient outcomes improved.

Before commending such an undertaking to further study it is necessary to answer several questions that relate to "typical" adult-type PTB. These questions include: in a high income, low TB and low HIV incidence country, what proportion of infectious PTB cases have "typical" versus "atypical" chest radiographic features; what proportion of infectious PTB cases with "typical" or "atypical" radiographic features have lung cavitation and/or a high bacillary burden, radiographic and mycobacteriologic features associated with increased transmission; and finally what proportion of all transmission events from infectious PTB cases are attributable to cases with "typical" versus "atypical" radiographic features. We hypothesize that "typical" cases are more common than "atypical" cases, more likely to have cavitation on chest radiograph and/or a high bacillary burden on mycobacteriology, and more likely to cause transmission events. This study provides the necessary information to support the development of a computer-aided detection system (CAD) to diagnose TB. A CAD system will reduce dependence upon human resources, reduce inter- and intra-observer variability and have global application.

1.2 Research objectives

The study objective is to determine whether “typical” cases are more common than “atypical” cases, more likely to have cavitation on chest radiograph and/or a high bacillary burden on mycobacteriology, and more likely to cause transmission events (tuberculin skin test [TST] converters or secondary cases) We hypothesize that “typical” cases (the type of TB we hypothesize is detectable

using a CAD system) are more common and responsible for more transmission events than those with 'atypical' CXRs (those without 'typical' findings on CXR).

1.3 Study design

Over 36 months beginning January 1, 2006, 97 adults (>14 years of age) were diagnosed with smear-positive pulmonary TB in the province of Alberta, Canada. Patient demographics and mycobacteriology were abstracted from public health records and the Provincial Laboratory for Public Health. Pre-treatment posterior-anterior and lateral CXRs were scored by a team of 3 independent expert readers from the Department of Radiology as 'typical' (having an upper lung zone infiltrate, with or without cavitation, but no discernable intrathoracic adenopathy) or 'atypical' (all others). Documentation of transmission events of each case was performed. This entailed searching, organizing, and tabulating all of the contact tracing data on each of the above described 97 smear-positive cases ('potential transmitters') during a 36 month transmission window (beginning 6 months before and ending 24 months after the date of diagnosis – the start date of treatment of each incident case).

Once cases were identified, their contact lists were assembled and cross-referenced against the provincial Registry to identify any secondary cases. The latter are of three varieties: *Type 1,* individuals diagnosed within a transmission window that extended from 6 months before to 24 months after the date of

diagnosis of the PTB case, listed as a contact of the PTB case, culture-positive, and infected with an isolate of *Mycobacterium tuberculosis* that matched (DNA fingerprint) that of the putative source case; *Type 2*, individuals notified with active disease within the same transmission window but who were culture-negative (mainly children). The date of diagnosis of the source case is defined as the start date of treatment. *Type 3* secondary cases are cases of TB in the province who were culture-positive with a DNA fingerprint matched isolate of *M. tuberculosis*, and were temporally (diagnosed in same 30-month transmission window) and spatially (lived in same forward sortation area [FSA] as determined by the first three digits of their postal code) linked to the source case.[*] The 30-month transmission window was chosen as it was expected that most contacts would become a secondary case within the period extending from 6 months before to 24 months after the data of diagnosis of their source case as the risk of disease after infection is highest during this period of time.

1.4 Researchers

The research activity was undertaken at the Tuberculosis Program Evaluation and Research Unit (TB PE&RU), Department of Medicine, University of Alberta. A multidisciplinary team of researchers worked conjointly to assist with the research.

[*] FSAs are the first three numbers and letters on a postal code that represent geographic units associated with a postal facility from which mail delivery originates.

1.5 Organization of thesis

This thesis is divided into seven chapters. Chapter one introduces the research topic and outlines the research questions and objectives used to guide the analysis, results and discussion. Chapter two and three are the literature review, which provides the contextual information that relates to the objectives of this thesis. Chapter two introduces TB as a disease and discusses the burden of disease in Canada and the current TB control strategy in place. Chapter three provides an overview of the current literature on computer-aided detection technology to diagnose TB. Chapter four, methodology, outlines the data collection and analysis and chapter five provides the results of the study. Finally, chapter six provides a discussion of the results, focusing on the translational aspects of the findings. A discussion on the strengths and limitations of the project will be detailed in chapter seven, along with an overview of the implications for future research. Chapter seven lists the references included in this thesis.

Chapter 2: Epidemiology of Tuberculosis

The literature review is subdivided into two chapters. This first chapter provides a brief introduction to TB as a disease, the burden of TB in Canada and globally, and the current TB control strategies implemented in Canada. T9he second chapter of the literature review will examine the diagnostic tools to detect TB, details of chest radiography, and current research on radiographic applications in medicine. The purpose of this literature review is to provide relevant contextual information for the study, as well as, highlight the current research body that reviews TB and chest radiography.

2.1 Global tuberculosis epidemiology

Tuberculosis (TB) is not a disease of the past; it continues to be a public health problem worldwide. According to the World Health Organization, TB ranks as one of the world's deadliest communicable diseases. There was an estimated 9.0 million new TB cases in 2013 and 1.5 million TB deaths (1.1 million among HIV-negative people and 0.4 million among HIV-positive people).[1] Despite the availability of affordable treatment, TB continues to be the major cause of morbidity and mortality in many parts of world, especially Asia and Africa.

TB is caused by the acid-fast mycobacterium, *M. tuberculosis*. Infection is predominantly acquired through the inhalation of infected droplet nuclei from a person with contagious TB, and rarely through ingestion of percutaneous

inoculation. Droplet nuclei are created by forceful expiratory efforts, such as coughing, sneezing, spitting or sneezing.[2] These respiratory droplet nuclei, of less than 5 microns, may be viable and suspended in the air for several hours.[3] Infectivity is dependent on several factors: such as the host's immune function, the proximity to the source case and duration of exposure, air circulation and ventilation, strain virulence, among other factors.[3] In most immunocompetent hosts, infection is generally self-limiting and followed by a variable latency period. It is estimated that in 5% of immunocompetent individuals with primary infection will progress to reactivation or post-primary TB at some time in their lives. For HIV co-infected patients, the annual risk of reactivation TB or post-primary TB is closer to 10%.[2]

2.2 Burden of tuberculosis in Canada

Improvement in public health measures to interrupt transmission and effective drug treatment has led to a rapid decline in Canadian TB disease and death rates in comparison to the first half of the 20th century.[2] In 2013, Canada had a total of 1,640 new active and re-treatment cases reported, corresponding to a case rate of 4.9 per 100,000 population.[4] This decrease in the total number of reported TB cases in Canada over the past decade is mainly a reflection of a decreasing number of cases in the Canadian-born non-Aboriginal populations. In Canadian born-Aboriginal and foreign-born persons, the number of cases have demonstrated a minimal decrease.[4] Evidently, TB disproportionately affects the under-privileged and marginalized members of society. In Alberta and Canada,

TB incidence rates in the Aboriginal and foreign-born individuals are 30 fold and 10 fold higher, respectively, than in Canadian-born non-Aboriginal persons.[5]

2.2.1 Tuberculosis in Canadian-born Aboriginal peoples

Unique challenges exist in the prevention and control of TB in the Aboriginal population, which includes Status and non-Status Indians, Inuit and Métis. TB rates in the Aboriginal peoples continues to be the higher than both Foreign-born peoples and Canadian-born non-Aboriginal peoples, being almost 6 times that of the overall Canadian TB rate of 4.9 per 100,000.[2] While the overall incidence of TB is higher in Aboriginal population, there is still a wide variation in incidence among regions and communities, with the highest incidence rates reported in Canada's North (which include the three territories, Yukon, Nunavut and Northwest Territories).

To address the high prevalence of TB in the Aboriginal communities, medical surveillance and treatment programs must be combined with community involvement in disease management and improvements in socioeconomic status.[6] TB disease in Aboriginal peoples is best understood through a social lens, in which factors of poverty, disparity, and inequity are considered. According to several studies, the risk of TB in high-risk populations is significantly influenced by overcrowded housing, inadequate nutrition, medical co-morbidities, social isolation, and accessibility to medical facilities.[7] Hence, policy makers and healthcare providers must recognize the unique challenges faced by the

Aboriginal population in order to implement successful TB prevention and treatment programs.

