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PREVALENCE AND DETERMINANTS OF TUBERCULIN REACTIVITY AMONG PHYSICIANS IN THE EDMONTON CAPITAL HEALTH AUTHORITY

by

SABRINA S. PLITT

A THESIS
SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

IN

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled *Prevalence and Determinants of Tuberculin Reactivity Among Physicians of the Edmonton Capital Health Authority* submitted by *Sabrina S. Plitt* in partial fulfillment of the requirements for the degree of Master of Science in Medical Sciences – Public Health Sciences.

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ABSTRACT

Health care workers (HCWs) have historically borne a heavier burden of tuberculosis (TB) infection and disease than the general population. Unfortunately, physicians are rarely included in HCW surveys. In this study, however, baseline prevalence is determined and risk factors for TB infection for the 1,732 physicians in the Edmonton Capital Health Authority are identified. Stratified random sampling was used to select 554 specialists and 219 general practitioners. Selected physicians were contacted personally by introductory letter and follow-up telephone call to solicit participation. In total, 560 physicians (72.4%) participated in the study by completing a questionnaire; all eligible physicians with either no recorded positive tuberculin test or a previously negative result were two-step tuberculin skin tested. The overall tuberculin reactivity for this population is 45.9%. Logistic regression analysis was used; the risk factors for reactivity are age over 45 years, foreign birth, previous BCG vaccination, foreign practice experience, and being a respiratory medicine specialist.

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CHAPTER ONE

TUBERCULOSIS - AN INTRODUCTION

The purpose of this study is to establish the prevalence of and determine risk factors for tuberculin reactivity among physicians in the Edmonton Capital Health Authority. In this chapter, a brief overview of the clinical and epidemiological aspects of tuberculosis is provided.

1.1 Introduction

In 1993, the World Health Organization (WHO) declared tuberculosis (TB) a global emergency. It was estimated that one-third of the world's population has been infected with TB (WHO, 1997). In 1995, there were more reported cases of TB than ever before, 3 million cases and 1.8 million deaths (WHO, 1996). TB is underreported, however, and estimates of the true number of cases and deaths of TB for 1995 were 8.8 million new cases and 3 million deaths, and the projection is for 11.9 million new cases by the year 2005 (Snider et al., 1994). These rising numbers of TB cases follow decades of decline. As improvements in public health control measures and the introduction of effective anti-tuberculous drug regimens in the 1950s provided hope for the elimination of TB, the number of TB cases declined sharply (Raviglione et al., 1995). However, in the developing world, TB remained endemic because TB control programs received scant attention. Because of this neglect, not only is the world experiencing a marked increase in the prevalence of TB, but poor drug management has led to multi-drug resistant TB (MDR-TB) (Raviglione et al., 1995).

There are several factors that have contributed to the resurgence of TB, not only in the developing world, but also in North America and Western Europe. Lack of public health funding resulted in inadequate, or absent, treatment for those with active TB and therefore uninhibited transmission. The Human Immunodeficiency Virus (HIV) pandemic introduced a factor that changed the risk of the co-infected from 10% likelihood of reactivation to 50% (Selwyn, 1989). Finally, the emergence of multi-

drug resistant (MDR) strains of TB reduced the likelihood of cure from nearly 100% to 50%, equivalent to untreated TB. (Bloom and Murray, 1992; Alberta Health, 1994, Raviglione et al., 1995).

1.2 The Canadian Tuberculosis (TB) Scenario

Despite the fact that the overall Canadian TB rate is one of the lowest in the world at 7.4/100,000 (Johnston, 1997), it would be both unsafe and naive to conclude that this global "emergency" does not affect Canada. Increased travel and migration have created a new dilemma in the control of tuberculosis in that no one country can remain untouched by the changes in TB rates and drug resistance. In 1987, after years declining TB rates, Canadian rates leveled at 7/100,000 (Long et al., 1998). In Canada, the shift of immigration source from Europe to Asia, Africa, and Latin America, regions where TB remains endemic, has resulted in increasing percentages of cases who are foreign born (Long et al., 1998). Of the 1,930 cases of TB recorded by Health Canada in 1995, 1,116 (57.8%) were among foreign-born (in 1980, 35% of cases were foreign-born (Stat. Canada, 1996)). In addition, this immigration has led to the occurrence of multi-drug resistant strains of TB in Canada. A 1993 study of drug resistant TB in Western Canada indicated that 78% of the 37 drug resistant cases occurred in foreign born patients (Long et al., 1996). Of the 156 TB cases in Alberta in 1996, 16 (12.6%) of the cases were drug resistant. Of these 16 cases, 15 were foreign-born persons (Alberta Health, 1995).

Another feature of TB in Canada is the disproportionately high rates of TB among the aboriginal communities (treaty and non-treaty native Indians, Metis, Inuit). In 1995, the Alberta total rate was 4.56/100,000, while the Alberta Aboriginal rate was 32.25/100,000 (Alberta Health, 1995). Even though aboriginal Canadians account for about 4% of the population, they account for 25% of the Canadian TB cases (Fanning and Fraser-Lee, 1996). An examination of 1989-1994 average provincial TB rates indicates substantially higher rates for the North West Territories (NWT, 55/100,000) and the Yukon (19.9/100,000), reflecting the higher rates among the aboriginal populations (the territories have large aboriginal populations) (Alberta Health, 1994).

Although TB rates in the NWT have fluctuated widely in past years, (ranging from 104.9/100,000 in 1989, to 34.8/100,000 in 1991, and then back up to 102.6/100,000 in 1994), they are consistently higher than the other provinces and territory (Alberta Health, 1995).

1.3 Tuberculosis (TB) Epidemiology

In general, TB mortality and morbidity rates increase with age and, in older populations, rates are higher among males than females. This increased risk with increasing age is strongly related to the higher incidence of previous TB infection in this group, and the consequent potential for disease from reactivation of a latent infection. Epidemics of TB have been reported among people assembled in enclosed spaces, such as in homeless shelters, nursing homes, hospitals, and prisons. TB rates are higher in urban than in rural areas (Benenson, 1995). In Alberta, approximately two-thirds of TB cases are urban dwellers, even though only about half of Albertans live in urban areas (Fanning and Fraser-Lee, 1996). In addition, TB rates are higher among those in lower socio-economic strata (Benenson, 1995); there is a clear trend noted for increasing TB rates and decreasing income quintile (Fanning and Fraser-Lee, 1996).

Globally, TB is mainly a disease of the developing world. The highest prevalence of TB is seen in Sub-Saharan Africa and South East Asia. In 1990, 49% of the 3.8 million cases worldwide were reported from South East Asia (Raviglione et al, 1995). Even with declining TB rates until the 1980's, TB remained endemic at approximately 200 cases/100,000 (Snider et al., 1994). The HIV pandemic is the major factor for the recent rise in the number of TB cases in the developing world (Schulzer et al., 1992). In developed countries, the rates, although relatively low, are increasing among populations with either a high prevalence of HIV infection, or with large numbers of persons from areas where TB is endemic (Benenson, 1995).

1.4 Clinical Tuberculosis (TB)

TB is a disease caused by the bacterium *Mycobacterium tuberculosis* (MTB). Although this disease is predominantly pulmonary (approximately 75% (CLA, 1996)), any part of the body can be infected. MTB is characterized by an extremely slow growth rate under optimal conditions (one generation every 17-18 hours (Grosset, 1993)), and immune recognition results in a dormant state. In more than 90% of those infected, TB is characterized by a post-infection period of good health and a small potential to reactivate years after the original infection (Bloom and Murray, 1992).

TB is most commonly transmitted through the inhalation of droplet nuclei containing MTB. These droplets are created by an active TB case during expiratory efforts, such as coughing, singing, talking, or sneezing. The aerosolized droplets of pulmonary secretions dry rapidly, leaving tiny droplet nucleii, which are of a small enough size (1-10 microns) to float in the air for a considerable period of time and easily reach the bronchioles and alveoli when inhaled (Bloom and Murray, 1992). These droplet nucleii, containing bacteria, are most often produced by patients with active pulmonary (including laryngeal) TB who have a productive cough and positive sputum smears (i.e., MTB is seen in sputum samples examined under light microscopy) (Benenson, 1995). Therefore, it is the close contacts of the smear positive patient who are at maximum risk of being infected. Fortunately, however, TB is not highly infectious; the infection rate among close contacts ranges from 25%-50%, even in the worst overcrowded and substandard conditions. (Moulding, 1988).

Infection through the pulmonary routes from handling contaminated fomites is not a significant problem, and infection by way of inoculation when bacilli are introduced into or through the skin, although possible, is infrequent. However, infection from this source has been documented among pathologists and laboratory workers who handle infected tissues or cultures (Moulding, 1988). Except in rare situations, extrapulmonary TB is generally not communicable, nor is minimal pulmonary TB with smear negative sputum and small bacterial population (Benenson, 1995).

The initial TB infection generally goes unnoticed, and tuberculin skin test sensitivity usually appears after 3-6 weeks. (Benenson, 1995) Of those initially infected individuals, 90%-95% will enter into a latent phase resulting in a small (~3%) lifelong risk of reactivation. However, in 5%-7% of normal hosts, the initial infection may progress directly to pulmonary TB, or through the lymphohematogenous dissemination of bacilli, miliary, meningeal, or other extrapulmonary involvement may occur. Serious outcome of the initial infection is more frequent among infants, adolescents, young adults and the immunosuppressed. (Benenson, 1995)

Diagnosis is based mainly on presence of tubercle bacilli in the sputum and also on the nature of the change seen on chest X-ray. The diagnostic gold standard is the culture of MTB. Approximately 85% of cases of pulmonary TB are confirmed by sputum culture (Health Canada, 1996). Common early symptoms of TB are cough, fatigue, fever, night sweats, and weight loss. Active disease is defined by culture, X-ray, pathology (Benenson, 1995), or occasionally, clinical response to treatment.

If active disease is left untreated, about half of cases will die within five years; the majority of these within the first 18 months. Appropriate completion of chemotherapy nearly always results in a cure, including those who are HIV infected. Tuberculosis patients should be given prompt treatment with an appropriate combination of anti-mycobacterial drugs, with the regular monitoring of sputum smears. In most areas, the currently accepted initial treatment consists of a four-drug therapy for two months (isoniazid (INH), rifampin, pyrazinamide, and ethambutol or streptomycin). After drug sensitivity results are available, usually, two drugs, INH and Rifampin, are given for four months (Benenson, 1995). Drug resistance requires special tailoring of the drug regimens. The alternative drugs used in multi-drug resistant TB (MDR-TB) cases are generally more toxic and less effective therefore dropping the cure rate to 50% (Bloom and Murray, 1992).

1.5 Tuberculosis (TB) Disease Prevention

The risk of progression from latent to active disease is reduced by approximately 90% by using a chemoprophylactic 6-12 month course of Isoniazid (INH) (Bloom and Murray,1992; CLA, 1996). This course is routinely recommended for infected individuals with recent skin test conversion or close association with a recent contact. The most significant side effect associated with this course is INH-induced hepatitis that occurs in 1.2% of those individuals between 35-49 years and 2.3% of individuals over the age of 50. Therefore, monitoring of hepatotoxicity is important (CLA, 1996).

The Bacille Calmette-Guérin (BCG) vaccine is not routinely used in North America, except for certain groups of people at high risk for TB exposure (CLA, 1996). Before 1980, many HCWs were routinely vaccinated (Holton et al., 1997). The effectiveness of the vaccine is uncertain, but ranges from 0% to 80% (Ildrihim et al. 1995). A recent meta-analysis estimates that the total protective effect of BCG is approximately 50% against tuberculous disease and higher for disseminated and meningeal TB (Colditz et al. 1994, Ildrihim et al. 1995). Post-vaccination tuberculin reactivity ranges from 0-19 mm of induration (CDC, 1996). It is estimated that reactivity occurs in 90% of vaccinated people (Benenson, 1995). This BCG reactivity wanes over time and is unlikely to last longer than 10 years. BCG vaccination is not a contraindication for tuberculin skin testing (CDC, 1996).

The most effective methods of TB control are also the most basic: early diagnosis (and treatment), contact tracing, and surveillance. It is a public health imperative to ensure that TB cases are rapidly diagnosed, and promptly and effectively treated to cure (Smith et al., 1994). Contact tracing is used to identify newly infected persons with whom the infectious case was in contact and, also, to identify the person from whom the case acquired the infection (Smith et al., 1994). Finally, surveillance consists of the routine collection and reporting of epidemiological data to monitor trends in TB infection and disease, and to identify high-risk groups for screening.

1.5.1 Tuberculin Skin Test Screening

Screening is usually conducted by tuberculin skin testing and is limited to high-risk groups (e.g., contacts and HCWs). This test involves injecting a small amount of protein derived from *Mycobacterium tuberculosis* (MTB) intra-dermally. If an individual has previously developed cell-mediated immunity to this tuberculin protein, a delayed hypersensitivity reaction will take place within 48-72 hours after the injection. (The testing protocol is discussed in more detail in Chapter 3.) Screening will aid in identifying active cases who then may be treated to prevent the further spread of infection. It also will identify infected persons who can be informed of their infection status and potentially be provided with prophylaxis to reduce the risk of developing active tuberculosis (CLA, 1996).

It should be noted that a positive tuberculin skin test result does not necessarily indicate MTB infection, but identifies the individual as a reactor to the tuberculin injected for Mantoux testing. Therefore, tuberculin skin testing usually indicates prior exposure to MTB, but, to a lesser extent, can indicate previous exposure to other environmental Mycobacteria or prior BCG vaccination. However, these usually result in smaller tuberculin skin test reactions (<10 mm) than a MTB exposure (Reichman et al.,1977). The prevalence of tuberculin reactivity (>9 mm reaction), therefore, is useful in providing an indication of the risk of MTB exposure to individuals.

CHAPTER TWO

TUBERCULOSIS INFECTION IN HEALTH CARE WORKERS

In this chapter, a discussion of the literature concerning tuberculosis (TB) infection among health care workers (HCWs), specifically physicians, is provided.

2.1 Tuberculosis (TB) in Health Care Workers (HCWs)

The risk of TB to HCWs has long been recognized as an occupational hazard. The rising rates of TB internationally, and some clusters of multi-drug resistant strains in the United States, as well as the changing distribution TB in Canada, has led to heightened concern and a renewed focus on workplace exposure for health personnel.

In the 1920s and 1930s, nurses were 500 times more likely to develop TB than the general public. One compelling study showed that 100% of nursing students converted from negative to positive skin tests during their four-year training and that half of these students converted within the first four months. Other studies focusing on medical students in the 1940s and 1950s showed similar increased levels of infection and disease compared to the general public (Sepkowitz, 1994).

The subsequent decline in TB incidence rates in the Western world after the 1950s was accompanied by a decrease in the concern for the safety and potential exposure of HCWs, and a concomitant decline in TB funding for screening and prevention programs (Bowden, 1994; Sepkowitz, 1994). By the 1980s, TB control programs in hospitals and clinics had lost priority, and many hospital employee tuberculin skin testing programs had been cut or limited to pre-employment screening only (Johnston, 1997).

In contrast to this lack of concern, however, HCWs continue to face higher rates of TB disease and infection than the general public. In 1997, Holton et al. in a survey of

Canadian Hospitals, estimated the HCW conversion rate (i.e., from negative to positive Mantoux results within two years) to be approximately 1.7%, and 4.4% in high-risk hospitals (i.e., six or more TB cases admitted per year). These numbers are compared to the annual infection rate of the Canadian general population of less than 0.1% (Menzies, 1997). A recent study of HCWs in Montreal showed that 38% of the 522 participants were tuberculin reactors; 12% of these reactions were recent conversions (Schwartzman, 1996). A higher proportion of tuberculin reactivity is seen among those HCWs who are foreign-born and those who have been BCG vaccinated (Sepkowitz, 1996, Schwartzman, 1996). Outbreaks of nosocomial multi-drug resistant TB (MDR-TB) in recent years in the United States have emphasized the vulnerability of the HCW because many of them have converted during these outbreaks and at least six HCWs have died from MDR-TB (Liss,1996).

2.2 Tuberculosis (TB) Infection among Physicians

Physicians, like other HCWs, are at a high risk for TB infection and disease. In Holton *et al*'s 1997 paper examining TB infection control programs in Canadian hospitals, physicians had a significantly higher tuberculin skin test (TST) conversion rate than any other occupational group. The risk may be further increased for the physician because he/she often is unknowingly the first HCW to encounter a patient with an active case of TB. The majority of patients with active TB are diagnosed upon presentation to their family doctor with symptoms, usually cough. For example, in Alberta, in 1994, this was the case for 69% of the 178 TB cases (Alberta Health, 1994).

Physicians also can be exposed to TB by unsuspected cases, during aerosol generating procedures such as bronchoscopies, gastroscopies, or post mortem exams (Ramphal-Naley, 1996). This risk is described in a 1990 study that compared the tuberculin conversion rate among pulmonary and infectious disease fellows. The pulmonary physicians in training had nearly a four times higher rate of conversion compared to the infectious disease fellows (Malasky et al. 1990).