2.2.2 Tuberculosis in Foreign-born peoples

Canada is a major immigrant receiving country, with an average of 225,000 immigrants and refugees arriving annually, 80% of whom originate from countries with a high TB incidence.[2] Between 1970 and 2007, the proportion of foreign-born TB cases nearly quadrupled, from 18% to 87%.[8] This increase in the proportion of foreign-born TB cases is consistent with the shift in immigration patterns to high TB incidence countries (see Figure 2.1). Foreign-born cases now account for over two-thirds of all reported TB cases in Canada.[9,10] The majority of foreign-born TB cases in Canada are reported from major metropolitan areas.[2]

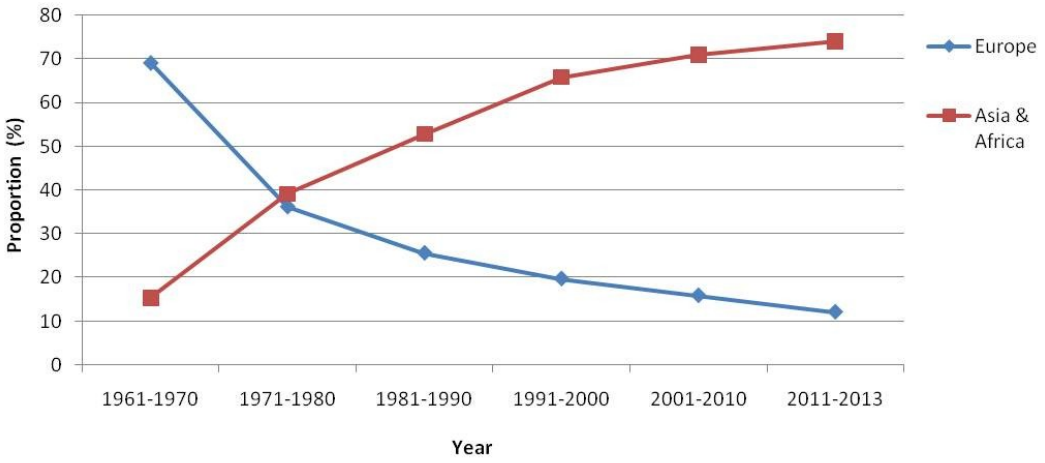


Figure 2.1. Proportion of new immigrants to Canada from Europe and Asia/Africa by time period. Source: Citizenship and Immigration Canada. Canadian Statistics: Immigrant population. Increasingly over the past 60 years immigrants to Canada have been arriving from high incidence countries.

It is estimated that, in high TB incidence countries, more than half of all adults have latent TB infection (LTBI).[9] Immigrants and refugees with LTBI are at highest risk of TB disease in the first 5 years after immigration. The risk of TB disease persists for many years post-arrival, with a decline of approximately 10% every year.[2]

2.3 TB control strategy

TB is a disease that knows no boundaries. Thus, TB control must be considered a global public good. Not only must there be a National TB Control Program (NTP) or its equivalent organized in every country, but there also needs to be international cooperation to set policies and strategies to enhance TB control. In 1993, the World Health Organization (WHO) approved a global strategy, Directly Observed Treatment, Short-course (DOTS), for TB treatment and control. A new "Stop TB Strategy" was subsequently implemented in 2006 to address the challenges of the spread of TB and HIV co-infection and multidrug-resistant TB.[11] This strategy aims to (1) achieve universal access to high-quality care for all people with TB; (2) reduce the human suffering and socioeconomic burden associated with TB; (3) protect vulnerable populations from TB, TB/HIV and multidrug-resistant TB; (4) support development of new tools and enable their timely and effective use; and (5) protect and promote human rights in TB prevention, care and control.[12]

2.3.1 TB control in Canada

In Canada, TB control activities are organized according to two models. The first model is a centralized control program that includes the provision of clinical services, and is implemented in the provinces of British Columbia, Alberta, Saskatchewan, and Manitoba, and the Yukon, Northwest and Nunavut territories. The second model has both centralized and decentralized public health elements and exists in Ontario, Quebec, New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador. The delivery of clinical services in these provinces is provided by community-based specialists and primary care physicians. In both models, there are three levels of government involved: local or regional, provincial/territorial, and federal.[2]

2.3.2 TB control in Alberta

In Alberta, where all 97 smear-positive pulmonary TB cases were diagnosed, the management of all active TB and latent TB cases is centralized out of Alberta Health Services (AHS). More specifically, TB services are provided by public health TB clinics, where each case is managed by a team that includes public health and community health nurses and a university based TB physician. Between 1989 and 1998, two clinics (one in Edmonton and one in Calgary) provided service to the north and south of the province, respectively. Subsequent to 1998, an additional 'Provincial' clinic was established to provide service to the remainder of the province, while the two clinics restricted service to their own urban areas.[13]

2.4 Current TB control strategy

The rise of drug resistant TB strains, the spread of HIV and the increase in global movement of persons from high to low TB incidence countries have significantly contributed to the growing health threat of TB. Early, and accurate, diagnosis of TB is critical to reduce mortality and ongoing transmission, and ensures that infected patients will be treated with appropriate therapies.

2.4.1 Case finding and case holding

The first component of the TB control program is case finding and case holding, which focuses on the rapid finding of active TB cases to prevent ongoing transmission and the timely initiation of therapy for all active TB cases, respectively.[2] Current TB control measures implemented in our Canadian healthcare system relies on a passive surveillance system which aims to reduce the incidence of disease and spread of infection through early case detection and treatment of persons with LTBI that have high risks of developing active disease. Instead of an active approach of screening populations, the TB control program in Canada attempts to identify TB through three main methods of TB detection: (1) the recognition of symptoms in patients presenting to public health facilities, (2) contact investigation and screening, and (3) immigration screening.

In Canada, the detection of TB in patients that present symptoms account for majority of the TB cases identified. This process, however, depends upon alert and informed medical practitioners.[2] A diagnosis of active TB involves a careful

evaluation of the combination of symptom compatible with diagnosis of infectious TB and consideration of those known to be in high-risk groups.[14] Subacute symptoms, such as a chronic cough over a 3 weeks' duration, and constitutional symptoms, such as weight loss or fever, are generally manifestations of TB. However, because the subacute and constitutional symptoms are non-specific, there needs be another layer of consideration, whether the patients belong in high risk groups.

According to the Canadian TB Standards, persons belonging to the following epidemiologic groups are of high-risk of reactivation of latent infection: (1) persons from countries of high TB incidence, (2) First-nations persons, (3) the poor or homeless, (4) staff and residents of long-term care and correctional facilities, and (5) those at risk of occupational exposure to TB, especially health care workers likely to be exposed to active cases of pulmonary TB. Persons having one or more of the following risk factors are also of high-risk of reactivation of latent infection: (1) HIV/AIDS infection, (2) transplantation or immunosuppressant therapy, (3) silicosis, (4) chronic renal failure requiring hemodialysis, (5) carcinoma of the head and neck, and (8) abnormal chest x-ray or fibronodular disease.[2]

To complete the clinical picture for a TB diagnosis, a chest radiograph (CXR) – a safe, cost-efficient, and widely available study– is usually performed. In the presence of abnormal chest radiographic findings, along with the

consideration of risk groups and presentation of symptoms, sputum for acid-fast bacteria smear and culture is usually acquired. The sputum culture and smear results, which are considered the gold standard in diagnosis, can confirm the diagnosis of TB in patients.[2]

If a patient is diagnosed with active TB, then the patient is put on directly observed therapy (DOT), which is the standard of care recommended by the WHO and the Canadian Tuberculosis Standards. DOT is a process whereby a health care provider administers and observes a patient swallow each dose of their prescribed medication. This method of treatment leads to higher treatment completion rates and has been shown to reduce drug resistance and relapse, as compared to self-administered therapy.[2]

2.4.2 Chemoprophylaxis

The second component of the regional program comprises of chemoprophylaxis. Chemoprophylaxis or preventive treatment is offered to individuals who are latently infected with TB or individuals who have high risk factors for TB. Preventive treatment refers to the treatment of latent TB infection (LTBI); treatment is only started once the diagnosis of active TB has been eliminated.[15]

2.4.3 Surveillance

Surveillance is the third key component of the regional TB program. Surveillance is an ongoing process of systematic collection, evaluation and timely dissemination of health information.[2] This process of surveillance is essential for effective disease control and prevention, and should be conducted at all levels of the public health system. Comprehensive surveillance on TB will strengthen policy making, improve allocation of resources and assist in establishing more effective TB services and programs.

2.4.3 Education and research

The last component of the regional TB screening program is ongoing staff training and education and academic research. As stated by Long and Ellis, appropriate training should be provided to all program staff to ensure that they have accurate and current knowledge of TB and its management. Moreover, education programs should aim to increase the awareness and understanding of TB control and prevention among patients, communities, and leaders.[2]

Academic research serves an essential role in the evaluation of program effectiveness and provides imperative information on TB epidemiology. In Alberta, the Tuberculosis Program and Evaluation Research (TB PE & RU), which was established in 1998 through funding from Alberta Health and Wellness (AH & W), provides programming and data analysis to all levels of the public health system and health care organizations to inform strategic planning and

resource management specific to TB prevention and control. The component of research, in conjunction with the other components of the regional TB program, allows for comprehensives in the management of TB.

2.5 Summary

This chapter provided a background on TB as a disease. It examined the burden of disease in Canada, and specifically among high-risk population groups, Canadian-born Aboriginal peoples and foreign-born peoples. The TB program and service delivery in Canada and Alberta were highlighted and the current control strategies were discussed. In chapter three, a review of current relevant literature will be presented.

Chapter 3: Literature Review

3.1 Introduction

This literature review was developed to review the relevant literature and current research on PTB case detection using computer-aided detection systems and public health consequences of PTB patients, with or without typical radiographic features.

A systematic review of relevant literature was performed using MEDLINE and EMBASE. With the assistant of the research librarian, the following search terms were identified: “pulmonary tuberculosis”, “transmission”, “automated detection”, and “chest radiograph*”.

3.2 Importance of case detection

Current case detection rates are low; in order to reach the targets under the global DOTS strategy, there needs to be development of new case finding strategies.[16] According to Styblo and Burmagarner, TB incidence could be reduced by 5-10% per year if a minimum of 70% of TB cases are detected and 85% of those cases are successfully treated.[17] This projection has been adopted by the WHO as its primary targets for TB control for the international STOP TB Strategy.[12,17] Dowdy and Chaisson developed a mathematical, compartmental difference-equation model that examined the effects of rapid scale-up of TB control efforts to a case detection rate of 70% and a treatment success rate of 85%. Their model shows that if such targets could be reached, TB incidence will decrease by an average of 10% per year for 10 years. Further improvement in case

detection, however, will lead to a more gradual decline in TB incidence at 3% annual decline). Once the case detection target levels are achieved, the TB incidence will stabilize within 10 years.[17]

Several studies proposed methods to improve case detection rates beyond target levels.[17,18] Dowdy and Chaisson suggests that improvement to case detection rates is most attainable by increasing the frequency of diagnostic attempts.[18] Future research into new diagnostic tools with improved diagnostic sensitivity may also increase diagnostic frequency, and thus, aid in improving case detection rates. In both developed and developing countries, there is a need for intensified case finding of infectious cases. WHO proposed a framework for which cure and case detection rates may be significantly improved: (1) wider involvement of community workers, (2) engagement of private practitioners, (3) proper management of drug-resistant tuberculosis, and (4) efforts focused on controlling tuberculosis and human immunodeficiency virus.[1,12] Such interventions signify a dramatic shift in the approach of TB control that is necessary for target case detection levels to be reached.

Case detection rates remain low in developing and low-income countries.[19,20] In developing countries, studies have attributed the poor case detection rate to the lack of skilled healthcare workers.[19,21,22] Datiko and Lindtjørn notes improvement in case detection and treatment success rates after training community health workers on how to identify suspects, collect sputum and

provide DOT. Emphasis should be placed on preventive strategies by use of pragmatic TB awareness programs and innovative screening methods.[21]

In developed countries, with low TB incidence, case detection rates are critically important as well. Diagnosis of TB is often missed because clinicians fail to think of TB beforehand. Morrison et al. emphasizes that investigation of people exposed to infectious TB cases is a key to TB control.[23] Were it possible to automate the process of detection of infectious PTB cases, diagnosis of TB can be reached earlier and transmission can be reduced.

3.3 Delayed diagnosis of TB

Despite the fact that the diagnosis of person with TB entails a rigorous and detailed evaluation, often times a diagnosis of disease can still be missed upon the patient's initial encounter in a health care facility. A missed or delayed diagnosis is usually attributed to the fact that clinicians or radiologists fail to consider the diagnosis of TB beforehand due to the symptoms and signs of TB being non-specific or patient is not considered at risk for TB. This is not rare especially in developed countries, such as Canada, where the TB incidence rates are low or developing countries, where there is a shortage of skilled workers. In such instances of a missed or delayed diagnosis, there is a consequent further risk of the infection being transmitted to others and a further increase in TB morbidity and mortality, ultimately resulting in a larger public health burden (Figure 3.1).

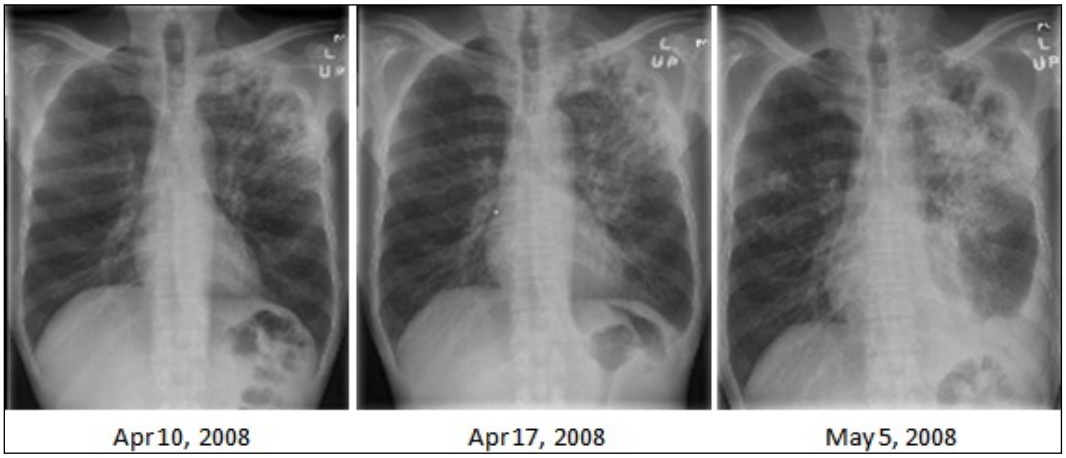


Figure 3.1. Serial CXRs of a middle aged foreign-born male who presented to a tertiary care emergency department on three occasions, April 10, 17, and May 5, 2008. CXRs were performed on each occasion but TB was not considered until the last visit, May 5 (delay 24 days).

A systematic review conducted by Storla et al. examined the delay in diagnosis and treatment of TB reported in 58 studies. Their findings suggested that diagnostic delays can be categorized as either involving patient or healthcare delay. For instance, factors related to patient delay include "alcohol or substance abuse, poverty, low access to health care facilities, rural residence, old age, belonging to an indigenous group and incomprehensive attitudes, beliefs and knowledge about TB".[24] On the other hand, factors related to health care delay also played a major role in delayed diagnosis, including the "coexistence of chronic cough and/or other lung diseases, having extra-pulmonary or negative sputum smear TB, less severe and indifferent symptoms or absence of hemoptysis, poor health care infrastructure and seeking traditional and private practitioners first".[24] Significantly, the researchers found that many studies identified the underlying problem to be the cycles of repeated visits to multitude

of healthcare providers before a diagnosis is reached. The authors attribute this finding to the poor training in diagnosing TB among health personnel among many developing countries.[24]

A separate systematic review by Sreeramareddy et al. examined specifically the time delays in diagnosis of PTB reported in 52 studies. Their results showed that there is a considerable time delay between the onset of symptoms, ranging from 25 to 185 days. The researchers noted that for effective TB control, the target for patient delay and health care delay should not be more than 2 -3 weeks and 3-4 weeks, respectively. However, their analysis reviewed that both patient delays and health delays far exceeded this acceptable limit by 10-15 days and 3-4 weeks, respectively. Sreeramareddy et al. concludes that both patient and health care factors contribute to the unacceptable delays.[16]

Both reviews stress the importance of time delays to diagnosis in TB prevention and control strategies. Shortening the delay in diagnosis will significantly reduce patient morbidity and disease transmission and improve TB control.[16,25] The researchers conclude that there needs to be improved skills among clinicians in order for early treatment and proper infection control measures to be implemented.[25]

3.4 Application of chest radiography in diagnosis of TB

To resolve this public health care problem in Canada and other developed countries where the disease is not common or in developing countries with a shortage of skilled healthcare workers, is not an easy task. However, new technology has offered a possible solution to overcome this barrier. In recent years, digital radiographs have come to replace film-based chest units, bringing along new applications for CXRs in the role of TB detection.