Many case reports have indicated that delayed diagnosis and isolation can expose high numbers of HCWs, including physicians, to infection (Ramphal-Naley et al., 1996). It has been reported that during one outbreak, a single patient with undiagnosed TB infected 45% of tuberculin negative medical student-contacts and physician-contacts (Barrett-Connor, 1979). In 1983, an infectious patient who spent four hours in an emergency room department, was responsible for the tuberculin conversion of 11 emergency room employees, 5 of whom developed active TB (Sepkowitz, 1994). Delay, or failure to diagnose TB may occur in countries like Canada where, owing to a relatively low incidence of disease, physicians and other HCWs have little experience with the variety of ways in which a case of TB can present. Another cause of delay in diagnosis is the atypical presentation of TB among those co-infected with HIV or other immunosuppressive conditions as this may lead to difficult clinical or radiology-based diagnosis (Goldman, 1988).

Despite the fact that physicians are at high risk for TB infection, they tend to be complacent about their own risk of TB exposure and disease. Fewer than 50% of TB-positive physicians comply with recommended chest X-rays (Goldman, 1988). One study showed that less than 50% of physicians who converted took the recommended chemoprophylaxis and, of these, more than 25% failed to complete the course (Barrett-Connor, 1979). Approximately one-half to two-thirds of physicians do not have annual tuberculin skin testing, despite this recommendation for HCWs. One study indicated that 35% of practicing physicians have not had a Mantoux test since medical school (Geiseler, 1986). Barrett-Connor suggested that this lack of concern on the part of the physician is based not only on pressure of other priorities, but also on a perceived lack of vulnerability (Chan and Tabak, 1985; Barrett-Connor, 1979)

In the same manner by which physicians may become infected by their TB patients, a physician with active disease may infect a patient. In the early 1980s, a physician in Britain, unaware of his active TB, infected 4 children suffering from immunodeficiency conditions in the pediatric department where he was working (Goldman, 1988). The progression to active disease is especially high for children. In

Canada, a medical resident at the University of Alberta Hospital in 1994 developed active TB. He was the identified source of 71 infections and 4 active cases among the 1,906 contacts tested (Alberta Health, 1994).

2.3 Previous Physician Tuberculosis (TB) Infection Prevalence Studies

Although there have been many studies of TB infection, as measured by prevalence of tuberculin reactivity and active disease, in HCWs, there is a noticeable gap in the literature concerning TB infection and disease rates among physicians. Four studies reported below were directed at physicians and physicians in training (Table 2.1).

TABLE 2.1: Previous Tuberculosis Infection Prevalence Studies Among Physician Populations

	Study Population	Prevalence of Tuberculin Reactors
Barrett-Connor, 1979	4,140 California physicians	42.5% of unvaccinated physicians considered themselves to tuberculin positive
Geiseler et al., 1986	4, 417 graduates from the Illinois College of Medicine (from 1938-81)	46% of physicians with no history of active TB considered themselves tuberculin positive
Fraser et al., 1994	351 physicians at an American teaching hospital	24.5% were tuberculin positive currently or by history
Ramphal-Naley et al., 1996	284 physicians (resident, attending, and associate) at an American teaching hospital	13% of resident and attending physicians 20% of associate physicians

Barrett-Connor in 1979 gathered data on 4,000 California physicians by mailed questionnaire. In this study, she reported that age-specific infections among physicians were at least twice that of the general population of the United States (Barrett-Connor, 1979). More recently in 1994, Fraser *et al,* reported that 24.5% of

351 physicians from an American university-associated tertiary care hospital were skin test positive currently or by history (Fraser et al., 1994).

2.4 Relevance of Prevalence Studies in the Edmonton Capital Health Authority

In the Edmonton-based Capital Health Authority, recent prevalence studies among medical residents and HCWs, excluding physicians, have shown surprisingly high proportions of tuberculin reactivity. House staff prevalence studies, conducted in 1993 and in 1995, found reactor rates of 22.3% and 19.3% respectively. In both of these studies, BCG and foreign birth were significant predictors of reactivity (Fanning et al, 1994, Fanning et al, 1996)

A large, trans-Canada multicentred study of nosocomial transmission of TB to HCWs was completed in 1996. This study indicated that at two Alberta Capital Health Authority hospitals the percentage of HCWs with significant reactions ranged from 12% to 76%, depending upon the unit examined. In this study, physicians were excluded as they could not be linked to specific hospital work units and shifts (Menzies, 1996).

In order to protect the physician, the patient, and the physician's family and friends, physicians must be aware of their TB infection status, as well as the risk factors associated with reactivity, and must be encouraged to follow up a positive tuberculin reaction with the appropriate course of chemoprophylactic therapy. The first step in this process is to ascertain a baseline prevalence level of tuberculin reactivity among physicians, which is one of the aims of the present study.

CHAPTER THREE
MATERIALS AND METHODS

3.1 Study Objectives and Hypotheses

This study had two related objectives:

1) To determine the prevalence of tuberculin reactivity among physicians practicing in Edmonton and the surrounding area (*i.e.* Region 10, Capital Health Authority).

2)To determine the risk factors associated with tuberculin reactivity.

In most studies, BCG and foreign birth are the two factors that are most predictive of tuberculin reactivity. It was our hypothesis that predictive factors for physicians also would include:

a) high-risk patient population: high percentage of aboriginal, foreign born and/or elderly

b)the location of practice: urban (inner city) vs. rural (high income suburbs/sub-divisions)

c) high exposure practices:

i) those physicians dealing with pulmonary disease, specifically infectious TB, that is, specialists of Respirology and Infectious Diseases

ii) those physicians who carry out endoscopic procedures which may be aerosol-generating; that is, specialists of gastroenterology, bronchoscopy, anesthesiology, post-mortem examination

The primary objective of this study is to determine the prevalence of tuberculin reactivity. Prevalence is the proportion of subjects who have a disease at a point in time. Because this measurement refers to the disease status at a point in time, it is also referred to as point prevalence (Hennekens, 1987). Most infectious diseases have such a rapid course that prevalence is an uninteresting measure. However, for chronic

infections, such as TB, prevalence gives an indication of the risk of exposure to susceptible individuals (Giesecke, 1994).

The realization of these two study objectives will allow the determination of a baseline prevalence for establishing future trends in reactivity trends and will provide the basis for implementing targeted programs to prevent the transmission of TB infection.

3.2 Study Design

The study protocol included a cross-sectional study of tuberculin reactors among practicing physicians of the Alberta Capital Health Authority (CHA). Stratified random sampling was used to select participants. The participants underwent tuberculin skin testing, if necessary, and were required to complete the study questionnaire.

3.3 Selection of Cohort

3.3.1 Physician Directory

Physician selection was based on the 1996 directory of the College of Physicians and Surgeons. This directory was provided on floppy disk from in the form of an Excel Spreadsheet. The directory contains the names, addresses, year and place of graduation, and specialty for all physicians who are presently licensed to practice in the province of Alberta.

3.3.2 Physician Sampling

The sampling for this study was done using stratified random sampling. In order to examine the risk factors for tuberculin reactivity and gain adequate information on practice types, the physicians were first stratified as specialist or non-specialist (i.e., general practitioner/family practitioner), as indicated by the College of Physicians and Surgeons directory. The specialist stratum then was sub-stratified according to the 29 specific specialties, while the general practitioner stratum was sub-stratified according to 11 postal code regions in the Capital Health Region (CHA). The sampling fractions for each of the two major strata are different in order to meet the objectives of this

study. Finally, this sampling strategy will allow an overall random sample to be drawn from the entire population of physicians and will be used to estimate an overall prevalence of tuberculin skin test positive physicians in the Capital Health Authority.

i) General Practitioner (GP) Sampling

According to the study's hypothesis, the patient population and location of practice will be predictors of tuberculin reactivity. Therefore, in order to obtain a random sample of general practitioners representative of all the districts in the Capital Health Authority, the GP stratum was sub-stratified by postal code. This postal code stratification was not done on the specialists' practice as these specialists differ from the family physician in that their referral base cuts across CHA postal code areas. Postal code region breakdowns as indicated by the CHA Population Health Division (Apppendix 1) were used to stratify the General Practitioners. These maps indicate 11 regions in the CHA. Physicians were sampled from these strata using random number tables.

ii) Specialist Sampling

In order to address the question of whether physicians in "high risk" specialties, which include pulmonary medicine, infectious disease, gastroenterology, anesthesia, and emergency medicine, have higher proportions of tuberculin reactivity than physicians in other specialties, the specialist stratum was stratified according to specialty prior to sampling. This was to ensure that all physician types were represented in the final study population. One out of two specialists was chosen from each stratum, except in cases of strata containing fewer than 20 individuals where the entire stratum was chosen to ensure adequate power.

3.3.3 Recruitment of the Cohort

The physicians who were chosen as potential participants were each sent personalized letters of introduction to the study (Appendix 2) which indicated that they would be contacted by a follow-up phone call within the next 2-3 weeks. Once contacted, the physicians were asked if they would be willing to participate.

3.3.4 Inclusion and Exclusion Criteria

Either prior to or after initial contact by letter and telephone call, the physician's participation status was assessed using the following criteria:

Inclusion Criteria

- the participant has completed his/her postgraduate medical training
- the participant is a licensed physician who is presently practicing medicine in Region 10 (Physicians who had retired since the publishing of the directory in July 1996, were included in the study if they could be contacted)
- the participant can provide written, witnessed informed consent

Exclusion Criteria:

- the participant presents contraindications to the tuberculin skin test (e.g. extensive skin diseases (psoriasis, eczema))
- the participant was presently on an extended leave of absence (sabbatical, maternity leave, sick leave)

If the participant chosen did not meet these criteria, he/she was replaced by another participant from the same stratum. The replacement participant was chosen by simply taking the next participant's name on the original stratified list. In the case where there were no other participants left in that stratum to choose from, no replacement was made.

3.4. Data Gathering Procedures

3.4.1 Questionnaires

A baseline questionnaire was administered to all participants. The questionnaire (Appendix 3) included items such as:

- Birth date
- Gender
- Country of birth (year of arrival in Canada)
- Past TB testing
- BCG history (year)
- Travel outside of North America, Western Europe, Australia and New Zealand (for longer than 1 month)
- Known TB exposures
- Year of graduation from medical school and work history
- Type of and years in practice
- Amount of patient contact (hours/week)
- Patient population (% Foreign Born, % Aboriginal, % Elderly)

3.4.2 Tuberculin Skin Testing

i)Tuberculin Skin Tests

All skin testing was done by the Mantoux method, whereby 5 tuberculin units of purified protein derivative (PPD) are injected intracutaneously into the volar region of the forearm. PPD from Connaught Laboratories was the only preparation used for this study (however different lots were used). The protocol for Mantoux testing used is attached in Appendix 4.

ii)Tuberculin Skin Test Reading

The tests were read 48-72 hours later; the transverse diameter of the induration was measured using calipers and recorded in millimetres. An induration of 10 mm or larger was considered to be a positive test (Can Lung Assoc, 1996).

The reading of the tuberculin skin test results was done by one of the four designated study staff. In order to ensure consistent and reliable readings, physician self-reading of PPD test results were accepted only in circumstances when the physician could not be met by one of the study personnel. The percentage of self-read tests was 17.3%

(116/669). Only 8.8% (26/295) of physicians who had a two-step tuberculin skin test done did not have either skin test read by one of the study staff.

If a physician claimed to have had a previously positive tuberculin skin test, but could show no documentation of the test, an attempt was made to contact the clinic where the test was done to confirm the result. When these test results could not be confirmed, the study clinician contacted the physician to confirm the validity of the tuberculin reactor status. Repeat tuberculin skin testing was carried out on those physicians who required another test, or those who simply agreed to re-testing.

iii) Two-Step Testing

Two-step testing was done for all those participants who had not had two-step testing in the past 10 years, or annual skin testing. Two-step testing is used to induce the "booster phenomenon". Over time immune memory for the tuberculin antigen fades, a tuberculin injection will "boost" the immune system's recognition of tuberculin. Therefore, a first skin test could be negative, but owing to "boosting", a second skin test as little as 7 to 21 days later could be positive. If a second test were done within the year, it could lead to the incorrect assumption of a conversion (i.e., a new infection/need for prophylaxis) (Can Lung Assoc, 1996). Therefore, during this study, a second test was done 7-21 days after the first, and the second result was reported.

iv) Tuberculin Skin Testing Algorithm

Some of the participating physicians did not need two-step skin testing because they had already had two-step or single tuberculosis testing through their Occupational Health offices within the past year, or had tested positive in the past and therefore did not require repeat Mantoux testing. Therefore, the following protocol was used for testing: (see Figure 3.1)

- prior two-step, no prior TST within 12 months -----> single TST
- prior two-step, prior TST within 12 months -----> record results
- no prior two-step, no TST within one year -----> two-step TST
- no prior two-step, prior TST within one year,

another prior TST within 2 years -----> record results as test 1 and test 2 of a two-step

- no prior two-step, prior TST within one year, no TST in previous year -----> single TST to be reported as test 2 of a two-step.
- prior positive two-step -----> no further testing required, record as positive (in mm)

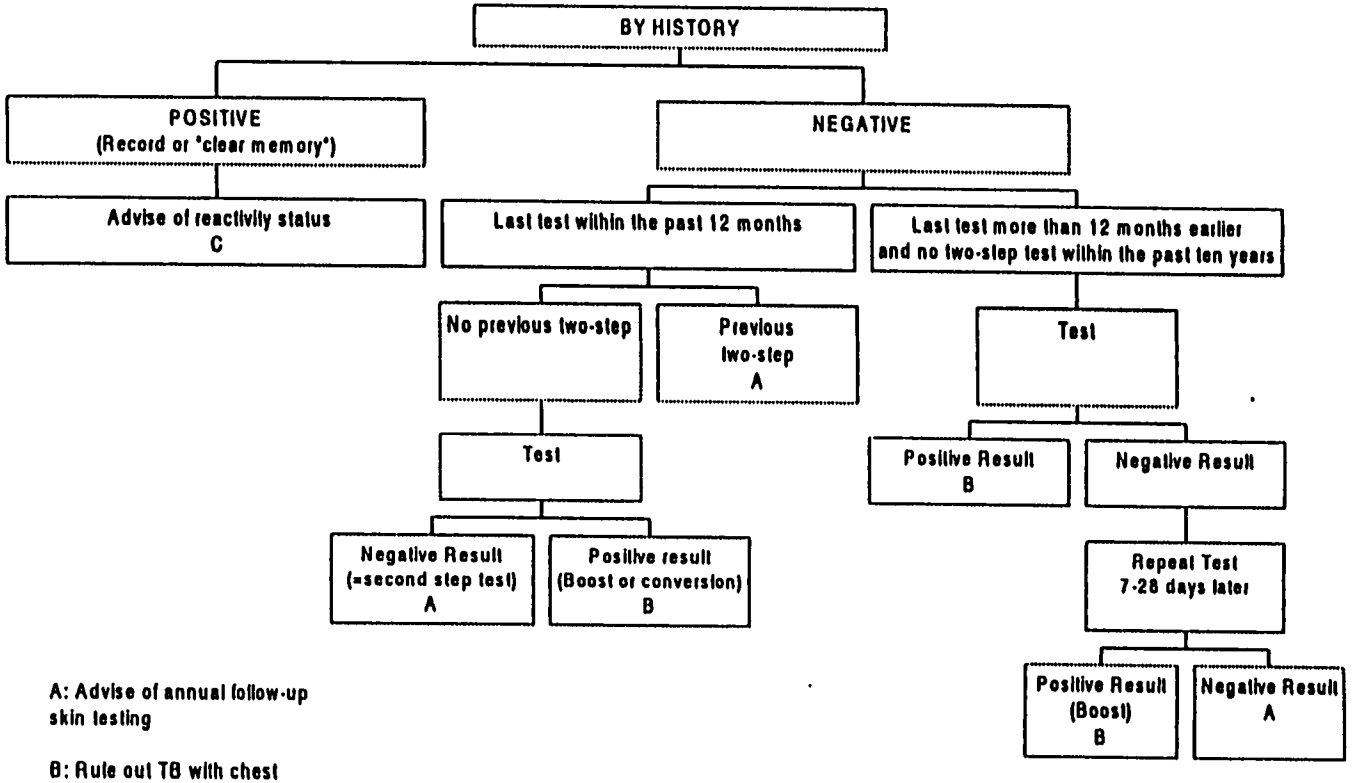
Any physician with a previous negative skin test who was a reactor during the course of this study was advised in writing (Appendix 5) to have a chest X-ray and submit sputum for culture. After TB was ruled out by inquiry, chest X-ray and sputum culture, the physician was advised to consider preventative drug therapy.

3.5. Sample Size Considerations

The primary objective of this study was to estimate the prevalence proportion for this study population, therefore to determine the required sample size the following formula was used: $n = pqz^2/d^2$, where p is an estimation of the proportion of interest, q is equal to1-p, d is the number of units on either side of the estimator, and z is the value of the standard normal distribution corresponding to a significant level of alpha (Daniel, 1974).

In 1996, there were 1,782 physicians in Region 10. Using a Type I error (alpha level) of 0.05 (z=1.96) and a predicted 26% tuberculin positive prevalence ($\pm$ 4%), the sample size was calculated to be: $n_1 = 0.74 \times 0.26\ (1.96/0.04)^2 = 461.95$. The necessary sample size is 462. The participation proportion for this study was predicted to be approximately 70%. (This was determined from a study examining tuberculin reactivity among nurses at two Edmonton hospitals where the participation was 87% (refusals 3%; non-response 10%). With physicians being more difficult to locate, not being attached to a specific work unit, and being recognized for their lack of concern with TB, the participation rate has been reduced to a more conservative estimate.) The required sample size was therefore targeted at 660 (462/ 0.70 =660).

FIGURE 3.1: ALGORITHM FOR TUBERCULIN SKIN TESTING



A: Advise of annual follow-up skin testing

B: Rule out TB with chest X-ray, sputum culture, consider INH

C:No follow-up, unless symptoms - cough
- fever
- weight loss
etc.

With the implementation of the sampling strategy discussed in Section 3.3, the required total sample size of 660 participants was achieved. The total number of physicians selected was larger than the required sample size because of the sampling method used.

941 Specialists	1:2 sampling (per stratum) ---------->	554 physicians
841 General Practitioners	1:4 sampling (per stratum) ---------->	219 physicians
		773 physicians

3.6. Data Management

The questionnaire data and Mantoux results were entered into a database management program (EpiInfo 6.0). This database consists of 773 files representing each participant in the study. In addition, the data were imported into SPSS 7.5 for coding and statistical manipulations. The SPSS database does not include the names of the physicians, but the records can be linked back to the EpiInfo files via identification numbers.

Data cleaning and verification were performed on the data-set. Initially, exploratory descriptive statistics were used to identify any obvious outliers. Following this, every database record was checked against its respective questionnaire. This manual review then was repeated to ensure data accuracy. Upon checking a random sample of 20 questionnaires, an error rate of 0.6% (based on total number of fields in the questionnaire) was found. This error rate was deemed acceptable for the study as the errors appeared to be random and, therefore, as with random misclassification, any effects the errors would have would be a bias towards the null.

All completed data collection forms are now stored in a locked filing cabinet in a locked office in the University of Alberta Hospital.

3.7. Statistical Analysis

All of the statistical analyses were performed using standard statistical software packages (EpiInfo, SPSS, Stata). The principal study outcome is the tuberculin skin

test reaction, either positive or negative. To detect significant differences in the tuberculin reactivity associated with potential risk factors, odds ratios were calculated with 95% confidence intervals. Exact methods were used when the number in any cell was less than five. For the comparison of continuous variables means, the student t-test was used to detect significant differences. Associations between the tuberculin skin test status and categorical variables were assessed using chi-square significance testing, whereas the chi-square for linear trend statistic was used to assess associations between the outcome and ordinal variables.

The preliminary analysis included all participating physicians. Because BCG vaccination and foreign birth have been found to be significant in many studies, a comparative secondary analysis of the data included only non-BCG vaccinated, Canadian-born physicians.

In these analyses, specific methods designed for stratified data were not used. The dataset was so finely stratified that many of the statistical manipulations became unreliable. Unstratified statistical analysis was thought to be adequate as the risk estimates derived from stratified (Mantel-Haenszel) and unstratified methods did not differ significantly. These preliminary analyses were useful in screening for significant variables prior to the multivariate analyses.

Both unconditional and conditional logistic regression methods were used to determine the risk factors associated with tuberculin reactivity, and to adjust for confounding factors. Conditional logistic regression was used because of the highly stratified study population. Unconditional logistic regression was then performed on the data set in order to determine risk estimates for the stratifying variable (specialty). For both logistic regression methods, a manual backward elimination stepwise regression was performed to obtain the most parsimonious model. Statistically and clinically non-significant variables were removed at each step of the model building process. The covariates and the associated coefficients from these two logistic regression models were compared, and a final model was derived. The goodness of

fit of this final regression model was checked using the Pearson chi-square test-statistic, and the Hosmer-Lemeshow test statistic. SPSS (Version 7.5) and Stata (5.0) were the statistical software packages used for the regression analyses (Hosmer and Lemeshow, 1989).

Linearity was examined for all continuous variables by graphical methods. For those continuous variables that were non-linear, the appropriate correction was made, or categories created.

3.8. Ethical Issues

Ethics approval for this research was obtained from the University of Alberta Ethics Review Board. In accordance with their approval, all participants signed an informed consent before beginning the study (Appendix 6). By signing this consent form, the participants agreed to complete the questionnaire, to undergo tuberculin skin testing, and to allow researchers to have access to their tuberculin health records in order to verify previous and/or recent TST results. The information on the physicians was kept strictly confidential and was not available to anyone other than the researchers directly involved in the study.

CHAPTER FOUR

RESULTS - DESCRIPTIVE

This chapter contains an overall descriptive analysis of the study population as a whole. The stratification of the population by specialty is not taken into consideration in this preliminary analysis of the data. Characteristics of the study population and preliminary prevalence rates are examined.

4.1. Study Participation

Of the 1,782 physicians in the Capital Health Authority, 773 (43.4%) physicians were selected as potential participants for the study. Of these, 88 (11.4%) physicians refused to participate, 104 (13.5%) did not respond to the introductory letter or telephone call, and 21 (2.7%) were unable to participate; leaving 560 (72.4%) participating physicians. Of these participants, 492 (63.6%) participated in full, 56 (7.2%) did not return their questionnaire and 12 (1.6%) did not receive the second step of their skin testing. (Table 4.1)

From the Alberta College of Physicians and Surgeons directory, information on the non-participants was obtained that allowed us to compare them with the participants on certain variables. There were significant differences found between the two populations. The non-participants were more likely to have attended medical school in a foreign country, to have graduated from medical school at an earlier year, and they were more likely to be male (Table 4.2). No difference was found in the numbers of specialists and non-specialists between the two groups.

All of the 560 participants were used in calculations of tuberculin reactivity prevalence; including the 12 with a single step. This was deemed acceptable owing to the small number of participants who fell into this group, together with the fact that they did not differ significantly from the participants who completed their testing (Table 4.3). In addition, the rate of boosting from first to second step was only 5.1%

(Table 4.4) and therefore the assumption was made that these participants would not have boosted.

Only those participants who completed the questionnaire could be used in the determination of risk factors. In total, 504 (90%) of the participants completed the questionnaire.

4.2 Characteristics of the Study Population

Demographic characteristics are shown in Table 4.5 for the 560 participants in this study. (Where possible, demographics are shown for the entire population, as well.) The mean age of the population was 47.5 years, 76.4% were male, and 65.1% were born in Canada.

The average length of time since the physician's graduation from medical school was 22.5 years and the majority of the physicians (76.2%) had attended medical school in Canada. Slightly less than half of the population (44%) had been previously BCG vaccinated. Two thirds of the physicians (65.2%) recall being in contact with a known TB case. 11.5% had traveled to a high-risk country[1], and 11.1% have practiced medicine in a high-risk country. Of the participants, 72.9% are specialists and the remaining 27.1% are family practitioners.

4. 3 Prevalence of Tuberculin Reactivity

The prevalence of Mantoux positive skin tests in the study population was 45.9% (n=257). As indicated in Table 4.6 below, 72.3% (n=186) of the skin test positive physicians had previously tested positive. Of these previously positive physicians, 14.5% (n=27) agreed to retesting, 28.5% (n=53) of tests were confirmed on the basis of Occupational Health records, previous chemoprophylaxis therapy, or active disease test. The remaining 57% (n=106) were not re-tested. The remaining 71 (27.6%) skin

[1] High Risk Country is defined as any country, not including Canada, the United States of America, Western European countries, Australia and New Zealand.

test positive physicians were classified as new positive. Of these, 38% (n=27) recalled a previously negative test.

TABLE 4.6: Proportions of Previously Positive and New Positive Results

	n (%)	
Previously Positive	186 (72.3%)	Re-tested: 27 (14.5%) Confirmed: 53 (28.5%) Not Confirmed: 106 (57.0%)
New Positive	71 (27.6%)	Previously negative:27 (38%) Unknown previous test result:44(62%)
Total	257 (45.9%)	

4.3.1 BCG and Foreign Birth

As mentioned previously, 44% of the physicians have previously been BCG vaccinated. Among these physicians, the prevalence of tuberculin reactivity was 69.9% (n=151). The average age of BCG vaccination for this population was 16.8 years and, on average, 33.7 years had elapsed since these physicians were vaccinated. It is interesting to note that it is has previously been reported that only 20%-25% of those BCG-vaccinated after the age of five will remain reactors due to the BCG vaccination 20-25 years later (Menzies, 1992).

Among the 34.9% of non-Canadian born physicians, the prevalence of tuberculin skin test positive results was 70.7% (n=123). The majority of foreign born physicians originated from Western Europe (44.2%) , Asia (29.1%), and Eastern Europe (18.8%). Prior BCG vaccination was reported for 63.5% of the foreign born.

Of those who were both foreign born and BCG vaccinated, 78.3% were tuberculin reactors. For Canadian-born physicians who were never BCG vaccinated, the

prevalence of tuberculin reactivity was 13.1%, compared to 61.5% of Canadian born physicians who had been vaccinated.

Scarring consistent with prior BCG was reported in 51% (n=84) of vaccinated physicians. The prevalence of reactivity among those with a BCG scar was 75.7%, whereas those vaccinated physicians without a scar had a prevalence of 33.1%. These results should be interpreted with caution, however, as the study personnel did not verify scarring at the time of Mantoux testing, and therefore this information may not be accurate. It is noteworthy that other studies report scarring rates of 75-82% among BCG recipients (Horowitz et al, 1995).

4.4 Previous Chemoprophylaxis and Disease

Of the 186 physicians who had tested positive for tuberculosis (TB) in the past, 16.1% (n=30) had previously been on medication for tuberculosis (including both preventative and active therapies). As many as 86.1% (n=186) of the previously positive physicians had never been on medication. Of these, 90.1% had never been offered medication and 9.9% had been offered but refused the chemoprophylaxis. *

Six (1.2%) physicians had reported having active TB in the past. Of these, four were foreign born and had attended medical school outside of Canada. One case occurred when the physician was a young child, whereas four of the cases occurred after graduation from medical school. Only one of the diseased physicians had been BCG vaccinated.

4.5 Boosted Tuberculin Reactions

Boosting from a negative to a positive result between the first and second steps of the test was examined in the 295 physicians who were initially negative and underwent a two-step test. In total, 5.1% of the participants boosted (Table 4.4). Boosting has been strictly defined as having a negative first step test, a positive second step test, and at least a 6mm increase in induration between the two tests. Using this more

* these percentages were based on 101 participants who answered this question

stringent definition, the boosting rate drops to 3.4%. This is comparable to boosting rates in other health care worker studies (Schwartzman, 1996).

BCG vaccination and older age have previously been reported to be significant risk factors for boosted reactions (Horowitz et al, 1995, Schwartzman et al, 1996). In this study population, 80% of those who had boosted reactions had been previously vaccinated. However, the mean age of those with boosted reactions was the same as that of the whole study population. Only 30.8% of boosted reactions were seen in physicians who were born in countries with endemic TB[1].

4.6 Respiratory Protection Use

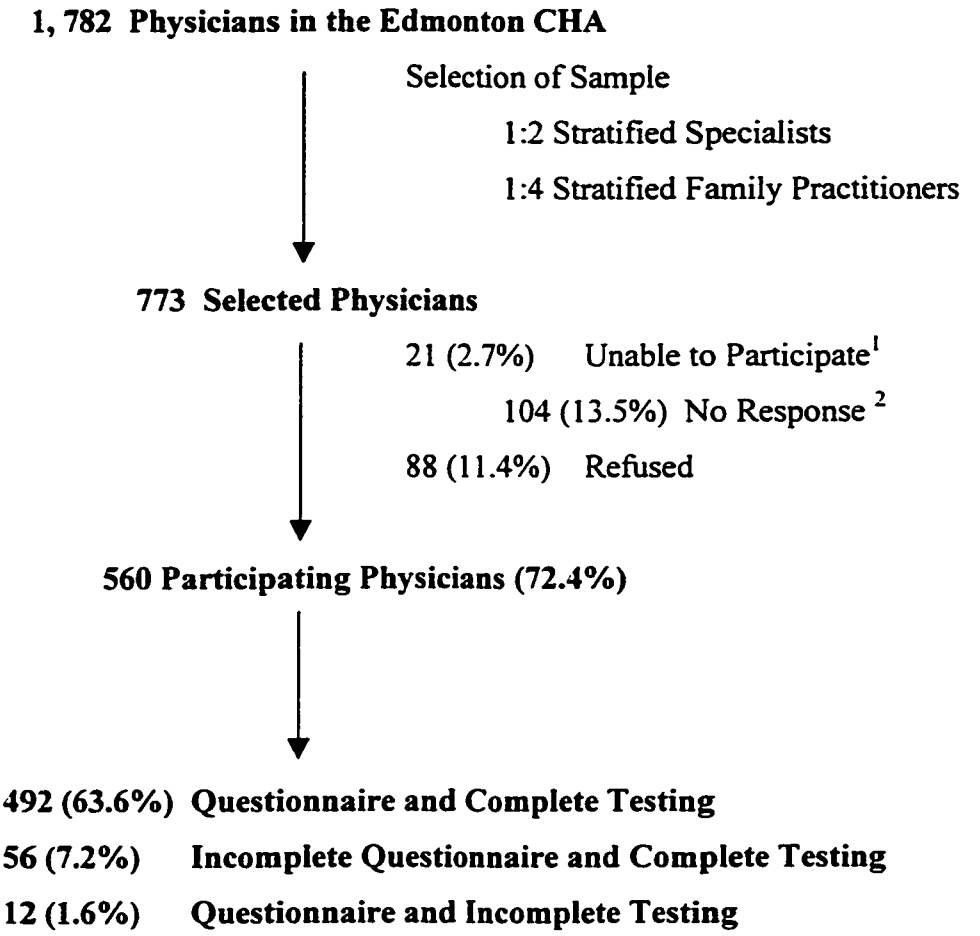
Of the participating physicians, 98% indicated that they felt it was extremely important for them to be protected from TB. It is interesting that although 61% of the study population would always wear a mask when entering the room of a patient in isolation, only 34% of the population agreed that masks were effective in protecting them from TB. When asked if the masks currently used were comfortable to wear, 28.7% of the physicians agreed (only 3.1% strongly agreed).

4.7 Conclusions

Examining this study population as a whole, the majority of the participants are Canadian born males. Approximately half of the population is tuberculin skin test positive. Two thirds of the physicians recall being in contact with a TB case and approximately a quarter have either traveled or practiced medicine in a high-risk country. About half of the physicians have been BCG vaccinated and one third are foreign born; these are two known risk factors for tuberculin reactivity. Of the BCG vaccinated physicians, two-thirds are tuberculin skin test positive, and among the foreign born physicians, slightly higher than two thirds of the physicians are tuberculin skin test positive.