A prospective study performed by Churchyard and colleagues examined the yield of TB cases detected using symptom and chest radiographic screening. They found that the addition of chest radiography to the screening process increased the number of definite TB cases by 2.5-fold, from 113 cases detected by symptom screening alone to 281 cases detected by both symptom and chest radiography screening.[26] This study was conducted among three gold mining companies, where TB incidence is relatively high. The authors concluded that the addition of chest radiography improves sensitivity of TB screening, resulting in fewer missed TB cases.

Similar findings were reported in other prevalence studies among miners in clinical settings and communities.[26-28] A TB prevalence survey performed in two urban communities in Cape Town, South Africa evaluated the relative contributions of symptom and chest radiographic screening in TB case detection.[28] den Boon et al. concluded that CXR screening is an effective

alternative to mass sputum examination and would greatly reduce the number of people who would otherwise have to undergo sputum examination. They report that the sensitivity of symptom screening for detection of TB cases was relatively low, even when examining for presence of at least one of five symptoms. This finding confirms with results of another study performed by Gothi et al. which similarly found that CXR screening was a satisfactory tool and that symptom screening did not lead to detection of more TB cases.[29]

Several studies examined the validity of CXR configurations in PTB prediction models.[30,31] Cohen and colleagues analyzed CXR findings which showed significant difference between TB and non-TB patients. Typical CXRs were significantly more frequent in patients with TB, especially patients with smear-positive TB. Very few TB patients were reported to have a normal CXR, none of which were smear-positive. The authors concluded that CXR configuration may help triage hospital resources to patients. Tattevin and colleagues similarly found CXR to be a significant predictive factor of culture-positive pulmonary TB in their predictive model ($p<0.00001$).[30]

Barnes and colleagues found that among 188 non-AIDS patients, 160 (85%) had either a typical pattern (which consisted of alveolar, interstitial, or cavitary infiltrates in the upper lung zones) or a miliary pattern. Of significance, 98% of those patients with CXRs that demonstrate either cavitation or extensive alveolar infiltrate were found to be smear-positive by sputum.[32] Similarly, Bock

and colleagues reported that CXR with upper lobe infiltrate or cavitation to be the strongest predictor for active TB and suitable as a guide for a respiratory isolation policy.[31]

There is limited research that examines whether chest radiography can be used to determine whether patients are more or less infectious than others (have more or less transmission events). Rodrigo and colleagues sought to determine the epidemiologic characteristics of smear-positive TB cases who generate secondary cases by analyzing predictive roles of radiology pattern, among other factors. The authors conclude that those index cases with cavitary radiology patterns have identified more secondary cases.[33]

3.5 Computer-aided detection systems

With appropriate programming, the digital CXR can learn to recognize radiologic features typical of post-primary disease and alert the radiologist, clinician, and public health department of the need for immediate action. In doing so, this detection system will prevent missed TB diagnoses attributed to clinicians or radiologists that fail to consider the diagnosis of TB beforehand. Ultimately, this detection system will aim to reduce the morbidity and mortality due to TB through decreasing the risk of a delayed or missed diagnosis.

Several papers have shown progress in the development of an automated detection system for diagnosing TB. In a recently published review article by Jaeger and colleagues, a total of 16 papers describing experimental screening programs developed for detection of PTB on chest radiographs were compared.[34] The majority of these systems were directed at recognizing all features of TB, with only a few focused on targeted detection of specific radiographic features, such as cavitation and infiltration. In their paper, they described the complexity in TB screening is attributed to the large variety of TB manifestations encountered, ranging from subtle military patterns to more obvious pleural effusions. The different papers each employ a different imaging techniques and approaches. What Jaeger et al. found was that it is near impossible to compare the performances of the proposed systems in a fair manner, especially since the datasets were not publicly available. Their group was optimistic, however, that CAD systems can reach a level of human performance, or possibly outperform expert radiologists in the near future.

In a recent prospective study done by Muyoyeta and colleagues, a CAD for scoring CXRs of presumptive TB patients was successfully tested in a real world setting. They employed a CAD4TB software which had been trained to distinguish between normal and abnormal CXRs in a primary health care facility in Lusaka, Zambia, which services a high TB and HIV burden population. They authors found that the CAD had a 100% negative predictive value and sensitivity,

but poor specificity of 23.2%. This suggests that the CAD can be used as an effective screening tool, especially in high burden settings. [35]

3.6 Public health consequences of TB patients

Rodrigo and colleagues also examined other variables associated with secondary case generation, including age, sex, intravenous drug use, AIDs, HIV infection, district of residence, history of imprisonment, alcoholism, smoking, history of TB, and treatment compliance.[33] Among 1079 smear-positive TB patients whom had undergone contact investigations, 78 (7.2%) had one secondary case and 30 (2.8%) had two or more secondary cases. The majority of secondary cases occurred in children and young adults, with relatively equal gender distribution. In terms of index cases, those that were intravenous drug users, those with cavitary radiology pattern, and those between 15-45 years of age were significantly more likely to be associated with secondary cases.

A study performed by Marks et al. examined the outcomes of contact investigations of 1080 pulmonary, smear-positive TB patients in a low incidence area. Household contacts and contacts to persons having cavitary to highly smear-positive disease were found to have the highest infection rates.[36] Similar findings were reported by Ansari et al. who evaluated the outcomes of contact investigations of 103 TB cases, and found that of the 707 contacts identified and screened, seven secondary cases were detected, all of whom were young, unvaccinated, close contacts of index cases with PTB.[37]

A study conducted by Liipo, Kulmala and Tala investigated the contacts of infectious PTB cases to determine whether different grades of sputum-smear positivity (scanty, moderate or heavy) have any impact on transmission events.[38] Out of 134 index cases, 609 close contacts were reported, with four contacts developing active TB. The four secondary cases were all close contacts of index cases that had a heavily positive smear.

Chapter 4: Methodology

4.1 Introduction

The following section outlines the details of the data collection and data analysis that was conducted for this thesis. A brief description of the patient characteristics and study setting is first provided. Next, a discussion of the study design for this project will be reviewed.

4.2 Patient characteristics

Over a 36 month period beginning January 1, 2006, sequential adult (>14 years) airway secretion smear-positive PTB cases diagnosed in the Province of Alberta, Canada (population 3,290,350 persons in 2006, Statistics Canada)[39], were identified in the Provincial TB Registry. Each case had one or more smear-positive, polymerase chain reaction (PCR)-positive airway specimens collected within 7 days of the start date of treatment.

Patient's demographic and clinical features were abstracted from public health and clinical records. 'High' and 'moderate' risk factors for the development of active TB in persons with presumed latent TB infection (LTBI), as described in the Canadian TB Standards, were identified for each case.[2]