[1] i.e. Sudan, India, Hong Kong, Guyana

TABLE 4.1: SUMMARY OF STUDY POPULATION: SELECTION AND PARTICIPATION PROCESS



[1] owing to maternity leave, extended sick leave, death, or moved away from Edmonton
[2] to introductory letter and two follow-up telephone calls

TABLE 4.2: DISTRIBUTION OF PARTICIPANTS AND NON-PARTICIPANTS ACCORDING TO SELECTED CHARACTERISTICS

	Responders (n=560) % (n)	Refusals/ Non-Responders/ Non-Participants (n=213) % (n)	p-value*
GENDER			
Male	76.4 (428)	84.4 (178)	**0.036**
Female	23.6 (132)	15.6 (33)	
LOCATION OF MED SCHOOL			
Canada	76.2 (428)	65.7 (140)	**0.031**
Foreign	23.8 (132)	34.3 (73)	
SPECIALTIES			
Specialist	72.9 (408)	69.5 (148)	0.35
Family Practitioner	27.1 (152)	30.5 (65)	
YEARS SINCE GRADUATION			
Average (yrs)	22.46	25.02	**0.0022****

* p-value based on chi-square test statistic, unless indicated otherwise

** p-value based on the t-test

TABLE 4.3: DISTRIBUTION OF THOSE PARTICIPANTS WITH COMPLETE AND INCOMPLETE TESTING ACCORDING TO SELECTED CHARACTERISTICS

	TESTING STATUS		
	COMPLETE (n=295) % (n)	NOT COMPLETE (n=12) % (n)	p-value*
GENDER			
Male	73.2 (216)	91.7 (11)	0.28
Female	26.8 (79)	8.3 (1)	
LOCATION OF MED SCHOOL			
Canada	88.1 (260)	83.3 (10)	0.95
Foreign	11.9 (35)	16.7 (2)	
SPECIALTIES			
Specialist	70.2 (207)	75 (9)	0.98
Family Practitioner	29.8 (88)	25 (3)	
YEARS SINCE GRADUATION			
Average	19.15 yrs	20.67 yrs	0.53**

* p-value based on chi-square test, except where otherwise indicated

** p-value based on the t-test

N.B. Using the entire study population:
Positive Mantoux in:
Population excluding those with "testing not complete": 46.9% +ve 0.82**
Population including those with "testing not complete": 45.9% +ve

TABLE 4.4: PROPORTION OF BOOSTED TUBERCULIN SKIN TESTS

First Step Test	n	Second Step Test	n	Proportion Boosting
00mm	280	>10mm	7	7/280 = 2.5%
01-09mm	15	>10mm	8	8/15 = 53.3%
00-09mm	295	>10mm	15	15/295 = 5.1%

TABLE 4.5: DESCRIPTIVE EXAMINATION OF SELECTED CHARACTERISTICS OF STUDY POPULATION

	n=560[P]		n=773[T]
GENDER, n (%)			
Male	428	(76.4)	606 (78.6)
Female	132	(23.6)	165 (21.4)
AGE(yrs), mean(SD)	47.47	(9.82)	
BCG, n (%)			
Yes	216	(44.0)	
No	275	(56.0)	
TIME SINCE BCG, mean (SD)	33.68	(8.81)	
AGE AT BCG, mean (SD)	16.8	(8.46)	
COUNTRY OF BIRTH, n (%)			
Canada	324	(65.1)	
Other	174	(34.9)	
LOCATION OF MEDICAL SCHOOL, n (%)			
Canada	427	(76.2)	568 (73.5)
Other	133	(23.8)	205 (26.5)
YEARS SINCE GRADUATION, mean (SD)	22.46	(9.86)	23.17 (10.42)
SPECIALTIES			
Specialists	408	(72.9)	556 (71.9)
Family Practitioners	152	(27.1)	217 (28.1)
KNOWN CONTACT WITH AN ACTIVE TB CASE			
Yes	321	(65.2)	
No	171	(34.8)	
FOREIGN TRAVEL for longer than a month			
None	388	(77.4)	
Travel only	57	(11.5)	
Practiced Medicine	55	(11.1)	

[P] study participants
[T] total population selected for the study

CHAPTER FIVE

RESULTS - BIVARIATE ANALYSIS

In this chapter, specific relationships between potential risk factors and the outcome, tuberculin reactivity, are examined for the study population. An examination of the study population as a whole is then followed by a bivariate analysis of a specific sub-group of physicians, Canadian-born and non-BCG vaccinated. This analysis is to screen the population for significant variables prior to the multivariate analysis in Chapter Six.

Because of the stratified nature of the sampling process, the data should theoretically be analysed using stratified data analysis based on the sampling strata. This posed a problem as the data was divided into 29 strata, many with extremely small sample sizes, making many of the statistical manipulations unreliable. Mantel-Haenszel odds ratios were calculated for some of the variables and the results were quite similar to the unstratified approaches. Thus, the majority of the analysis of the study population was performed by unstratified methods. This will be discussed further at the end of this chapter.

5. 1. Demographic and Tuberculosis Related Factors

A bivariate analysis between tuberculin reactivity and the demographic and tuberculosis related factors is shown in Tables 5.1 and 5.2. Gender was the only variable examined in this portion of the analysis that did not vary significantly with tuberculin reactivity. Higher tuberculin reactivity was significantly associated with increasing age, foreign birth, previous BCG vaccination, and previous exposure to an active TB case. In addition, those physicians who had practiced medicine in a high-risk country[1] had a significant risk of a positive tuberculin skin test.

[1] High Risk Country is defined as any country, not including Canada, the United States of America, Western European countries, Australia and New Zealand.

Birth outside of Canada had a significant odds ratio of 5.81. There appears to be an association between the age of moving to Canada and tuberculin skin test status among the foreign born physicians. Those physicians who moved to Canada after the age of 10 years have a much greater chance of tuberculin reactivity than those who moved to Canada before the age of 10 (OR=5.14; 95% C.I. 2.16-12.3). In Table 5.3, the relationship of country of birth to tuberculin reactivity is presented. This table clearly demonstrates the lower prevalence among those physicians born in North America.

As mentioned previously, those physicians who have practiced medicine in a foreign country have high risk of tuberculin reactivity. Table 5.4 illustrates the effect that country of practice has on one's tuberculin reactivity status. Although the numbers are small, those Canadian born physicians who have practiced in Asia and Africa appear to have a high prevalence of tuberculin reactivity.

In addition, it is interesting to note the difference between the age at which the tuberculin reactors and non-reactors received their BCG vaccination (Table 5.2). The reactors were, on average, younger when they received the vaccine and had been vaccinated for a longer period of time. The only statistically significant difference found was in years since BCG vaccination.

5.1.1 Confounding and Effect Modification

Relationships between various potential risk factors were examined by stratifying the population. The study population was stratified both by BCG vaccination (Table 5.5), by Country of Birth (Table 5.6), and Age over 45 yrs (Table 5.7). These variables were chosen for stratification (as opposed to other variables) because they are previously reported risk factors for tuberculin reactivity, and they were considered to be associated with other risk factors (for example, BCG vaccination is routinely administered in non-North American countries). The risk estimates calculated for each stratum were compared to the overall crude odds ratio and the Mantel-Haenszel

odds ratio. In addition, the Mantel-Haenszel chi-square statistic was calculated for each variable. The results showed that these three variables are confounders and effect modifiers of the three variables shown in Table 5.5 and 5.6. They are confounding variables because they contribute to the underestimation or overestimation of the relationship between tuberculin reactivity and the identified risk factors. In addition, there is effect modification as the magnitude of the association between tuberculin reactivity and the identified risk factors varies with the level of the BCG, Country of Birth and Age variables (Hennekens, 1987).

Table 5.5 indicates that prior BCG vaccination dilutes the effect of the other risk factors. For the three variables examined, the odds ratios were not significant, or less significant, for those persons who had previously been BCG vaccinated. The odds ratios for age and country of birth are significantly different since the 95% confidence intervals do not overlap. Because the odds ratios for non-BCG vaccinated persons are not equal to BCG vaccinated persons, BCG is an effect modifier of country of birth, age, and foreign practice. BCG is also a confounder as the failure to adjust for BCG status led to a bias in the estimated effect on country of birth, age, and foreign practice, as indicated by comparing the Mantel-Haenszel and crude odds ratios.

In the case of stratification by Canadian/Non-Canadian birth (Table 5.6), Non-Canadian birth seems to have a similar "diluting effect" on the three risk factors examined. The risk factors lose significance in the Non-Canadian birth strata. Based on an examination of the confidence intervals, the odds ratios for country of birth are significantly different, whereas the odds ratios for age are approaching a significant difference. As with the BCG variable, the country of birth variable appears to be an effect modifier and a confounder.

Similar trends of confounding and effect modification are seen when the population is stratified by the variable of age (Table 5.7). Those physicians under the age of 45 years are at increased risk for all three variables examined. The stronger effect of the BCG vaccination on the younger population correlates with the fading over time of

reactivity attributable to the vaccination. The foreign practice variable loses significance in the older population.

The problems of effect modification and confounding associated with BCG, foreign birth and age will be examined by multivariate analysis in Chapter Six.

5.2 Practice Related Factors

When the physicians' practice-related factors were examined, significant associations between tuberculin reactivity and having attended a foreign medical school, and increasing years since graduation were noted (Table 5.8). Being a specialist or having hospital admitting privileges were not associated with a positive Mantoux test. Although no dose-response trend was noted for number of gastrointestinal (GI) procedures and tuberculin reactivity, performing 10-30 GI procedures per month was associated with a significant risk (OR=3.65, 95% C.I. 1.25-8.25).

Most patient population characteristics did not seem to be significant in this analysis (Table 5.9). A dose-response relationship was seen in practice among the elderly populations. However, instead of physicians with a larger elderly patient population being at higher risk than those with a smaller elderly patient population, the dose-response trend actually was in the opposite direction. The physicians with greater than 75% elderly patients in their population had a lower proportion of non-reactors (OR=0.07; 95%C.I. 0.00-0.56). This trend is supported by the fact that no tuberculin reactors were found among those physicians in the specialty of geriatric medicine. However, in both cases the sample size was very small and therefore it is difficult to obtain stable risk estimates or to attain statistical significance.

There are small sample sizes associated with certain strata associated with the categorical variables dealing with Aboriginal, Elderly and Foreign Born patient populations, and GI procedures. Therefore, strata were combined into clinically and statistically significant groups for analysis (Table 5.10). An increased sample size would aid in proving the significance or non-significance of this variable. The chi-

square statistic and odds ratios calculated for the GI procedure and foreign and aboriginal patient population variables were not significant. For the elderly patient population, the trend of physicians with a larger elderly patient population having lower rates of tuberculin reactivity is still present. However, none of the stratum-associated odds ratios are significant.

5.3 Specialties

The prevalence of tuberculin reactivity was calculated for each of the specialty strata (Table 5.11). Owing to small numbers in some of the strata, these results must be interpreted with caution, and statistical significance was difficult to achieve for many of the strata. The family practice specialty was used as the referent category because of the broad spectrum of cases and patient types that these physicians treat. The specialties which appear to have a high prevalence of TB reactivity are Respiratory Medicine (83.3%, $p<0.001$, $n=18$), General Surgery (70%, $p=0.01$, $n=20$), and Internal Medicine (68%, $p=0.09$, $n=25$). All three of these high prevalence specialties are associated with significant odds ratios when family practice is used as the referent (Table 5.11), as well as when they are compared to the remainder of the physician population (Table 5.12). Specialties which exhibited low prevalence proportions (and sample sizes greater than ten) were Cardiology (26.7%, $p=0.01$,$n=15$), Ophthalmology (23.1%, $n=13$), and Obstetrics/Gynecology (33.3%, $n=21$).

Odds ratios were calculated for the various specialty groups in order to assess differences in their relationships with potential risk factors. Unfortunately, this proved to be very uninformative owing to the small sample size of the various specialties; the risk estimates had very large confidence intervals that made it difficult to differentiate the odds ratios of the specialties as being different from one another. This low statistical power created difficulties in the ability to draw conclusions relating to the specific risk estimates for the majority of the specialties.

5.3.1 Respiratory Medicine

The specialty of respiratory medicine showed the highest proportion (83.3%) of reactivity of all the specialties (Table 5.11). In the bivariate analysis of Table 5.12, the respiratory medicine specialty had the highest odds ratio of all specialties examined (6.20, 95% C.I. 1.77-21.66). In the following multivariate analysis in Chapter Six, all specialty variables other than Respiratory Medicine lose significance. This variable (Respiratory Medicine vs. all other specialties) is included in the final regression model. Although there are obvious clinical reasons for the high proportion of reactivity among these specialists, other risk factors for reactivity were examined. Compared to the other specialties combined, the respiratory medicine specialists had a non-significantly higher rate of BCG vaccination. In addition to this, the respiratory medicine specialists performed statistically significantly higher rates of upper gastrointestinal procedures. However, the GI procedures were not a significant risk factor for the reactivity in this group of physicians.

5.4 Regions of Practice

In order to examine the effect of region of practice on a physician's tuberculin reactivity status, the family practitioners were stratified by postal code area of the city and the prevalence of reactivity was examined for each stratum (Table 5.13). The group of family practitioners in the Mill Woods area of the city had the highest prevalence at 69.2% (n=13). This was statistically higher than the total prevalence of the other areas (p=0.03). Compared to the other regions, physicians in Mill Woods were more likely to be older, foreign born and previously BCG-vaccinated, but none of these differences was statistically significant. One significant difference, however, was the higher proportion of foreign born in the patient population of physicians in the Mill Woods area compared to the physicians in the other regions (36% vs. 11.2%; p=0.04). The postal code distribution was grouped into larger city regions to enhance the sample size. The strata were combined into 5 regions based on known socio-demographic-economic characteristics of the postal code regions (Table 5.14). The Southern areas of the city remained significantly higher than the other areas (p=0.019), probably attributable to the high prevalence among those physicians in the Mill

Woods region. The combined Central, West Central, and Castledowns areas are significantly lower than the other regions (p=0.045). Unfortunately, with the small sample sizes from the different regions, and consequent low power, no significant conclusions can be drawn from this examination.

5.5 Canadian Born and non-BCG Vaccinated Physicians

Because foreign birth and previous BCG vaccination have been documented in many studies as the two major risk factors of tuberculin reactivity, the sub-group of Canadian-born physicians with no BCG vaccination was examined separately (Tables 5.15, 5.16, 5.17). Many variables that showed a statistically significant association with tuberculin reactivity when examining the study population as a whole did not achieve significance in this sub-group analysis. Age, previous exposure to a TB case, and years since graduation from medical school were not significant in this analysis. The only variable which did remain significant was a period of at least one month in foreign practice (OR=7.92; 95% C.I. 2.06-30.53).

As was done in Section 5.2, the strata of those variables dealing with patient population and GI procedures were combined owing to small sample sizes (Table 5.18). No significant risk estimates were found for tuberculin reactivity and the three patient population variables. The risk estimate associated with the GI procedure variable approaches significance (OR 2.67; 95%C.I. 0.95-7.31) and has a significant chi-square measurement (0.032). An increased sample size would aid in the attainment of statistical significance or non-significance of this variable.

5.6 *A priori* hypotheses

During the analysis, two other potential risk factors were identified: having practiced in the North West Territories or the Yukon, and having practiced at the Charles Campsell Hospital, a city hospital with a high Aboriginal patient population. Both these factors were examined. However, no significant tuberculin reactivity risk differences were found between those physicians who had practiced in these areas and

those who had not. Some cell numbers were quite small, however, and therefore, may have led to inaccurate risk estimates.

5.7 Stratified Analyses

As mentioned at the beginning of this chapter, unstratified methods of analysis were used for this bivariate analysis instead of the preferred stratified methods. This was done because small cell numbers arose from stratification on 29 specialties. Table 5.19 compares the values of risk estimates calculated by unstratified methods (crude odds ratios) and stratified methods (Mantel-Haenszel odds ratios). Where possible, stratified analyses were performed on 3 different datasets: one stratified by the 29 specialties used for sample selection, one stratified by 9 specialty groups based on clinical reasoning (see Appendix 7), and another dataset stratified by a dichotomous variable, respiratory medicine specialty or other specialty (for the reasons discussed in Section 5.3.1). This comparison indicates that there appears to be very little difference between the methods of analysis used. All the variables examined, with the exception of the gender variable, showed very similar risk estimates and associated confidence intervals. Therefore, the use of unstratified analyses in the preceding bivariate analysis appears to be justified.

5.8 Conclusions

When the study population was examined as a whole, many variables including foreign birth, BCG, older age, previous contact, and foreign practice demonstrated significant associations with tuberculin reactivity. Respiratory medicine, internal medicine and general surgery showed the highest prevalence proportions of tuberculin reactivity of all the specialties. Contrary to the initial hypothesis, those physicians whose current practice included higher numbers of high-risk[1] patients did not have an increased risk of tuberculin reactivity. A sub-analysis of Canadian Born-non-BCG-vaccinated physicians was performed and only two variables remained significant:

[1] i.e. patients who are either aboriginal, elderly, or foreign born

having practiced in a foreign country and age over 45 years. Analyses of the population stratified by BCG vaccination status, place of birth, and age indicated that confounding and effect modification from these three variables was present. In order to control the confounding variables, determine the true effect of the effect modification, and gain a better understanding of the relationship between the potential risk factors and tuberculin reactivity, multivariate regression analysis was performed on the study population (Chapter Six).