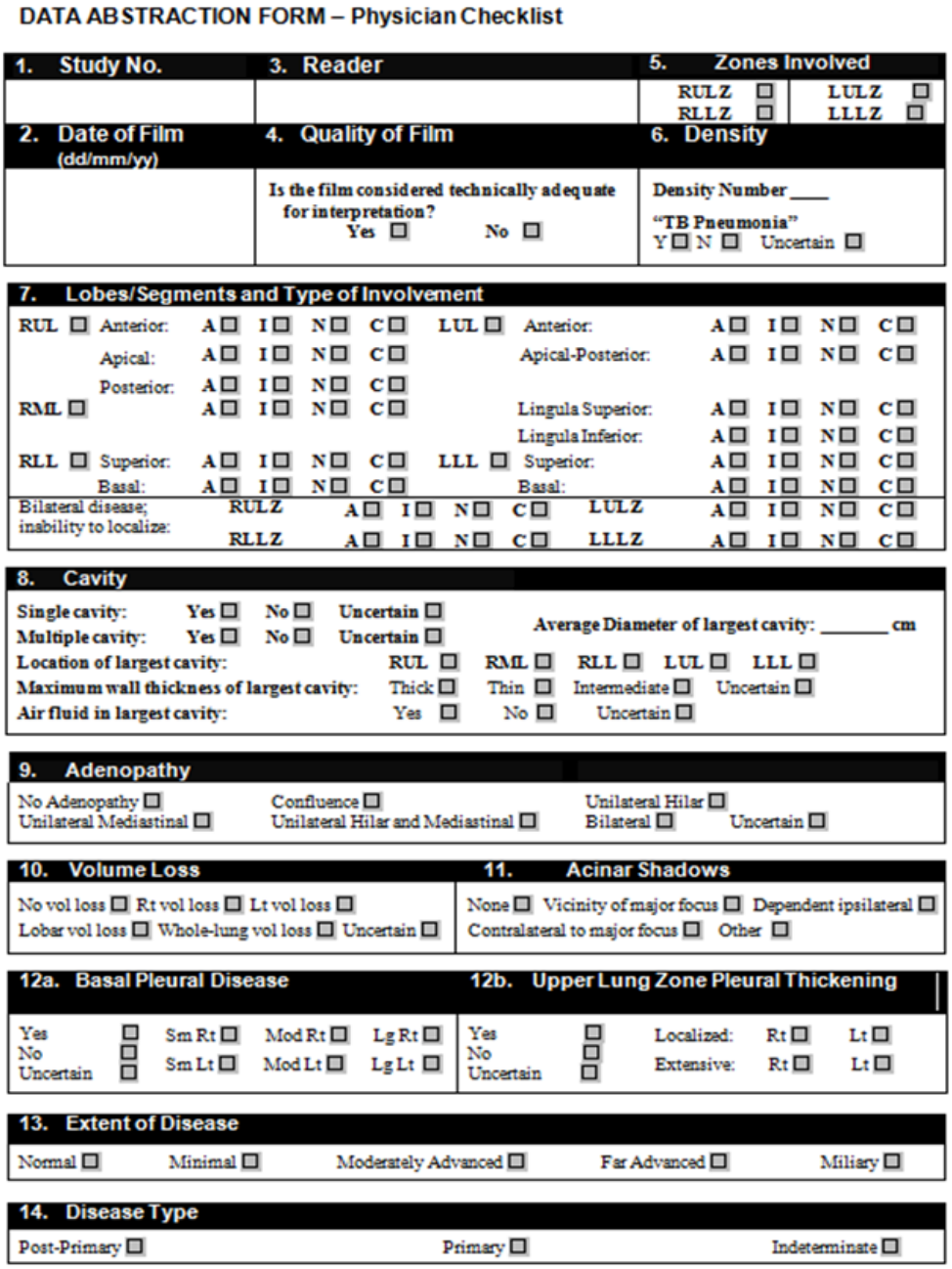
Patient mycobacteriologic histories were abstracted from the Provincial Laboratory for Public Health (PLPH), where all mycobacteriology in the province is performed. Histories included the number, type, semi-quantitative smear size,

and time-to-culture-positivity of all smear-positive airway secretion specimens collected within 7 days of the start date of treatment. Airway secretion specimens included spontaneous and induced sputum, auger suction, endotracheal or tracheal tube suctionings, bronchial wash, broncho-alveolar lavage, and airway secretions collected at post-mortem.[2]

4.3 Radiographic features

Posterior-anterior (PA) and lateral (LAT) Digital Imaging and Communications in Medicine (DICOM) chest images acquired closest to the start date of treatment were assembled and read by three independent readers (a TB pulmonologist and two university-based chest radiologists). A data abstraction form and accompanying data dictionary was used to report and categorize the chest radiograph (see Figure 4.1). Documented were the presence or absence of: (1) parenchymal infiltrates and their location; for the purpose of this study no distinction was made between infiltrates that were airspace, interstitial, nodular or some combination of these; segments and zones of involvement were recorded; an imaginary horizontal line midway between the apex of the lung and the dome of the diaphragm, divided each lung into two zones, upper and lower; (2) cavities, defined as parenchymal cysts greater than 1 cm in diameter, the widest diameter of the largest cavity and the number of cavities (single or multiple); (3) adenopathy – hilar, mediastinal or both; if parenchymal shadows confluent with the hila or paratracheal mediastinum rendered it impossible to exclude adenopathy, the presence of 'confluence' was reported; and (4) pleural effusion.

Information on parenchymal infiltrates, cavitation, adenopathy, and pleural effusion was subsequently used to categorize patients as having "typical" or "atypical" radiographs (see Figure 4.2). For those patients with infiltration localized to or predominantly in the upper lung zones, with or without cavitation, but with no discernable intrathoracic adenopathy, the radiograph was categorized as "typical" for adult-type PTB.[40-43] In patients with: (1) no abnormality; (2) intrathoracic adenopathy with or without parenchymal disease; (3) a localized or predominant lower lung zone infiltrate, with or without cavitation; (4) an isolated pleural effusion; and (5) a miliary (diffuse micronodular) pattern, the radiograph was categorized as "atypical" for adult-type PTB. An inter-reader variability analysis was performed and any discordance resolved by consensus.



DATA ABSTRACTION FORM – Physician Checklist

1. Study No.

3. Reader

5. Zones Involved

RULZ ☐ LULZ ☐
RLLZ ☐ LLLZ ☐

2. Date of Film (dd/mm/yy)

4. Quality of Film

Is the film considered technically adequate for interpretation?
Yes ☐ No ☐

6. Density

Density Number ____

"TB Pneumonia"
Y ☐ N ☐ Uncertain ☐

7. Lobes/Segments and Type of Involvement

RUL ☐	Anterior:	A ☐	I ☐	N ☐	C ☐	LUL ☐	Anterior:	A ☐	I ☐	N ☐	C ☐
	Apical:	A ☐	I ☐	N ☐	C ☐		Apical-Posterior:	A ☐	I ☐	N ☐	C ☐
	Posterior:	A ☐	I ☐	N ☐	C ☐						
RML ☐		A ☐	I ☐	N ☐	C ☐		Lingula Superior:	A ☐	I ☐	N ☐	C ☐
							Lingula Inferior:	A ☐	I ☐	N ☐	C ☐
RLL ☐	Superior:	A ☐	I ☐	N ☐	C ☐	LLL ☐	Superior:	A ☐	I ☐	N ☐	C ☐
	Basal:	A ☐	I ☐	N ☐	C ☐		Basal:	A ☐	I ☐	N ☐	C ☐
Bilateral disease; inability to localize:	RULZ	A ☐	I ☐	N ☐	C ☐	LULZ		A ☐	I ☐	N ☐	C ☐
	RLLZ	A ☐	I ☐	N ☐	C ☐	LLLZ		A ☐	I ☐	N ☐	C ☐

8. Cavity

Single cavity: Yes ☐ No ☐ Uncertain ☐
Multiple cavity: Yes ☐ No ☐ Uncertain ☐
Average Diameter of largest cavity: _____ cm
Location of largest cavity: RUL ☐ RML ☐ RLL ☐ LUL ☐ LLL ☐
Maximum wall thickness of largest cavity: Thick ☐ Thin ☐ Intermediate ☐ Uncertain ☐
Air fluid in largest cavity: Yes ☐ No ☐ Uncertain ☐

9. Adenopathy

No Adenopathy ☐ Confluence ☐ Unilateral Hilar ☐
Unilateral Mediastinal ☐ Unilateral Hilar and Mediastinal ☐ Bilateral ☐ Uncertain ☐

10. Volume Loss

No vol loss ☐ Rt vol loss ☐ Lt vol loss ☐
Lobar vol loss ☐ Whole-lung vol loss ☐ Uncertain ☐

11. Acinar Shadows

None ☐ Vicinity of major focus ☐ Dependent ipsilateral ☐
Contralateral to major focus ☐ Other ☐

12a. Basal Pleural Disease

Yes ☐ Sm Rt ☐ Mod Rt ☐ Lg Rt ☐
No ☐ Sm Lt ☐ Mod Lt ☐ Lg Lt ☐
Uncertain ☐

12b. Upper Lung Zone Pleural Thickening

Yes ☐ Localized: Rt ☐ Lt ☐
No ☐ Extensive: Rt ☐ Lt ☐
Uncertain ☐

13. Extent of Disease

Normal ☐ Minimal ☐ Moderately Advanced ☐ Far Advanced ☐ Miliary ☐

14. Disease Type

Post-Primary ☐ Primary ☐ Indeterminate ☐

Figure 4.1: Data abstraction form used to categorize patients as being typical (post-primary) or atypical (primary or indeterminate).