TABLE 5.1 TUBERCULIN REACTIVITY ACCORDING TO DEMOGRAPHIC VARIABLES

	MANTOUX		
	POSITIVE n (%)	NEGATIVE n (%)	p-value* OR [95% CI]
TOTAL	257 (45.9)	303 (54.1)	
GENDER			0.130
Male	204 (79.4)	224 (73.9)	1.36 [0.9-2.06]
Female	53 (20.6)	79 (26.1)	
AGE			
Mean (sd)	51.5 (10.4)	44.4 (8.12)	**0.000****
>45 yrs	147 (67.7)	98 (35.6)	**< 0.0001**
<45 yrs	70 (32.3)	177 (64.4)	**3.79 [2.61-5.53]**
COUNTRY OF BIRTH			**<0.0001**
Foreign Born	123 (54)	51 (18.2)	**5.81 [3.80-8.92]**
Canadian Born	95 (43.6)	229 (81.8)	

*p-value calculated by chi-square statistic, except where otherwise indicated
**p-value calculated by t-test statistic

TABLE 5.2 TUBERCULIN REACTIVITY ACCORDING TO TUBERCULOSIS RELATED VARIABLES

	MANTOUX POSITIVE n (%)	MANTOUX NEGATIVE n (%)	p-value* OR [95% CI]
TOTAL	257 (45.9)	303 (54.1)	
BCG			**<0.0001**
Yes	151 (70.2)	65 (23.6)	**7.66 [5.02-11.7]**
No	64 (29.8)	211 (76.4)	
BCG CHARACTERISTICS (mean (SD))			
Age at BCG	16.2 (8.7)	18.4 (7.8)	0.088**
Years Since BCG	34.6 (8.9)	31.6 (8.3)	**0.027**
PREVIOUS EXPOSURE TO AN ACTIVE TB CASE			**0.021**
Yes	153 (70.3)	168 (60.9)	**1.56 [1.05-2.33]**
No	63 (29.2)	108 (39.1)	
FOREIGN TRAVEL AND PRACTICE			
-for longer than one month			X^2 **trend <0.0001**
No Travel	151(69.6)	233 (83.5)	1.00
Travel Only	26 (12.0)	31 (11.1)	1.29 [0.85-1.58]
Travel and Practice	40 (18.4)	15 (5.4)	**4.11 [2.11-8.10]**

*p-value calculated by chi-square statistic, except where otherwise indicated
**p-value calculated by t-test statistic

TABLE 5.3: TUBERCULIN REACTIVITY ACCORDING TO COUNTRY OF BIRTH

	MANTOUX RESULT Positive n (%)	Total	p-value * OR [95% C.I.]
North America	98 (29.4)	333	Referent
Latin America	7 (70.0)	10	0.011 5.60 [1.24-34.2]
West Europe	50 (68.5)	73	<0.001 5.21 [2.92-9.36]
East Europe	15 (93.8)	16	<0.0001 35.67 [4.89-740.08]
Asia	35 (72.9)	48	<0.0001 6.36 [3.13-13.49]
Africa	8 (61.5)	13	0.027 3.84 [1.07-15.23]
Australia	1 (100)	1	ns **
Middle East	4 (100)	4	0.008 **

* p-value based on chi-square test statistic; ns=non-significant
** zero cells therefore no odds ratio calculated

TABLE 5.4 TUBERCULIN REACTIVITY ACCORDING TO COUNTRY OF FOREIGN PRACTICE

	MANTOUX RESULT		
	Positive	Negative	Total
Latin America	4 80.0%	1 20.0%	5
East Europe	3 50.0%	3 50.0%	6
Asia	11 73.3%	4 26.7%	15
Africa	19 82.6%	4 17.4%	23
Middle East	3 50.0%	3 50.0%	6

CANADIAN BORN PHYSICIANS ONLY

	MANTOUX RESULT		
	Positive	Negative	Total
Latin America	1 50.0%	1 50.0%	2
East Europe	0	2 100.0%	2
Asia	7 77.8%	2 22.2%	9
Africa	11 78.6%	3 21.4%	14
Middle East	2 40.0%	3 60.0%	5

TABLE 5. 5: TUBERCULIN REACTIVITY ACCORDING TO SELECTED VARIABLES AFTER STRATIFICATION BY BCG

		Mantoux Result Positive	Negative	OR [95% C.I.]
Country of Birth				
BCG	Non-Can. Born	84	22	**2.39 [1.30-4.39]**
	Canadian Born	67	42	
No BCG	Non-Can. Born	35	26	**8.89 [4.67-16.95]**
	Canadian Born	28	185	
			Crude OR = 5.81 [3.80 - 8.92]	
			Mantel-Haenszel OR = 4.21 [2.86 - 7.42]	
			Mantel-Haenszel X^2 p <0.00001	
Age				
BCG	>45 years	101	42	1.13 [0.61-2.08]
	<45 years	49	23	
No BCG	>45 years	42	53	
	<45 years	21	152	**5.74 [3.12-10.6]**
			Crude OR = 3.76 [2.53-5.60]	
			Mantel-Haenszel OR = 2.52 [1.67-4.03]	
			Mantel-Haenszel X^2 p <0.00001	
Foreign Travel and Practice				
	No Travel	108	49	referent
BCG	Foreign Travel	14	10	0.64 [0.24-1.67]
	Foreign Practice	27	6	2.04 [0.76-6.42]
No BCG	No Travel	40	179	referent
	Foreign Travel	12	19	**2.83 [1.18-6.73]**
	Foreign Practice	12	10	**5.37 [1.99-14.58]**
Foreign Travel Crude OR = 1.29 [0.85-1.58]				M-H OR =1.37 [0.72-2.90] M-H X^2 p = 0.34
Foreign Practice Crude OR = 4.11 [2.11-8.10]				M-H OR =3.13 [1.65-7.49] M-H X^2 p < 0.001

TABLE 5.6: TUBERCULIN REACTIVITY ACCORDING TO SELECTED VARIABLES AFTER STRATIFICATION BY COUNTRY OF BIRTH

			Mantoux Result: Positive	Negative	OR [95% C.I.]
BCG Status:					
Canadian Birth	BCG	Yes	68	41	**9.72[5.43-17.50]**
		No	28	185	
Non-Canadian Birth	BCG	Yes	83	23	**2.62 [1.25-5.51]**
		No	35	26	
			Crude OR = 7.66 [5.02-11.7]		
			Mantel-Haenszel OR = 6.20 [4.17 - 10.22]		
			Mantel-Haenszel X^2 p <0.00001		
Age					
Canadian Birth	>45 years		68	70	**5.27 [3.13-8.90]**
	<45 years		28	152	
Non-Canadian Birth	>45 years		79	28	1.65 [0.85-3.21]
	<45 years		41	24	
			Crude OR = 3.76 [2.53-5.60]		
			Mantel-Haenszel OR = 3.39 [2.25 - 5.25]		
			Mantel-Haenszel X^2 p <0.00001		
Foreign Practice and Travel					
Canadian Birth	No Travel		67	190	referent
	Foreign Travel		9	23	1.11 [0.45-2.67]
	Foreign Practice		20	12	**4.73 [2.07-10.93]**
Non-Canadian Birth	No Travel		82	41	referent
	Foreign Travel		18	7	0.71 [0.46-3.71]
	Foreign Practice		19	4	2.38 [0.72-10.17]
Foreign Travel: Crude OR = 1.29 [0.85-1.58]					M-H OR =1.18 [0.61-2.28] M-H X^2 p = 0.71
Foreign Practice: Crude OR = 4.11 [2.11-8.10]					M-H OR = 3.68 [1.93-7.93] M-H X^2 p <0.0001

TABLE 5. 7: TUBERCULIN REACTIVITY ACCORDING TO SELECTED VARIABLES AFTER STRATIFICATION BY AGE

		Mantoux Result Positive	Negative	OR [95% C.I.]
Country of Birth				
<45 yrs	Non-Can. Born	41	24	**9.27 [4.87-17.7]**
	Canadian Born	28	152	
>45 yrs	Non-Can. Born	79	28	**2.91 [1.68-5.01]**
	Canadian Born	68	70	
				Crude OR = 3.76 [2.53 - 5.60]
				Mantel-Haenszel OR = 4.57 [3.13 - 7.58]
BCG				
<45 yrs	BCG Yes	49	23	**15.4 [7.86-30.2]**
	No	21	152	
>45 yrs	BCG Yes	101	42	**3.04 [1.77-5.44]**
	No	42	53	
				Crude OR = 7.66 [5.02-11.7]
				Mantel-Haenszel OR = 5.64 [3.95-9.50]
Foreign Practice				
<45 yrs	No Travel	48	150	referent
	Foreign Travel	5	19	0.82 [0.23-2.44]
	Foreign Practice	17	7	**7.59 [2.75-21.63]**
>45 yrs	No Travel	103	78	referent
	Foreign Travel	21	12	1.33 [0.58-3.06]
	Foreign Practice	22	8	2.08 [0.83-5.40]

Foreign Travel: Crude OR = 1.29 [0.85-1.58] M-H OR =1.12 [0.59-2.11]
M-H X^2 p = 0.84

Foreign Practice: Crude OR = 3.62 [2.00-8.25] M-H OR = 3.62 [2.00-8.25]
M-H X^2 p <0.0001

TABLE 5.8: TUBERCULIN REACTIVITY ACCORDING TO PRACTICE RELATED VARIABLES

	MANTOUX RESULT Positive n (%)	Negative n (%)	p-value OR [95% CI]
SPECIALITY			p=0.095
Specialist	196 (76.3)	212 (70.0)	1.38 [0.93-2.05]
Family Practitioner	61 (23.7)	91 (30.0)	
LOCATION OF MEDICAL SCHOOL			**p<0.0001.**
Non Canadian	103 (40.1)	30 (9.9)	**6.09 [3.79-9.82]**
Canadian	154 (59.9)	273 (90.1)	
YEARS SINCE GRADUATION			
Mean (sd)	26.5 (10.24)	19.0 (8.10)	**p=0.000****
ADMITTING PRIVILEGES			p=0.524
Yes	160 (73.4)	211 (75.9)	0.88 [0.57-1.34]
No	58 (26.6)	67 (24.1)	
PERCENTAGE OF TIME IN HOSPITAL			
Mean (sd)	43.5 (39.7)	42.2 (39.3)	p=0.72 **
GI PROCEDURES (per month)			X^2trend p= 0.45
1.None	154 (68.6)	219 (78.2)	1.00
2.1-10	26 (12.7)	23 (8.2)	1.54 ns
3.10-30	18 (8.8)	8 (2.9)	**3.65 [1.25-8.25]**
4.30-60	8 (3.9)	9 (3.2)	1.26 ns
5.>60	12 (5.9)	21 (7.5)	0.88 ns

*p-value calculated by chi-square statistic, except where otherwise indicated
**p-value calculated by t-test statistic

TABLE 5.9: TUBERCULIN REACTIVITY ACCORDING TO PATIENT POPULATION VARIABLES

	MANTOUX RESULT		
	Positive n (%)	Negative n (%)	OR [95% C.I.]
ABORIGINAL			X^2 trend p= 0.45
1. None	18 (8.4)	11 (4)	1.00
2. 1-10%	152 (70)	214 (77.3)	**0.43 [0.19-1.00]**
3. 11-25%	36 (16.6)	45 (16)	0.49 [0.19-1.26]
4. 26-50%	7 (3.2)	8 (2.8)	0.53 [0.12-2.24]
5. 51-75%	1 (0.5)	1 (0.4)	0.61 [0.01-52.3]
6. >75%	0	0	ns
ELDERLY			X^2 trend p= **0.013**
1. None	37 (17.1)	26 (9.3)	1.00
2. 1-10%	46 (21.2)	66 (23.6)	**0.49 [0.25-0.96]**
3. 11-25%	62 (28.6)	71(25.4)	0.61 [0.32-1.17]
4. 26-50%	48 (22.1)	76 (27)	**0.44 [0.23-0.86]**
5. 51-75%	23 (10.6)	31 (11)	0.52 [0.23-1.16]
6. >75%	1 (0.5)	10 (3.6)	**0.07 [0.00-0.56]**
FOREIGN			X^2 trend p= 0.48
1. None	15 (6.9)	4 (1.4)	1.00
2. 1-10%	104 (47.9)	166 (59.3)	**0.17 [0.04-0.55]**
3. 11-25%	74 (34.1)	91 (32.5)	**0.22 [0.05-0.72]**
4. 26-50%	18 (8.3)	11 (3.9)	0.38 [0.08-1.91]
5. 51-75%	3 (1.4)	6 (2.1)	0.13 [0.02-1.03]
6. >75%	3 (1.4)	2 (0.7)	0.4 [0.03-6.61]

TABLE 5.10: TUBERCULIN REACTIVITY ACCORDING TO DICHOTOMIZED GI PROCEDURES AND PATIENT POPULATION VARIABLES

GASTROINTESTINAL PROCEDURES PERFORMED

	MANTOUX RESULT		
	Positive	Negative	p-value*/OR [95% C.I.]
>10	38	38	**p=0.23**
<10	180	242	OR=1.17 [0.91-1.51]

PATIENT POPULATION VARIABLES

	MANTOUX RESULT		
	Positive	Negative	p-value*/OR [95% C.I.]
ABORIGINAL			p=0.739
>10%	44	54	1.08 [0.67-1.72]
0 - 10%	170	225	
FOREIGN			p=0.19
>10%	98	110	1.27 [0.87-1.85]
0-10%	119	170	
ELDERLY			X^2 trend p=0.04
>50%	24	41	0.65 [0.35-1.21]
11-50%	110	147	0.83 [0.55-1.24]
0-10%	83	92	referent

* p-value calculated from chi-square test statistic

TABLE 5.11: TUBERCULIN REACTIVITY ACCORDING TO PHYSICIAN SPECIALTY

	MANTOUX POSITIVE n (%)	TOTAL	p-value*	OR [95%CI]
Family Practice	61 (40.1)	152		referent
Anesthesia	15 (45.5)	33	ns	1.24 [0.55-2.38]
Cardiology	4 (26.7)	15	ns	0.54 [0.12-1.95]
Community Medicine	2 (33.3)	6	ns	0.75 [0.07-5.40]
Dermatology	5 (38.5)	13	ns	0.93 [0.23-3.41]
Diagnostic Radiology	18 (56.3)	32	ns	1.92 [0.83-4.44]
Emergency Medicine	1 (20)	5	ns	0.37 [0.01-3.91]
Endocrinology	2 (33.3)	6	ns	0.75 [0.07-5.40]
Gastroenterology	8 (57.1)	14	ns	1.99 [0.57-7.30]
Geriatric Medicine	0	6	ns	0.11 [0.00-1.73]
General Surgery	14 (70.0)	20	**0.011**	**3.48 [1.17-11.6]**
Infectious Diseases	6 (42.9)	14	ns	1.12 [0.30-3.88]
Internal Medicine	17 (68.0)	25	**0.009**	**3.17 [1.2-8.61]**
Medical Genetics/ Biochemistry	2 (66.7)	3	ns	2.98 [0.15-177.92]
Med. Oncology	6 (54.5)	11	ns	1.79 [0.25-2.74]

* p-value calculated by Chi-square statistic; ns=non-significant

TABLE 5.11 -cont'd

	MANTOUX POSITIVE n (%)	TOTAL	p-value*	OR [95%CI]
Nephrology	3 (60.0)	5	ns	2.44 [0.2-4.40]
Neurology	4 (40.0)	10	ns	0.99 [0.2-4.40]
Obstetrics and Gynecology	7 (33.3)	21	ns	0.75 [0.25-2.12]
Ophthalmology	3 (23.1)	13	ns	0.45 [0.08-1.84]
Orthopedic Surgery	7 (50.0)	15	ns	1.16 [0.65-2.07]
Otolaryngology	4 (57.1)	7	ns	1.99 [0.32-13.99]
Pathology	7 (41.2)	17	ns	1.04 [0.34-3.19]
Pediatrics	22 (59.5)	37	**0.034**	2.19 [0.99-4.85]
Physical Med./Rehab.	1 (16.7)	6	ns	0.30 [0.01-2.78]
Plastic Surgery	2 (25.0)	8	ns	0.50 [0.05-2.91]
Psychology	12 (41.4)	29	ns	1.05 [0.44-2.53]
Respiratory Medicine	15 (83.3)	18	**<0.001**	**7.46 [1.97-41.42]**
Rheumatology	3 (42.9)	7	ns	1.12 [0.16-6.86]
Urology	6 (50.0)	12	ns	1.49 [0.38-5.85]

*p-value calculated by chi-square statistic; ns=non-significant

TABLE 5.12: TUBERCULIN REACTIVITY ACCORDING TO SELECTED SPECIALTIES

	MANTOUX RESULT Positive n	Negative n	p-value* OR [95% CI]
SPECIALTY			
Anesthesia	15	18	0.96
Other	242	285	0.98 [0.48 -1.99]
Diagnostic Radiology	18	14	0.23
Other	289	239	1.56 [0.76-3.19]
Gastroenterology	8	6	0.43
Other	249	297	1.59 [0.55-4.65]
General Surgery	14	6	**0.028**
Other	243	297	**2.85 [1.08-7.53]**
Infectious Diseases	6	8	0.82
Other	250	296	0.89 [0.25-2.96]
Internal Medicine	17	8	**0.023**
Other	240	295	**2.61 [1.11-6.16]**
Otolaryngology	4	3	0.71
Other	253	300	1.58 [0.35-7.13]
Pediatrics	22	15	0.087
Other	235	288	1.80 [0.91-3.54]
Respiratory Medicine	15	3	**0.001**
Other	242	300	**6.20 [1.77-21.66]**