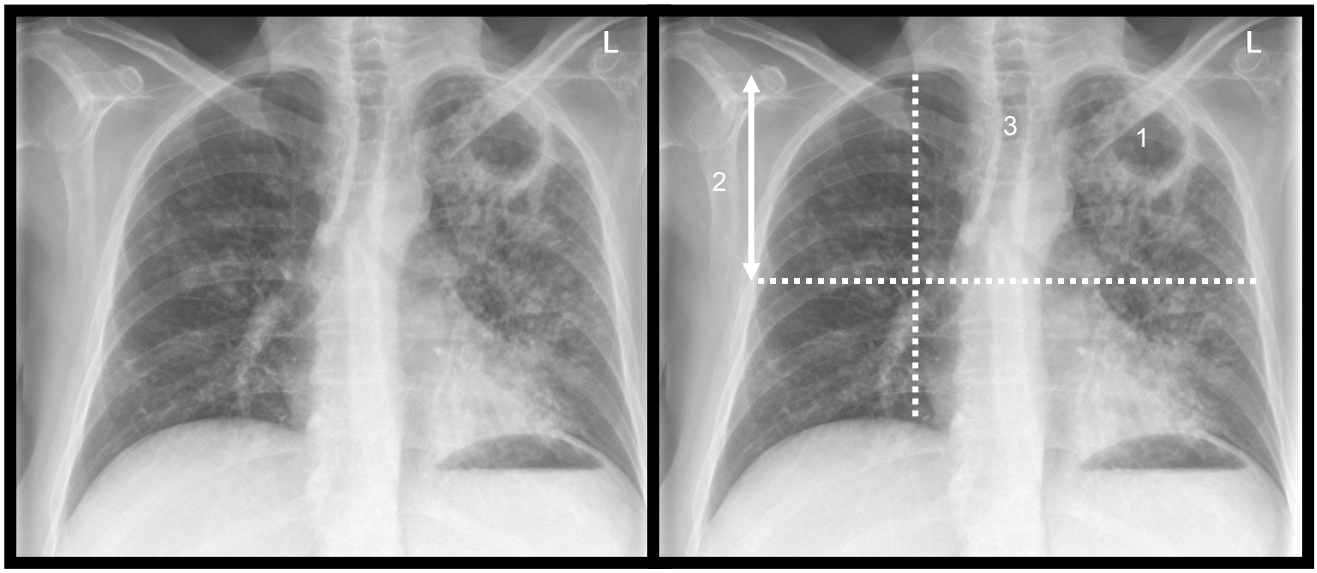


Figure 4.2: Plain chest radiograph that identifies infectious tuberculosis

LEGEND

1. **CAVITATION:**

   (i) at site of airspace/interstitial disease (present in 50% of cases);

   (ii) usually round (the broncho-cavitary junction behaves as a check-valve) and thick walled;

   (iii) may be multiple;

   (iv) (iv) air-fluid levels are uncommon.

2. **UPPER LOBE DISTRIBUTION:**

   (i) airspace interstitial process involving the apical-posterior segment of the upper lobe and/or the superior segment of the lower lobe;

   (ii) may be bilateral; if not the contra-lateral lung may be used for comparison.

3. **VOLUME LOSS:**

   (i) may be seen in chronic disease due to fibrosis of lung;

   (ii) often deviates trachea towards affected side.

4. **ACINAR SHADOWS:**

   (i) multiple poorly defined nodules 4-10mm in diameter in the vicinity of the major site of disease, dependent or contralateral to the major site of disease

4.4 Transmission Events

Information on the number, assessment, tuberculin skin test (TST), and disease status of contacts of each infectious PTB case was abstracted from public health records. 'TST conversion' was defined according to the Canadian TB Standards. Initial isolates of *Mycobacterium tuberculosis* from all culture-positive TB patients in the province between July 1st, 2005, i.e. 6 months before the date of diagnosis of the first infectious PTB case, and December 31st, 2010, i.e. 24 month after the date of diagnosis of the last of the infectious PTB case regardless of whether or not they belonged to the above smear-positive PTB cohort, were DNA fingerprinted using restriction fragment-length polymorphism (RFLP) supplemented as necessary by spoligotyping in isolates with five or fewer copies of the insertion sequence, *6110*. Once cases were identified, their contact lists were assembled and cross-referenced against the provincial Registry to identify any secondary cases.[44] Secondary cases were grouped as *Type 1* or *Type 2* based

on their conventional and molecular epidemiologic links to infectious PTB cases as follows:

Type 1, individuals diagnosed within a transmission window that extended from 6 months before to 24 months after the date of diagnosis of the PTB case, listed as a contact of the PTB case, culture-positive, and infected with an isolate of *M. tuberculosis* that matched (DNA fingerprint) that of the putative source case; *Type 2*, individuals notified with active disease within the same transmission window but who were culture-negative (mainly children). The date of diagnosis of the source case is defined as the start date of treatment. To account for the possibility that PTB cases had incomplete contact lists, secondary cases were searched for among notified cases of TB in the province who were culture-positive with a DNA fingerprint matched isolate of *M. tuberculosis*, and were temporally (diagnosed in same 30-month transmission window) and spatially (lived in same forward sortation area [FSA]* as determined by the first three digits of their postal code) linked to the source case. These were termed *Type 3* secondary cases. Secondary cases that were diagnosed before the date of diagnosis of the source case had to have primary disease. The 30-month transmission window was chosen as it was expected that most contacts would become a secondary case within the period extending from 6 months before to 24 months after the data of diagnosis of their source case as the risk of disease after infection is highest during this period of time.[45,46] In the event that a study source case, either "typical" or "atypical" was themselves a secondary case of someone else, transmission events attributed

to them were scrutinized for plausibility to ascertain whether their "secondary" cases were not more appropriately attributed to their own source case.

4.5 DNA fingerprinting methodology

Isolates of *M. tuberculosis* from all culture-positive cases of TB diagnosed in the Province of Alberta are routinely fingerprinted using restriction fragment-length polymorphism (RFLP), supplemented in those isolates with five or fewer copies of the insertion sequence *6110*, by spoligotyping.[46] The analysis is performed on coded specimens in a blinded fashion. The images are digitized using an imager video camera system, and subsequently analyzed in a blinded fashion using the Gelcompar II software. To improve accuracy, all isolates matched as identical by the computer were manually confirmed by visual comparison of the original autoradiographs. Over the six months preceding the study period, the three year study period, and the two years following the study period, all incident case isolates of *M. tuberculosis* (n=535) were DNA fingerprinted.

4.6 Statistical analysis

The IBM SPSS Statistics software version 17.0 was used for statistical analysis of the data. Generalized kappa statistics were performed to quantify the level of agreement between the expert readers, with the standard error reported as the asymptotic variance. Association between the demographic and mycobacteriologic characteristics of "typical" versus "atypical" cases was

evaluated with either binary or multinominal logistic regression. The logistic regression was used to estimate the odds ratio (OR) of characteristics of "typical" versus "atypical" cases, along with their 95% confidence interval (95% CI). Univariate analysis was performed for categorical data, including the analysis of transmission events, using the Pearson's chi-squared test or the Fisher's exact test as appropriate. A two-tailed p-value <0.05 was taken as statistically significant. For comparison of the mean number of assessed contacts per case and the mean number of days to assessment of TST converters between "typical" and "atypical" cases, a *t*-test was employed. All statistical analyses were reviewed with a statistician.

Study approval was obtained from the University of Alberta Health Research Ethics Board (HREB). Retrospective analysis of anonymous and routinely collected surveillance data did not require direct patient contact; therefore the need for patient's informed consent was waived by HREB.

Chapter 5: Results

5.1 Introduction

This chapter outlines the results from all analyses performed in this study. Demographic information of the study population will first be provided. Next, the mycobacteriologic data analysis of typical and atypical cases will be compared. Lastly, the public health consequences of the typical and atypical cases will be detailed.

5.2 Demographic characteristics

Between January 1, 2006 and December 31, 2008, 99 adult (age >14 years) smear-positive PTB patients were diagnosed in the province of Alberta, Canada, and notified in the Provincial TB Registry. Two patients were excluded from the analysis because their radiographs were technically inadequate for interpretation.

The four key radiographic features judged to be the most important for the purpose of determining the "typical" or "atypical" nature of a case-patient's lung disease were: (i) distribution (predominantly upper lung zone disease), (ii) cavitation, (iii) volume loss, and (iv) endobronchial spread (acinar shadows); see Figure 1. Kappa statistics showed substantial agreement (>0.60) for disease type, distribution, and cavitation, and fair agreement (<0.3) for volume loss and endobronchial spread (see Table 5.1).[47]

Table 5.1: Expert inter-reader variability of chest radiographic interpretations

Expert reader interpretation*	Agreement	Kappa statistic	Asymptotic standard error (ASE)
Disease type ("typical" vs "atypical")	Substantial	0.660	0.082
Presence or absence of cavitation	Substantial	0.749	0.067
Presence or absence of upper lung zone	Substantial	0.643	0.097
Presence or absence of volume loss	Fair	0.352	0.074
Presence or absence of acinar shadows	Fair	0.257	0.059

*See text for definition of terms

Of the 97 cases that were included in the analysis, 69 (71.1%) had "typical" and 28 (28.9%) had "atypical" chest radiographs. Patients with "typical" and "atypical" chest radiographs did not differ by age, sex, or population group (Table 5.2). Not surprisingly, HIV co-infected patients were more likely to have "atypical" chest radiographs (OR 0.17 [0.05-0.55]).