* p-value calculated by the chi-square statistic

TABLE 5.13: TUBERCULIN REACTIVITY ACCORDING TO REGION OF PRACTICE AMONG FAMILY PRACTITIONERS

Region	Positive	Negative	Total
Central	3 37.5%	5 62.5%	8
Castle-downs	3 20.0%	12 80.0%	15
Mill Woods	9 69.2%	4 30.8%	13
North Central	8 50.0%	7 50.0%	14
North East	8 50.0%	8 50.0%	16
St.Albert	5 29.4%	12 70.6%	17
South Central	6 46.2%	7 53.8%	13
Sherwood Park	6 40.0%	9 60.0%	15
South West	5 35.7%	9 64.3%	14
West	5 35.7%	9 64.3%	14
West Central	4 30.8%	9 69.2%	13
Total	61 40.1%	91 59.9%	152

TABLE 5.14: TUBERCULIN REACTIVITY ACCORDING TO COMBINED REGIONS OF FAMILY PRACTICE

Region	Positive	Negative	Total
1. St. Albert Sherwood Park (n=108,371)	11 34.4%	21 65.6%	32
2. North Central North East (n= 122,060)	15 50.0%	15 50.0%	30
3. Central West Central Castledowns (n=155,829)	10 27.8%	26 72.2%	36
4. West South West (n=208,117)	10 35.7%	18 64.3%	28
5. South Central Mill Woods (n=140, 993)	16 61.5%	10 38.5%	26

TABLE 5.15: CANADIAN BORN-NO BCG POPULATION: TUBERCULIN REACTIVITY ACCORDING TO DEMOGRAPHIC AND TUBERCULOSIS RELATED VARIABLES

CANADIAN BORN-NO BCG (n=213)

	MANTOUX RESULT		
	Positive n (%)	Negative n (%)	p-value* OR [95%C.I.]
TOTAL	28 (13.1)	185 (86.9)	
DEMOGRAPHIC VARIABLES			
GENDER			0.56
Male	18 (64.3)	129 (69.7)	0.78 [0.32-1.95]
Female	10 (35.7)	56 (30.3)	
AGE			
Mean (sd)	46.1 (12.6)	42.1 (7.1)	0.21**
>45 yrs	12 (42.9)	38 (21.2)	**0.013**
<45 yrs	16 (57.1)	141 (78.8)	**2.78 [1.21-6.38]**
TUBERCULOSIS RELATED			
PREVIOUS EXPOSURE TO AN ACTIVE TB CASE			0.32
Yes	19 (67.9)	106 (57.9)	1.53 [0.62-3.89]
No	9 (32.1)	77 (42.1)	
FOREIGN TRAVEL AND PRACTICE (> one month)			X^2 **trend <0.0001**
No Travel	17 (60.7)	157 (86.3)	1.00
Travel Only	5 (17.9)	18 (9.9)	2.57 [0.66-8.41]
Travel and Practice	6 (21.4)	7 (3.8)	**7.92 [2.06-30.5]**

*p-value calculated by chi-square statistic, except where otherwise indicated
**p-value calculated by t-test statistic

TABLE 5.16: CANADIAN BORN-NO BCG POPULATION: TUBERCULIN REACTIVITY ACCORDING TO PRACTICE RELATED VARIABLES

	MANTOUX RESULT		
	Positive n (%)	Negative n (%)	p-value* OR [95%C.I.]
SPECIALITY			0.22
Specialist	22 (78.6)	124 (67)	1.80 [0.66-5.71]
Family Practice	6 (21.4)	61 (33)	
LOCATION OF MEDICAL SCHOOL			0.98
Canadian	28 (100)	184 (99.5)	
Non-Canadian	0	1 (0.5)	
YEARS SINCE GRADUATION			
Mean (sd)	21.1 (12.6)	16.8 (7.1)	0.19**
ADMITTING PRIVILEGES			0.94
Yes	21 (75)	140 (75.7)	0.96 [0.36-2.69]
No	7 (25)	45 (24.3)	
PERCENTAGE OF TIME IN HOSPITAL			
Mean (sd)	45.7 (43.5)	44.7 (40.35)	0.91**
GI PROCEDURES (per month)			X^2 trend p= 0.12
1.None	19 (67.9)	144 (77.8)	Referent
2.1-10	1 (3.6)	16 (8.6)	0.47 [0.01-3.42]
3.10-30	3 (10.7)	6 (3.2)	3.79 [0.56-19.37]
4.30-60	2 (7.1)	5 (2.7)	3.03 [0.27-19.99]
5.>60	3 (10.7)	13 (7)	1.75 [0.29-7.20]

*p-value calculated by chi-square statistic, except where otherwise indicated
**p-value calculated by t-test statistic

TABLE 5.17: CANADIAN BORN-NO BCG POPULATION: TUBERCULIN REACTIVITY ACCORDING TO PATIENT POPULATION VARIABLES

	MANTOUX RESULT		
	Positive n (%) (n=28)	Negative n (%) (n=184)	p-value*
ABORIGINAL			X^2 trend p = 0.49
1. None	3 (10.7)	4 (2.2)	ns
2. 1-10%	12 (46.4)	111 (60.3)	ns
3. 11-25%	13 (42.9)	62 (33.7)	ns
4. 26-50%	----------	3 (1.6)	------
5. 51-75%	----------	1 (0.5)	------
6. >75%	----------	----------	------
ELDERLY			X^2 trend p = 0.47
1. None	6 (21.4)	18 (9.8)	ns
2. 1-10%	3 (10.7)	43 (23.4)	ns
3. 11-25%	8 (28.6)	49 (26.6)	ns
4. 26-50%	8 (28.6)	48 (26.1)	ns
5. 51-75%	3 (10.7)	19 (10.3)	ns
6. >75%	----------	7 (3.8)	------
FOREIGN			X^2 trend = 0.42
1. None	2 (7.1)	9 (4.9)	ns
2. 1-10%	19 (67.9)	136 (73.9)	ns
3. 11-25%	7 (25)	32 (17.4)	ns
4. 26-50%	--------	6 (3.3)	-----
5. 51-75%	--------	1 (0.5)	-----
6. >75%	--------	---------	-----

* calculated from chi-square test statistic

TABLE 5.18: CANADIAN BORN – NO BCG POPULATION: TUBERCULIN REACTIVITY ACCORDING TO DICHOTOMIZED GI PROCEDURES AND PATIENT POPULATION VARIABLES

GASTROINTESTINAL PROCEDURES PERFORMED

	MANTOUX RESULT		
	Positive	Negative	p-value*/OR [95% C.I.]
>10	8	24	**0.032**
0-10	20	160	2.67 [0.95-7.31]

DESCRIPTION OF PATIENT POPULATION

	MANTOUX RESULT		
	Positive	Negative	p-value*/OR [95% C.I.]
ABORIGINAL			0.31
>10%	13	66	1.51 [0.63-3.61]
0 - 10%	15	115	
ELDERLY			0.92
>10%	19	123	1.05 [0.45-2.45]
0-10%	9	16	
FOREIGN			0.65
>10%	7	39	1.24 [0.44-3.37]
0-10%	21	145	

* calculated from chi-square test statistic

TABLE 5.19: COMPARISON OF UNSTRATIFIED AND STRATIFIED ANALYSES ON SELECTED VARIABLES

	Odds Ratio	p-value*
Age (>45 years/<45 years)		
Crude	3.75 [2.58-5.47]	<0.0001
Clinical Grouping	3.79 [3.59-5.70]	<0.0001
Respiratory Med. vs. Other	3.46 [2.43-5.47]	<0.0001
BCG		
Crude	7.66 [5.02-11.70]	<0.0001
Clinical Grouping	7.52 [4.99-11.95]	<0.0001
Respiratory Med. vs. Other	7.45 [4.87-11.41]	<0.0001
All 29 strata	6.55 [4.29-11.31]	<0.0001
Foreign Birth		
Crude	5.81 [3.79-8.91]	<0.0001
Clinical Grouping	5.89 [3.90-9.48]	<0.0001
Respiratory Med. vs. Other	5.54 [3.64-8.49]	<0.0001
All 29 strata	5.10 [3.42-9.15]	<0.0001
Foreign Practice		
Crude	3.99 [2.14-7.45]	<0.0001
Clinical Grouping	4.14 [2.13-8.11]	<0.0001
Respiratory Med. vs. Other	4.21 [2.07-8.94]	<0.0001
Gastrointestinal Procedures (>10/month/<10/month)		
Crude	1.17 [0.91-1.51]	0.23
Clinical Grouping	1.09 [0.71-1.67]	0.75
Respiratory Med. vs. Other	1.33 [0.86-9.48]	0.22
Gender		
Crude	1.36 [0.90-2.06]	0.13
Clinical Grouping	0.82 [0.53-1.26]	0.40
Respiratory Med. vs. Other	0.77 [0.51-1.17]	0.43
Previous Contact with a TB case		
Crude	1.52 [1.05-2.23]	0.021
Clinical Grouping	1.51 [1.01-2.31]	0.045
Respiratory Med. vs. Other	1.55 [1.04-2.32]	0.034
All 29 Strata	1.59 [1.02-2.56]	0.026

* based on chi-square statistics; Mantel-Haenszel chi-square used for stratified analyses

CHAPTER SIX

RESULTS - MULTIVARIATE LOGISTIC REGRESSION

The purpose of this analysis is to examine the determinants associated with tuberculin reactivity among the physician study population. This multivariate analysis is not meant to create a predictive model, but instead to identify potential risk factors, while controlling for confounding variables. Logistic regression is used for this analysis owing to the dichotomous nature of the outcome variable, tuberculin skin test positive or negative. Both unconditional and conditional logistic regression analyses were performed.

The general logistic model is as follows:

$$\ln (P/[1-P]) = B_0 + B_1X_1 + B_2X_2 + \ldots + B_i X_i + e$$

P represents the probability of the dichotomous outcome, therefore P/[1-P] is the odds of the outcome. B_0 is the grand mean, and is not present in the conditional logistic model. B_i is the coefficient of the ith independent variable, and e is the independent random error. The independent variable coefficients are the natural logarithm associated with the odds ratios for these variables.

There are specific assumptions to be examined during logistic regression analysis. One must assure that the cases are independent of each other. In this analysis, the cases can be assumed to be independent as the response of one case did not depend on the response of another. In addition, none of the x variables can be a linear function of each other, that is no variables can demonstrate collinearity. Also, it should be verified that no separation of variables exists, this occurs when there is no overlap of the covariate distribution between the outcome groups. Both collinearity and separation must be checked as these numerical problems will lead to biased estimates and inflated

standard errors. Fortunately, the statistical software packages used for this analysis recognize these two problems and contains diagnostic checks which will drop variables from the analysis which show these characteristics. None of the covariates entered into the analysis showed signs of these numerical problems (Hosmer & Lemeshow, 1989).

6.1 Conditional Regression Analysis

Conditional logistic regression was used because of the highly stratified study population (Kleinbaum et al, 1982, Hosmer & Lemeshow, 1989). In this study, the sample was selected by stratified random sampling. This sampling procedure resulted in a sample with 29 strata, some of which contained very few participants. With this highly stratified population optimal maximum likelihood estimators are not achieved using unconditional regression analysis. One reason for the biased estimates is that the nature of the unconditional likelihood equation requires that all parameters be estimated. In highly stratified populations the number of parameters to be estimated becomes too large relative to the amount of data available. Using conditional logistic regression, the stratum-specific parameters are regarded as nuisance parameters and are not estimated. Holding the stratum totals constant, it then is possible to estimate maximum likelihood estimators based on a conditional likelihood. Therefore, conditional methods are used with stratified sampling methods instead. Specific software programs containing a conditional logistic program must be used for this type of analysis. In this study, the Stata software package was used (StataCorp, 1997).

The full conditional likelihood is the product of the conditional probabilities of a positive outcome for risk factor x, for each observation, m, of all strata, as follows:

$$\prod_{g=1}^{G} \left[\prod_{i=1}^{m_{1g}} \exp(B'x_{ig}) \Big/ \sum_{u} \left\{ \left[\prod_{i_u=1}^{m_{1g}} \exp(B'x_{iug}) \right\} \right] \right]$$

where G is the number of strata. Within each stratum (g), there are m_{1g} observations with positive tuberculin reactivity (~ cases) and m_{0g} negative outcomes (~controls) thus $m_g = m_{1g} + m_{0g}$. *B* is the coefficient associated with covariate x, i represents all observations, and u denotes all possible combinations for choosing m_{1g} out of m_g subjects (Kleinbaum et al, 1982, Hosmer & Lemeshow, 1989).

6.1.1 Variable Selection

All the variables considered in the analysis are listed in Appendix 8. The variables to be analysed in this regression were analysed by examining the bivariate analysis from Chapter 5 and a univariate analysis.

The variables Years since Graduation and Age were highly correlated (97.4%). The variable Age was more significant than Years since Graduation in the univariate analysis, and also Age is the predominant variable used in related HCW literature, therefore Age was used instead. The variable Age was dichotomized, as there was a clear break at the midpoint (i.e., 45 years) when examining a plot of the quartile midpoints and the associated logit. Percentage of Time in Hospital had a non-linear relationship and therefore the variable was broken down into a categorical variable for this analysis. In addition, Country of Birth and Location of Medical School were highly correlated (75%). Separate regression analyses were conducted using each variable; both variables had nearly identical associated coefficients, however the model containing Country of Birth was more significant, thus Country of Birth was chosen as the variable to use. Once again, Country of Birth is the variable used predominantly in the literature.

In order to gain adequate sample size for all strata in the patient populations and GI procedure variables, the categories were combined into clinically and statistically significant groups.

All remaining variables with a univariate significance of $p<0.25$ were included in the first block of the regression analysis (Table 6.1).

6.1.2 Model Building

A manual backward elimination stepwise regression was performed to obtain the most parsimonious model. Statistically and clinically non-significant variables were removed at each step of the model building process.

At each step of the model building process, a log likelihood statistic(-2*ln(likelihood)) for the model was calculated by the computer software. The change in log likelihood from one model to the next was examined to monitor for any large, statistically significant changes when variables were removed. This change is specifically shown by the log likelihood ratio which is defined as minus twice the difference between the two log likelihoods of the models being compared. This statistic has a chi-square distribution under the null hypothesis that there is no effect from the removed variables (Hosmer and Lemeshow, 1994, Vollmer, 1996).

The computer software also calculated a pseudo-R squared and a chi square measurement at each step. The R-squared equals "1-(LLo-LLp)", where LLo and LLp are the values of the log-likelihood functions for the constant only model and the model with p covariates, respectively (StataCorp, 1997). The chi-squared statistic that is reported is the model chi-square, with p degrees of freedom. This represents the change in log likelihood between the constant only model and the model with p covariates. These measurements are somewhat useful in assessing the significance of the covariates included in the model.

The inclusion and exclusion of variables was based on an assessment of the variables at each model building step. The assessment was based on the change in log likelihood (log likelihood ratios) of the models, and the specific statistics associated with individual variables, such as the Wald p-values, the odds ratios (beta-coefficients), and the associated 95% confidence intervals. Finally, the biological and clinical importance of the variables was considered as well.

Therefore, the conditional main effects model is as follows:

Covariates	OR	Std. Err.	z	P>|z|	[95% Conf. Interval]
Age	2.75	.71	3.93	0.000	1.66 - 4.57
BCG	4.33	1.05	5.99	0.000	2.68 - 6.99
Foreign Birth	4.56	1.15	6.00	0.000	2.77 - 7.48
Foreign Practice	4.04	1.70	3.31	0.001	1.77 - 9.21

Log Likelihood = -178.38
R-squared=31.12%
Number of observations = 456

6.1.3 Interactions

Interactions were examined for all of the four variables included in the final model, Age, BCG, Foreign Birth, and Foreign Practice. A "univariate analysis" was performed on each interaction term by adding it to the main-effects model. Of all the interaction terms, the only significant term was Age*Foreign Practice; it produced a marginally significant improvement in the model (log Likelihood Ratio p-value = 0.04). Because of the effect modification from BCG, Country of Birth, and Age seen in Chapter 5, it was predicted that there may be many significant interaction terms in the regression model. However, this was not the case. Inclusion of interaction terms in the final regression model will be examined following the subsequent unconditional analysis.

6.2 Unconditional Regression Analysis

Unconditional regression is not theoretically appropriate for highly stratified data, for the reasons discussed above in Section 6.1. A stratified random sampling method was used in this study in order to gain information on the hypothesized high-risk specialties, most of which do not contain a large number of physicians. These high-risk specialties may have been missed if simple random sampling had been used. In order to determine risk estimates for the stratifying variable (specialty), an

unconditional method must be used. An unstratified unconditional regression analysis was performed containing a term for the specialties.

The unconditional likelihood equation is the product of the probabilities of a positive outcome for risk factor x, for each observation, m (m_1 being cases and m_0 being controls):

$$\prod_{\ell=1}^{m_1} \exp(\alpha+Bx_\ell) \Big/ \prod_{\ell=1}^{m_1} [1 + \exp(\alpha + Bx_\ell)]$$

where α is the intercept function reflecting the overall probability of a positive outcome, B is the coefficient associated with risk factor, x (Kleinbaum et al, 1982, Vollmer R, 1996).