Table 5.2: Demographic and clinical features of smear-positive PTB patients with "typical" and "atypical" chest radiographic features

Patient Demographics and Clinical Features	Total No. (%)	CXR Category		OR (95% CI)
		"Typical" No. (%)	"Atypical" No. (%)	
No. Assessed	97 (100.0)	69 (71.1)	28 (28.9)	
Age				
15 – 64	71 (73.2)	54 (78.3)	17 (60.7)	1.0
≥65	26 (26.8)	15 (21.7)	11 (39.3)	0.43 (0.17-1.11)
Sex				
Male	53 (54.6)	40 (58.0)	13 (46.4)	1.0
Female	44 (45.4)	29 (42.0)	15 (53.6)	0.63 (0.26-1.52)
Population Group				
CBA and CBNA	30 (30.9)	22 (31.9)	8 (28.6)	1.0
FB	67 (69.1)	47 (68.1)	20 (71.4)	0.86 (0.33-2.24)
HIV Status				
Negative	73 (75.3)	56 (81.2)	17 (60.7)	1.0
Unknown	10 (10.3)	8 (11.6)	2 (7.1)	
Positive	14 (14.4)	5 (7.2)	9 (32.1)	0.17 (0.05-0.55)
Other Risk Factors				
None or Unknown	44 (45.3)	29 (42.0)	15 (53.6)	1.0
1 or more	53 (54.6)	40 (58.0)	13 (46.4)	1.59 (0.66-3.85)

*Abbreviations: PTB pulmonary TB; CXR chest radiograph; CI confidence interval; CBA Canadian-born Aboriginal; CBNA Canadian-born non Aboriginal; FB foreign-born

5.3 Mycobacteriologic characteristics

The bacillary burden and presence or absence of cavitation on chest radiograph of PTB patients at the time of diagnosis is described in Table 5.3. The number of specimens collected was not statistically significantly different among the "typical" and "atypical" groups. Compared to case-patients with "atypical" chest radiographs, case-patients with "typical" chest radiographs were more likely to have specimens with a large (>3+) semi-quantitative smear size. All positive

AFB smears were 1+ or greater; all 3+ or greater positive AFB smears had >10AFB per high power field using Fuchsin stain.[2] Consistent with a high bacillary burden, patients with "typical" chest radiographs were more likely to have specimens with shorter times-to-liquid culture positivity, within one week vs >1 week (p=0.03). Time-to-liquid culture positivity is understood to be a quantitative measurement of metabolic activity inversely related to the number of viable bacilli innoculated.[48] Patients with "typical" chest radiographs were more likely than those with "atypical" chest radiographs to have cavitary disease and, if cavitary, to have larger cavities (>3 x 3cm), (p=0.001 and p=0.001, respectively; data not shown).

Table 5.3: Bacillary burden and cavitation in smear-positive PTB cases with "typical" and "atypical" chest radiographic features

Radiographic and Mycobacteriologic Features	CXR Category		OR (95% CI)
	"Typical" No. (%) (n=69)	"Atypical" No. (%) (n=28)	
Number of Airway Specimens Collected[†]			
1 or 2	32 (46.4)	19 (67.9)	1.0
≥3	37 (53.6)	9 (32.1)	2.44 (0.97-6.15)
Semi-quantitative Smear Size			
<3+	36 (52.2)	21 (75.0)	1.0
≥3+	33 (47.8)	7 (25.0)	2.75 (1.04-7.31)
Time-to-culture Positivity (Days)			
Less than one week	39 (56.5)	9 (32.1)	1.0
One week or greater	30 (42.5)	19 (67.9)	0.36 (0.14-0.92)
Cavitation			
No Cavitation	33 (47.8)	25 (89.3)	1.0
Cavitation Present	36 (52.1)	3 (10.7)	9.10 (2.51-32.94)

[*]Abbreviations: PTB pulmonary TB; CXR chest radiograph; CI confidence interval

5.4 Transmission events

The number of close contacts identified and assessed per PTB case was similar among patients with "typical" and "atypical" chest radiographs (p=0.789 and p=0.257, see Table 5.4). "Typical cases" had more TST converters than "atypical" cases (p=0.002). The number of days to assessment of TST converters were not significantly different among the two groups (p=0.462). Unsurprisingly, typical cases had on average more TST converters who were secondary cases

(p=0.010). Moreover, "typical" cases also had more secondary cases per TST converter or a higher attack rate compared to "atypical" cases (p=0.001).

Conventional and molecular epidemiology identified 42 secondary cases, 17, 8, and 17 *Type 1*, *2*, and *3*, respectively (see table 5). Compared to "atypical" cases, "typical" cases were responsible for more secondary cases of all three types (p=0.001). When broken into subcategories, typical cases were found to have significantly more *Type 1* and *Type 3* secondary cases (p=0.002 and 0.020, respectively). Although typical cases were responsible for more *Type 2* secondary cases, the total number of *Type 2* secondary cases was not found to be of statistical significance (p=0.420).

Patients with "typical" and "atypical" chest radiographs were further broken down into those with or without transmission events (see appendix A). Radiographic characteristics of cases with and without secondary cases are described in Appendix B. Lastly, a complete list of the "typical" and "atypical" cases with one or more TST converter or secondary case is summarized in Appendix C and D.

Table 5.4: Transmission events among close contacts of smear-positive PTB Cases according to chest radiograph category

	Total	CXR Category		p-value
		Typical (n=69)	Atypical (n=28)	
No. Contacts Identified	1442	1000	442	0.789
No. Contacts Assessed (% of those identified)	1161 (80.5)	813 (81.3)	348 (78.7)	0.257
No. Assessed Contacts Per Case (Mean±SD)	12.0±17.6	11.8±18.2	12.4±16.4	0.861
No. Contacts with TST Conversion*	86	67	19	0.002
No. Days to Assessment of TST Converters (Mean±SD)	90.2±102.3	85.8±92.1	105.5±134.2	0.462
No. of TST Converters Who Were Secondary Cases	25	24	1	0.010
No. of Secondary Cases Per TST Converter (Attack Rate)	0.29	0.36	0.05	0.001

Abbreviations: PTB pulmonary TB; CXR chest radiograph; No. number; TST tuberculin skin test; SD standard deviation

* No. of contacts with TST conversion include Type 1 and 2 secondary cases

Table 5.5: Secondary cases among smear-positive PTB patients according to chest radiograph category

Secondary Cases by Type*	Total	CXR Category		*p*-value
		Typical (n=69)	Atypical (n=28)	
Type 1	17	17	0	0.002
Type 2	8	7	1	0.420
Type3	17	16	1	0.020
All Types	42	40	2	0.001

Abbreviations: PTB pulmonary TB; CXR chest radiograph

Chapter 6: Discussion

Tuberculosis remains a public health problem of global proportions. Making a timely diagnosis of pulmonary TB in developed countries where the disease is not common or in developing countries where technological advances or skilled workers may be in short supply is a daunting task. If, through inexperience or inadequate human resources, a diagnosis of TB is delayed or not made by the clinician or the radiologist, transmission is ongoing and outcomes potentially poorer. Currently available digital technology should make it possible to automate the detection of "typical" post-primary or adult-type pulmonary tuberculosis on chest radiographs.[49-52] The development of a computer-aided detection (CAD) system is especially warranted if it can be demonstrated that patients with "typical" (vs. "atypical") chest radiographs are responsible for most transmission events (public health consequences). To our knowledge, there have been no studies that have compared the transmission events of patients with radiographically "typical" versus "atypical" adult-type pulmonary TB.

In our study, we hypothesized that compared to "atypical" cases, "typical" cases were more common, more likely to have cavitation on chest radiograph and/or a high bacillary burden on mycobacteriology, and more likely to have transmission events. We found that "typical" cases were indeed more common than "atypical" cases, accounting for over two-thirds of all smear-positive, culture-positive pulmonary TB cases in our study setting, an immigrant receiving province of Canada. Smear-positive PTB is well known to be about five times

more infectious than smear-negative PTB.[41,53] "Typical" cases were also more likely to have cavitations on chest radiograph and/or high bacillary burdens. Cavitary disease is itself known to be associated with higher bacillary burdens and to be an independent risk factor for transmission.[54-57] Given these findings, it is not surprising that we found "typical" cases had more transmission events than "atypical" cases, accounting for 78% of TST conversions and 95% of secondary cases.

TST converters of smear-positive PTB cases are known to be more likely to have disease than TST converters of smear-negative PTB cases presumably because of the higher probability of re-infection from smear-positive cases; each infection within the first 12-24 months of the initial infection understood to have a similar risk of causing disease.[58,59] Conceivably, cavitation and a high bacillary burden in smear-positive "typical" cases results in a higher probability of re-infection and disease than in smear-positive "atypical" cases. Therefore, although "atypical" cases can cause transmission, their TST converters are less likely to develop disease because, we hypothesize, their re-infection risk is lower than in "typical" cases. We found that 24 out of the 67 TST converters from "typical" cases became secondary cases versus only 1 out of the 19 TST converters from "atypical" cases.

One of the strengths of this study was that 98% of consecutive smear-positive cases within our study period were included in the analysis, with only

two cases being excluded due to technically inadequate radiographs. A comprehensive film library was assembled for all 97 cases, and three expert readers independently analyzed and categorized the films as being "typical" versus "atypical" using a standardized data abstraction tool (see Fig. 4.1). Transmission events from all 97 cases were abstracted from public health records. One of the advantages of the study taking place within a single jurisdiction is that contact tracing was performed in a systematic fashion. To account for the possibility of incomplete contact lists among source cases, we conducted a search for secondary cases among all notified cases of TB in the province that were culture-positive with a DNA fingerprint matching the initial isolate of *M. tuberculosis* from the source case. Of those cases with a DNA fingerprint match, we accepted only those that were spatially and temporally linked to the source case to be a *Type 3* secondary case. The fingerprint database over the 5.5 study years was also very comprehensive (of 784 cases, 652 [83.2%] grew M. tuberculosis and of those that grew M. tuberculosis, 650 [99.7%] were fingerprinted). The main limitation of this study is that it is retrospective. Were this a prospective study, specimen collection could be performed in a systematic manner. The source cases varied in the number of respiratory specimens collected, ranging from one to seven specimens collected within one week of the start date of treatment. Another obvious limitation of this study is the relatively small number of adult smear-positive PTB cases (n=97). This study could be repeated in a larger center to ensure results are comparable in other settings and/or are generalizable.

In conclusion, "typical" cases are more common than "atypical" cases, more likely to have cavitation on chest radiograph and/or a high bacillary burden on mycobacteriology, and most importantly, are responsible for more transmission events. If the detection of this cohort of PTB patients, most likely to transmit and cause transmission events could be automated, infectious PTB might be diagnosed earlier. In countries with low-incidence of TB, this point-of-care tool can alert physicians to provide further workup or investigation for suspect PTB cases. Several papers have shown progress in the development of an automated detection system for diagnosing TB. In a recently published review article by Jaeger et al., a total of 16 papers describing experimental screening programs developed for detection of PTB on chest radiographs were compared.[34] The majority of these systems were directed

at all features of TB, with only a few focused on targeted detection of specific radiographic features, such as cavitation and infiltration.[60] Automated reading has been found to be comparable to interpretations by clinical officers in a study by Maduskar et al.[61] Unfortunately it is difficult to compare the performance of these experimental systems, as the datasets are not publicly available. Another possibility is to develop a CAD system that provides a probability score.[62,63] The information from radiographic features of "typical" patients can be combined with clinical information to provide a probability score that can guide clinicians to taking further measures. This raises an important research question that has not yet been answered- how would a CAD system compare with field readers in influencing rates of TB transmission. We believe that with a CAD system that

targets “typical” features of PTB, a diagnosis of the most infectious PTB can be reached earlier, TB transmission will be interrupted and patient outcomes improved.

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APPENDIX A: Characteristics of Typical and Atypical PTB Patients with and without Transmission Events*

Characteristic of Source Case	Typicals		p-value	Atypicals		p-value
	with transmission events (n=33)	without transmission events (n=36)		with transmission events (n=13)	without transmission events (n=15)	
Age						
15-64yo	27	27	0.136	8	9	0.958
≥65yo	6	9	0.544	5	6	0.948
Cavitation						
Yes	21	15	0.207	3	0	0.001
No	12	21	0.187	10	15	0.011
Smear Size						
<3+	14	22	0.283	11	10	0.584
≥3+	19	14	0.262	2	5	0.343

Abbreviations: PTB pulmonary TB; TST tuberculin skin test

*Transmission events are defined as TST converters or secondary cases

APPENDIX B: Characteristics on Chest Radiograph of Cases with and without Secondary Cases on Chest Radiographs

Characteristics on Chest Radiograph	Cases without Secondary Cases (n=75)	Cases with Secondary Cases (n=22)
Zones of Involvement		
No involvement	4	0
Upper lung zone	53	20
Lower lung zone	18	2
Cavity		
Single	16	9
Multiple	7	7
Largest diameter of cavity ≥3x3cm	12	8
Largest diameter of cavity <3x3cm	11	8
Air fluid level present in cavity	1	0
Volume Loss		
Yes	18	12
No	57	10
Acinar Shadows		
Present	30	16
Absent	45	6
Pleural disease		
Present	16	18
Absent	59	4
Extent of disease		
Minimal advanced	24	1
Moderately advanced	27	10
Far advanced	15	11
Other	9	0

APPENDIX C: Summary of Typical Cases with Transmission Events

Typical Transmitters	Cavitation on CXR	Smear Size	TST Converters	Secondary cases								
				Type 1			Type 2			Type 3		
				0-14yo	15-64yo	>64yo	0-14yo	15-64yo	>64yo	0-14yo	15-64yo	>64yo
CXR 001	No	<3+	0	0	0		2(1)	0				
CXR 008	Yes	≥3	1									
CXR 013	Yes	≥3	2									
CXR 015	No	≥3	1									
CXR 019	Yes	≥3	0		2(0)							1(0)
CXR 021	No	<3+	2									
CXR 031	Yes	<3+	0[								1(1)	
CXR 033	No	≥3	0		1(0)							
CXR 039	Yes	<3+	1		1(0)							
CXR 044	Yes	<3+	1									
CXR 046	Yes	≥3	4								1(0)	
CXR 047	No	≥3	1									
CXR 048	Yes	≥3	4		1(0)							
CXR 051	No	<3+	1									
CXR 052	Yes	<3+	0								2(0)	
CXR 058	No	<3+	6									
CXR 061	Yes	≥3	0							1(1)		
CXR 063	Yes	≥3	0								1(0)	
CXR 065	Yes	≥3	2		2(0)						3(0)	
CXR 069	No	≥3	1									
CXR 070	No	<3+	9		2(0)		1(0)				1(0)	
CXR 079	Yes	≥3	0	1(0)								
CXR 081	No	<3+	0								1(0)	
CXR 082	Yes	≥3	0								4(2)	
CXR 083	Yes	≥3	1									
CXR 086	Yes	≥3	2	2(1)	1(0)							
CXR 087	Yes	<3+	0				1(1)					
CXR 088	Yes	≥3	0		1(1)							
CXR 090	No	≥3	1									
CXR 096	Yes	<3+	1									
CXR 098	Yes	<3+	0	1(0)			1(1)					
CXR 099	Yes	≥3	0		2(0)		2(1)					
CXR 100	No	<3+	2									

APPENDIX D: Summary of Atypical Cases with Transmission Events

Atypical Transmitters	Cavitation on CXR	Smear Size	TST Converters	Secondary cases								
				Type 1			Type 2			Type 3		
				0-14yo	15-64yo	>64yo	0-14yo	15-64yo	>64yo	0-14yo	15-64yo	>64
CXR 003	No	<3	1									
CXR 017	No	<3	1									
CXR 022	No	<3	1									
CXR 023	No	≥3	3									
CXR 028	No	<3	0						1(0)			
CXR 032	No	<3	3			1(1)						
CXR 037	No	<3	2									
CXR 041	No	<3	1									
CXR 042	Yes	<3	1									
CXR 043	Yes	<3	1								s	
CXR 049	Yes	≥3	1									
CXR 059	No	<3	1									
CXR 078	No	<3	2									