6.2.1 Variable Selection

The variables to be entered into the model were chosen in a similar manner to those of the conditional logistic regression model (Table 6.2). In addition, a term was placed in the analysis for specialty. The odds ratios and associated confidence intervals were analysed for the 29 different specialties and all were approximately the same, except for three specialties which had higher odds ratios: Internal Medicine, General Surgery and Respiratory Medicine. The significance of these three specialties is consistent with the previous specialty analysis of Table 5.11 which indicated that these were the three specialties that showed significantly higher proportions of reactivity. Initially, these three specialties were added separately into the model, whereas the other 26 specialties were combined into one stratum.

6.2.2. Model Building

As in the model building process for the conditional regression analysis, a manual backwards elimination stepwise method was used, whereby clinically and statistically non-significant variables were removed from the model until the final model was reached. (Refer to Section 6.1.2 for more details on the model building process.)

In order to obtain the most parsimonious model possible, i.e. the fewest terms that account for the most variation, the Internal Medicine and General Surgery strata of the specialties variable were combined with the other specialties in the referent group. The odds ratios associated with these two specialties were approaching one and were both non-significant. Therefore, the specialty variable was dichotomized, and consists of respiratory medicine and all other specialties. The model was run first with the original categorical variable and then with the dichotomous variable, the coefficients and log likelihood associated with the two models were nearly identical and therefore, it was deemed acceptable to use the dichotomous variable.

The unconditional logistic regression main effects model is:

Covariates	O.R.	Std. Err.	z	P>|z|	[95% Conf. Interval]
Age	2.64	.62	4.073	0.000	1.65 - 4.19
BCG	4.76	1.11	6.665	0.000	3.00 - 7.52
Foreign Birth	4.47	1.07	6.226	0.000	2.78 - 7.15
Foreign Practice	4.37	1.68	3.823	0.000	2.05 - 9.31
Respiratory Med	7.58	5.77	2.657	0.008	1.70 - 33.74

Log Likelihood = -229.17
Pseudo R-squared = 28.98%
Number of observations: 470

6.2.3.Interactions

As in the conditional regression, the significance of the interaction terms was assessed by adding each term separately to the main effects model. Once again, the interaction term of Age and Foreign Practice was the most significant of the interaction terms. However, it did not produce a statistically significant improvement in the main effects model (log likelihood ratio p-value=0.06).

6.3. Final Model Derivation

All the risk factors found to be significant in the conditional regression analysis were also found to be significant and had nearly identical coefficients/odds ratios in the unconditional logistic regression analysis. The unconditional model also included a

variable for respiratory medicine. The interaction term of Age*Foreign Practice only led to marginal significance in the conditional regression and was not statistically significant in the unconditional model and therefore was not included in the final regression model. Therefore, the final unconditional main effects model (see above) was used as the final regression model for this analysis.

6.4 Conclusions:

Although stratified unconditional logistic regression was not performed on this data-set, the strong similarities between the conditional and unconditional logistic regression models indicates that the estimates are not strongly biased by using the unconditional logistic regression rather than the conditional regression methods. The similar coefficients give credence to the fact that the unconditional model is representative of the model we would have expected to find using stratified analysis. Because the unconditional model has a term for specialty included, this is the final regression model for this study.

It is important also to note the consistency between these multivariate analyses and the previous more simple bivariate analysis in Chapter Five. In the bivariate analysis of Canadian born-non-BCG-vaccinated physicians (Tables 5.15 and 5.16), age over 45 years and foreign practice were the only factors to remain significant. This correlates well with the four significant variables of the conditional regression, older age, previous BCG, non-Canadian birth and foreign practice. The unconditional regression model also identified these four factors as being significant, as well as the respiratory medicine specialty, which showed the highest proportion of reactivity in the bivariate analysis. In addition, the odds ratios determined from these regression analyses are comparable to the Mantel-Haenszel odds ratios calculated in the stratification analyses in Chapter 5 (Tables 5.5, 5.6, 5.7) to examine confounding by Country of Birth and previous BCG-vaccination.

In order to check the effectiveness of the final unconditional model in describing the outcome variable, i.e., tuberculin reactivity among the physician population,

goodness-of-fit measures were calculated. The Pearson chi-square test statistic was 17.89 with 16 degrees of freedom, with an associated non-significant p-value of 0.33. The Hosmer-Lemeshow goodness of fit statistic is calculated to be 5.44 with 5 degrees of freedom, with an associated p-value of 0.36. Both measures are non-significant which indicates that the difference between the expected and observed probabilities is non-significant and therefore, the model is adequate.

TABLE 6.1: UNIVARIATE ANALYSIS FOR THE CONDITIONAL LOGISTIC REGRESSION ANALYSIS

Variable	OR	z	p-value
ABORIGINAL PATIENTS	1.07	0.287	0.772
ADMITTING PRIVILEGES	0.67	-1.655	**0.098**
AGE	4.06	6.527	**0.000**
BCG	7.04	8.161	**0.000**
CC HOSPITAL	1.55	1.056	0.291
PREVIOUS CONTACT	1.21	0.902	0.488
ELDERLY PATIENTS (2)	0.79	-0.967	**0.334**
ELDERLY PATIENTS (3)	0.60	-1.256	**0.209**
FOREIGN BIRTH	6.50	8.053	**0.000**
FOREIGN PATIENTS	1.22	0.794	0.271
FOREIGN PRACTICE	4.10	4.084	**0.000**
GENDER	0.82	-0.904	0.366
GI PROCEDURES	0.93	-0.171	0.864
NWT	1.45	0.752	0.452
PERCENTAGE HOSP. TIME(2)	0.69	-1.168	0.243
PERCENTAGE HOSP. TIME(3)	0.85	-0.469	0.639

* **bold** type identifies the p-values < 0.25 ; the associated variables are selected for entry into regression analysis

TABLE 6.2: UNIVARIATE ANALYSIS FOR THE UNCONDITIONAL LOGISTIC REGRESSION ANALYSIS

Variable	OR	z	p-value
ABORIGINAL PATIENTS	1.07	0.283	0.777
ADMITTING PRIVILEGES	0.84	-0.849	0.396
AGE	3.68	6.673	**0.000**
BCG	7.71	9.730	**0.000**
CC HOSPITAL	1.41	0.896	0.370
ELDERLY PATIENTS(2)	0.90	-0.518	0.604
ELDERLY PATIENTS(3)	0.79	-0.815	0.415
FOREIGN BIRTH	6.09	8.439	**0.000**
FOREIGN PATIENTS	1.07	0.327	0.567
FOREIGN PRACTICE	3.96	4.275	**0.000**
GENDER	0.74	-1.485	**0.131**
GI PROCEDURES	1.42	1.341	**0.180**
NWT	1.47	0.818	0.413
PERCENTAGE HOSP. TIME(2)	0.76	-1.309	**0.191**
PERCENTAGE HOSP. TIME(3)	1.01	0.029	0.977
PREVIOUS CONTACT	1.54	2.194	**0.028**
SPECIALTIES:			
GENERAL SURGERY	2.82	2.414	**0.016**
INTERNAL MEDICINE	2.65	2.320	**0.020**
RESPIRATORY MEDICINE	6.62	2.995	**0.003**

* **bold** type identifies the p-values < 0.25 ; the associated variables are selected for entry into regression analysis

CHAPTER SEVEN

CONCLUSIONS, DISCUSSION AND RECOMMENDATIONS

The results of this study indicate that approximately one half of physicians (45.9%) in the Edmonton Capital Health region are tuberculin skin test reactors. This is compared to an approximate 7% prevalence of tuberculin reactivity in the general Canadian population (Cameron, 1997). Although BCG vaccination and foreign birth account for a large proportion of this reactivity, we can assume that some of the excess risk seen among physicians is from their medical practice.

7.1 Summary of Results

In other studies on tuberculin reactivity among Health Care Workers, prior BCG vaccination and foreign birth are two of the major factors associated with tuberculin reactivity among the physician population. The regression analysis indicated that along with these two factors, age over 45 years, having practiced in a high-risk country[1] for longer than one month and practicing respiratory medicine were three other risk factors for reactivity. Although no interaction terms were included in the multivariate analysis, the bivariate analysis indicated effect modifications from BCG vaccination, foreign birth and age. Thus, those physicians who are Canadian born and/or those with no prior BCG history and/or younger age are associated with a higher risk estimate for all significant risk factors.

The initial hypothesis was that there would be specific risk factors associated with the physicians' practice. High-risk patient populations (i.e., Aboriginal, elderly, foreign born) did not seem to lead to increased proportions of positive tuberculin skin tests

[1] High Risk Country is defined as any country, not including Canada, the United States of America, Western European countries, Australia and New Zealand.

among the physicians. Those physicians with a high proportion of elderly patients, however, exhibited a low risk of tuberculin reactivity.

Regarding practice location and prevalence of tuberculin reactivity, the physicians from the Mill Woods area had a significantly higher rate of reactivity than all other regions combined. The physicians in this region significantly differed from other family practitioners by the high proportion of foreign born in their patient population. They did not show any other statistical differences. It was hypothesized that a difference in prevalence may be noted between those physicians working in the inner city and those physicians working in high-income suburbs. No difference was noted, however. Unfortunately, only seven physicians from the Central region of Edmonton (which contains the downtown core and inner city area) participated in the study. The low statistical power makes any conclusions difficult to draw.

It also was hypothesized that those physicians practicing high TB exposure specialties would have a higher proportion of tuberculin reactivity. Pulmonary physicians had an extremely high prevalence of reactivity compared to the other specialty groups: 83% for the 18 physicians examined. None of the other hypothesized high exposure specialties (Emergency Medicine, Gastroenterology, Infectious Diseases, Anesthesia, and Pathology) had significantly high proportions of tuberculin reactivity (ranging from 20% for Emergency to 57.1% for Gastroenterology specialists). However, General Surgeons had a 70% prevalence and a statistically significant odds ratio (OR) of 3.48 (95% C.I. 1.17-11.6), and 68% of the Internal Medicine physicians examined were reactors with a statistically significant OR of 3.17 (1.20-6.81). However, for all of these specialties, the sample sizes were below 30 and therefore lacked the power required for attaining statistical significance differences.

7.2 Agreement of Findings with other Tuberculin Reactivity Prevalence Studies

These results correlate with other tuberculin reactivity prevalence studies among physicians and HCWs. Positive tuberculin skin test results are associated with the foreign born, older age, and previous BCG in the majority of other studies

(Schwartzman et al, 1996; Barrett-Connor, 1979; Fraser et al., 1994, Geiseler et al, 1986). In addition, the percentage of Canadian-born, non-BCG vaccinated reactors is 13 % in this study, slightly less than the 18% reactivity found among Canadian born, non-BCG vaccinated HCWs in a recent Montreal study (Schwartzman, 1996).

The prevalence among the different specialties is not as well-defined in previous literature concerning studies on HCWs and physicians. Internal medicine and family medicine specialties have historically shown high tuberculin reactivity (Ramphal-Naley et al, 1995). Recent HCW studies have produced varying results on which specialties have high proportions of tuberculin reactors. The high tuberculosis exposure in pulmonary medicine was previously discussed by Malasky *et al* in their study indicating that 11% of pulmonary fellows converted their tuberculin reactor status within a time span of 4 years (Malasky et al, 1990).

7.3 Strengths and Limitations of the Study

This study has both a notable strength and some limitations.

7.3.1 Two-Step Tuberculin Skin Testing

Unlike most other studies performed on the tuberculin reactivity status of HCWs, two-step tuberculin skin testing was the protocol for testing in this study; 95.6% of the physicians in this study were two-step tested. Two-step testing will help in eliminating false negative results, perhaps up to 80% (Horowitz *et al*, 1995), and will provide a more accurate baseline prevalence.

7.3.2 Recall Bias

The recall of tuberculin status is an important potential source of bias in this study. Schwartzman et al. reported self-recall among HCWs to be inaccurate; 12% who claimed no prior positive tuberculin skin tests had a documented positive result and one-third of those who reported prior positive tests had no documentation of this. In a study of a non-medical cohort, only 42.2% of people who claimed to be tuberculin reactors, actually did test positive (Reichman, 1977). The issue of recall is an inherent

problem associated with tuberculin prevalence studies. Because of the historical contraindication to retesting a previous strongly positive skin test, one has to rely on the recall of the participants, or face an underestimation in the true number of reactors if those who refuse re-testing, owing to an undocumented positive skin test, are excluded.

To address this issue of potential misclassification, a sensitivity analysis was undertaken to analyze the effect if 50% of those physicians who claimed to have "clear memory" of a previously positive skin test were actually negative. A logistic regression analysis performed on this altered data set showed the same risk factors, with very similar coefficients, to be significant when compared with the actual data. Therefore, any potential misclassification would probably not have any significant effects on the determination of risk factors for tuberculin reactivity among this study population.

The retrospective nature of the data collection in this study is a limitation for other variables in this study as well. The required recall on other questions such as BCG vaccination, past travel, and tuberculosis exposures, might lead to inaccuracies in the data collected.

7.3.3 Participation Bias

A participation bias might exist in this study because those who are known reactors may not have been as willing to participate in the study. This potential bias may be indicated by comparing participants and non-participants in this study, as discussed in Chapter 3. A significantly higher number of foreign born and older physicians did not participate. The assumption may be made that the older physicians were more likely to have been BCG vaccinated. Consequently, the non-participants may have a higher percentage of the two primary risk factors for tuberculin reactivity, foreign birth and BCG vaccination. The prevalence found in this study might therefore be an underestimation of the true proportion. However, not retesting those physicians who were able to provide documentation or had a clear memory of previously positive

tuberculin skin tests may have decreased this bias. In addition, another participation bias might have occurred in that those physicians who perceived themselves to be more at risk might have been more likely to participate.

7.3.4 Statistical Power

Finally, in many cases, it was difficult to examine variables thoroughly owing to associated small cell numbers. This was the case for some specialties, and with the examination of the effect of region of practice on tuberculin reactivity. Because of the stratification used for sampling in this study, this led to many strata, some with extremely small cell numbers and consequently to low statistical power. Perhaps these questions could be examined more closely in future research with larger sample sizes.

7.4 Interpretation of Tuberculin Skin Test Results

The tuberculin skin test is an extremely effective screening tool. Tuberculin reactivity, however, may be associated with previous BCG immunization and exposure to non-tuberculous mycobacteria, and not necessarily tuberculosis infection.

7.4.1. Sensitivity and Specificity of Tuberculin Skin Tests

The positive predictive value of the tuberculin skin test is high (>95%) in populations where the prevalence of infection is high. Because health care workers fall into this high prevalence population (greater than 25% infected), tuberculin skin testing remains a useful and accurate diagnostic test in such populations. The sensitivity of the tuberculin skin test among the physician population is also good, because false negatives occur in association with poor health and this population is relatively healthy (Bass, 1993). Incorrect tuberculin skin test results also may be linked to poor test administration and reading, and to the commercial brand of tuberculin used for testing. Only one brand of commercial tuberculin was used throughout this study (Connaught) to ensure consistency. Four individuals were involved in the administration and reading of tuberculin skin tests throughout the course of the study. However, for consistency, one member of the study team did the vast majority of the

testing (LZ) and another the reading (SP). The specificity of the tuberculin skin test also is high (at >95%) among HCWs (Bass, 1993).

7.4.2 Effects of Prior BCG Vaccination and Non-Tuberculous Mycobacterial Exposure

An inherent flaw associated with the examination of tuberculin reactivity is the inability to differentiate between reactivity caused by prior BCG vaccination and by MTB exposure. In order to have eliminated this source of confusion from the present study, the study population would have had to consist of only non-BCG-vaccinated persons. Until the 1980s, however, it was common practice to give BCG vaccinations to students beginning medical school. Therefore, many physicians practicing today had been vaccinated. Excluding BCG-vaccinated physicians from the study population would lead to an overall younger population. In addition, the population would be predominately North American, because BCG vaccinations are still routinely administered in most parts of the world. Although this study design may help in determining the work-related risk of tuberculosis exposure, it would not be generalizable to the physician population practicing today in the Edmonton Capital Health Authority.

Evidence has shown that the effect of the BCG vaccination on the tuberculin skin test can be ignored for those physicians who had the vaccination in infancy. If vaccinated between the ages of 2-5 years, reactivity remains for 10%-15% of these individuals even after 20-25 years. When vaccinated after 5 years of age, the reactivity remains in 20%-25% of the individuals (CLA, 1996). Of the participating physicians in this study: 13 had been BCG vaccinated in infancy, 84.6% of them tested positive; 14 were vaccinated between the ages of 2-5 years, 64.3% remain positive; and 171 had been BCG vaccinated after the age of 5 years, 70.2% of them are positive. Therefore, although the evidence of tuberculin reactivity as related to prior BCG vaccination indicates that only 20.3% (40.25/198) of the physicians should still show tuberculin reactivity from the BCG vaccination, 69.9% of the BCG-vaccinated physicians in this

study are tuberculin reactors. This discrepancy would suggest that the reactivity in previously BCG-vaccinated physicians can not be fully attributed to the BCG itself.

Finally, exposure to non-tuberculous bacteria can also cause a reaction to the tuberculin skin test. However, it does not usually result in reactions larger than 10mm (CLA, 1996). It has been reported that fewer than 5% of young adults in Montreal have positive reactions to a non-tuberculous mycobacterial antigen (Schwartzman, 1996)

7.5 Previous Tuberculosis Exposure

As with all cross-sectional studies, it is impossible to separate cause and effect in this study because they are both being measured at the same point in time. Although the assumption is made throughout the study that TB infection will be patient–related, it is important to acknowledge that some of the exposure experienced by the physicians may have occurred prior to them becoming involved in the medical profession, or from another non-medial source. However, in order to assess this assumption, a question on previous known exposures was included on the questionnaire. The responses to this question indicate that only 4.7% (15/321) of those physicians with known exposures had encountered an exposure prior to beginning medical school. Of these physicians, 87% (n=13) are tuberculin reactors. Three of these reactors indicated that it was this pre-medical school exposure that led to their conversion to positive tuberculin skin tests.

7.6 Tuberculosis Screening Programs among Health Care Workers

Both the Canadian and American guidelines for preventing nosocomial transmission of TB in health care facilities outline the requirements of a successful TB infection-control program. These include the need for institutional commitment, effective engineering controls, appropriate management of patients with suspected or confirmed infectious TB, employee surveillance and education, and an evaluation of the program's effectiveness. Effective employee surveillance requires that tuberculin skin

testing be performed at the time of hiring, annually, and after an exposure. (CDC, 1994; Health Canada, 1996)

Physicians should be no exception to this surveillance. However, regrettably, this does not appear to be the case. Although physicians have been shown to have the highest conversion rate of any occupational group in Canadian hospitals, they are the least monitored for infection (Holton, 1997). In this prevalence study, the average length of time since the last tuberculin skin test for those physicians who are non-reactors was 9.6 years (7 physicians (i.e., 1.4%) indicated that they had never been tested). In many instances, physicians are not part of tuberculosis screening programs because they work at several hospitals (Ramirez, 1992). Therefore, the physicians go for testing only when they feel it is important. At one hospital in this study where all other staff is required to undergo regular tuberculosis screening, physicians are not included in the screening because they are deemed too difficult to reach. This appears to be a common sentiment; a recent study showed that although more than 70% of the Canadian hospitals examined had tuberculosis screening programs for nursing, respiratory, or laboratory staff, less than half had screening programs for the medical staff (Holton et al., 1997).

The goal of occupational TB screening programs is to keep the risk of exposure no higher than that of the community. Awareness and acknowledgement of potential nosocomial exposure is an important step to reducing the infection of physicians and all other HCWs. In addition, adherence to a well-maintained TB control program should significantly reduce the risk to persons in these high-risk settings (CDC, 1994; Health Canada, 1996). Examinations of American hospitals in which nosocomial outbreaks have occurred documented that there was incomplete implementation of TB infection control guidelines. Follow-up studies indicated that after subsequent implementation of control guidelines, there was a significant reduction, or complete elimination, of nosocomial transmission of MTB to patients and/or HCWs (CDC, 1994; Maloney, 1995).

7.7 Recommendations

- It is the opinion of the study personnel that this research raised awareness of tuberculosis reactivity, exposure and infection among physicians. There appeared to be the false sense of protection among many physicians who have been previously been BCG-vaccinated that they now have a lifelong protection from TB. In addition, there is a common belief among many physicians that prior BCG is a contraindication for any tuberculin skin testing in the future. The good response rate for this study (72.4%) indicates that physicians are amenable to participation in such screening programs and research, contrary to what investigators may believe.

- It may be worthwhile to reexamine the effect that performing upper gastrointestinal endoscopy has on the prevalence of tuberculin reactivity. The number of individuals in the higher exposure strata was small and appropriate statistical power was not achieved. In addition, the question was slightly ambiguous, as the definition of upper GI procedure was not well defined on the questionnaire. It may be interesting to discriminate between bronchoscopies and other less cough-inducing endoscopic procedures when examining this variable in the future. The fact that this variable was approaching significance in the non-BCG vaccinated and Canadian born physicians indicates that this may be an important source of exposure to TB for physicians.

- Even though the physicians in this study had a rate of tuberculin reactivity comparable to that of other HCWs, this prevalence is considerably greater than that of the general public. This study reported that Canadian-born-non-BCG-vaccinated physicians have twice the prevalence of tuberculin reactivity as that of the general Canadian public. However, the lack of regular screening for physicians does not correspond well with this increased level of infection. Although it is certainly acknowledged that physicians are busy and very difficult to locate, there is a need for annual tuberculin skin testing for physicians. This

monitoring may be even more important for those physicians practicing specialties such as Respiratory Medicine, General Surgery, and Internal Medicine, which have demonstrated high proportions of tuberculin reactivity. Also, where appropriate, those physicians who do convert should be offered and should consider chemoprophylaxis to reduce their risk of developing active disease

- It is of utmost importance for physicians with positive tuberculin skin tests to acknowledge their potential to develop active disease. Those physicians who have previously been BCG-vaccinated should not disregard the possibility that their reactivity may be from TB infection and not from the BCG vaccine. All reactors should engage in appropriate follow-up. Also, they should be aware of the symptoms associated with active TB (i.e., persistent cough, weight loss, fever, fatigue) and upon development of symptoms, they should consult their family physician.

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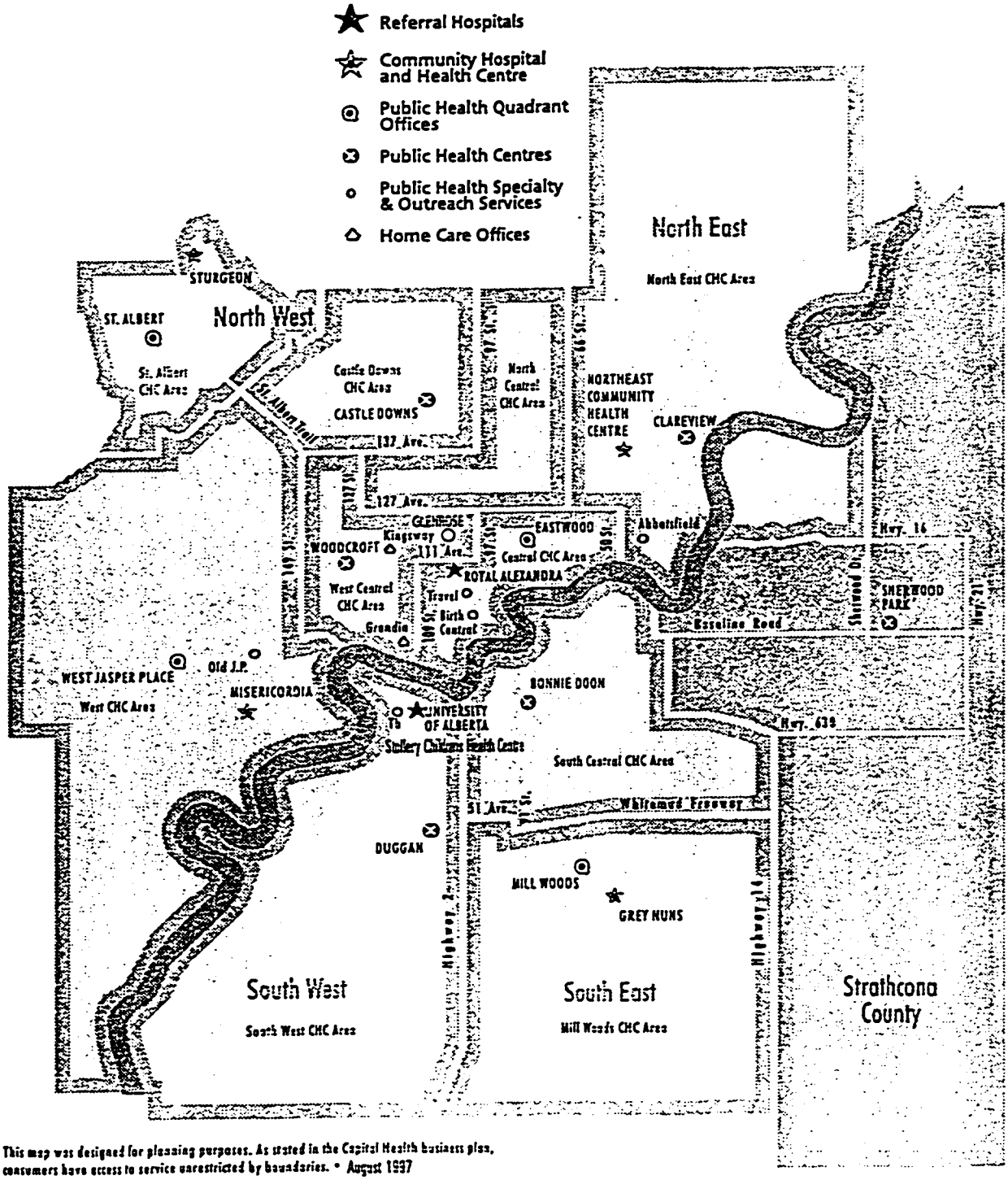
Appendix 1:
Map of Edmonton Capital Health Authority

**(printed with permission from
the Capital Health Authority)**

Capital Health



This map was designed for planning purposes. As stated in the Capital Health business plan, consumers have access to service unrestricted by boundaries. • August 1997

Appendix 2:
Letter of Introduction

<Date>

Dear Dr. <LastName>,

Re: **Tuberculosis Infection (TB) Prevalence and Determinants of Infection among Physicians**

Tuberculosis (TB) rates, unfortunately, are rising globally. There is concern that TB's impact in Alberta will be seen first by health care workers and, in particular, by physicians. You are one of almost 700 physicians of the Capital Health Authority who has been randomly chosen to participate in a study designed to measure this impact.

Because physicians often are the first health care professionals to encounter a patient with active TB, their risk of infection may be higher than that seen among other health care workers. This is especially relevant for those seeing patients who fall into high TB incident populations, that is the foreign born and Aboriginal Canadians.

A recently completed national health care worker study revealed very high tuberculin reactivity rates for permanent staff at two Edmonton hospitals where, at the **Royal Alexandra Hospital, 44.2% reactivity** was observed and, at the **University of Alberta Hospital, 46.9% reactivity** was observed. **This study DID NOT include physicians.** The omission of physicians from these studies is common in the scientific literature because physicians are seldom attached to a specific unit and their busy practices make it difficult for them to submit to the required skin testing protocol. Therefore, at the present time, information concerning TB reactivity among physicians is limited. Despite this, it is important to study physicians because of their **real risk** of TB infection from both known and unknown sources. Early recognition can be beneficial and help dramatically in limiting the further spread of infection among colleagues, patients, family, friends and others.

Therefore, Dr. Anne Fanning of the Division of Infectious Diseases and Dr. Colin Soskolne of the Department of Public Health Sciences, Faculty of Medicine and Oral Health Sciences, University of Alberta are examining TB infection rates and risk factors for tuberculin reactivity among physicians of the Capital Health Authority. We ask you to participate in this study, funded by the Alberta Lung Association. Participation means taking about 15 minutes to complete a consent form, as well as a six-page questionnaire concerning your place of birth, your medical training, your history of BCG and prior skin testing, and other relevant information concerning your potential for exposure to TB. In addition, we would ask that if you do not have a record of a positive skin test that you permit us to skin test you, in your office or place of your choice, at a time convenient to you, and to return 48-72 hours later to read the skin test. If you are a reactor, we will provide you with currently recommended follow-up options.

The questionnaire information and skin test result will be entered into a database and will be used to analyze the risk of infection based on age, gender, place of birth, BCG, exposure history, and type of medical practice. This information will be held in the strictest confidence by the researchers.

We know how full your daily schedule likely is. However, **we ask for your cooperation.** Our staff will contact your office by telephone over the next approximately 2 weeks to establish your willingness to participate in this study and, if willing, to schedule a time for tuberculin skin testing. We commit to providing you with a summary of the overall study results within the year.

Yours truly,

E. Anne Fanning, M.D., F.R.C.P. (C)
Professor, Infectious Diseases Division
Tel. 492-6455

Colin L. Soskolne,Ph.D.,F.A.C.E.
Professor, Public Heath Sciences
Tel. 492-6013

Appendix 3:
Questionnaire

TUBERCULOSIS (TB) INFECTION PREVALENCE AND DETERMINANTS OF INFECTION AMONG PHYSICIANS

I. BACKGROUND INFORMATION

Last Name:_____

First Name:_____

Work Address:_____

_____

Postal Code:_____

Telephone Number: Home:_____

Work:_____

Gender: M F

Date of Birth: _____
YY/MM/DD

Country of Birth:_____

If not Canada, in what year did you arrive in Canada?_____

II. TUBERCULIN SKIN TESTING, EXPOSURE AND BCG HISTORY:

Date of your last Tuberculin skin test (Mantoux, PPD):_____
YY/MM/DD

Result of test (in millimetres):_____mm

Where was this skin test done?_____

Was it a two-step test? (i.e., was the test repeated 7-21 days later?)

Y N

Do you have a written record of your last tuberculin skin test?

Y N

Have you ever been diagnosed with active tuberculosis? Y N

If Yes, what year? _____

where?_____

Have you previously been on medication for tuberculosis? Y N

If Yes, was it Preventative
or, Active

If No, have you ever been offered TB medication, but refused it?

Y N

To your knowledge, have you ever been in direct contact with a TB case?

Y N

If Yes, please give dates of contact, beginning with the most recent:

____/____ ____/____ ____/____ ____/____

YY/MM YY/MM YY/MM YY/MM

Are you aware if any of these contacts were sputum smear-positive for acid-fast bacteria?

Y N Unknown

If Yes, please circle the appropriate contact dates.

Have you ever received a BCG vaccination? Y N

If Yes, what year?_____

Do you have a BCG vaccination scar? Y N

III. FOREIGN TRAVEL:

NOTE: Foreign Travel is defined in this study as travelling outside of North America, Western Europe, Australia, and New Zealand **for longer than one month.**

Please complete the following table concerning your most recent Foreign Travel.

	Country	Year	Length of Stay
1.	_____	_____	_____
2.	_____	_____	_____
3.	_____	_____	_____

Did you practice medicine during your foreign travel? Y N

If Yes, in which countries?_____

IV. EDUCATION, TRAINING, AND WORK EXPERIENCE

In what year did you graduate from Medical School?_____

Location of Medical School:_____

Post-Graduate training: Please fill in the following table.

	START (YY/MM)	END (YY/MM)	PROGRAM	LOCATION
1.	_____	_____	_____	_____
2.	_____	_____	_____	_____
3.	_____	_____	_____	_____

IV. PRACTICE

What is your specialty?_____

In total, how many years have you spent practicing medicine?_____ yrs

At the present time:

Do you have hospital admitting priveledges? Y N

What percentage of time do you spend in a hospital setting?_____hrs/wk

How many upper airway and/or upper GI procedures do you perform **per month**? Circle the correct response.

A. None
B. 1-10
C. 10-30
D. 30-60
E. More than 60

Please estimate to the best of your ability the percentage of your patients falling into each category, and circle the response that best fits with your experience.

Born outside of Canada, US, Western Europe, Australia and New Zealand:

A. None
B. 1-10%
C. 11-25%
D. 26-50%
E. 51-75%
F. More than 75%

Aboriginal

A. None
B. 1-10%
C. 11-25%
D. 26-50%
E. 51-75%
F. More than 75%

Elderly (ie. over 70 years old)

A. None
B. 1-10%
C. 11-25%
D. 26-50%
E. 51-75%
F. More than 75%

Please fill in the following table, providing all the jobs in health care after receiving your initial medical training. Please begin with your most recent work experience.

START (Yr/Mo)	END (Yr/Mo)	POSITION	LOCATION	PATIENT CONTACT (hrs/wk)

V. RESPIRATORY PROTECTION USE -

Using the following response key, please circle the response which best represents your opinion of each item:

SD = Strongly Disagree
D = Disagree
N = Neither Agree Nor Disagree
A = Agree
SA = Strongly Agree

I always wear a mask when entering an isolation room of a patient with TB.

SD D N A SA

I feel it is extremely important for physicians to be protected from TB.

SD D N A SA

The masks which are currently available are effective in protecting me from TB.

SD D N A SA

The masks currently used are comfortable to wear.

SD D N A SA

Appendix 4:
Protocol for Tuberculin Skin Testing

PROTOCOL FOR TB SKIN TESTING

Testing Time Frame

PPD-T1 should be done when the consent is signed and when you are sure that the reading can be done within 48-72 hours. If the reading cannot be done within the time frame, the testing should be rescheduled.

PPD-T2 (i.e. the second test for the booster phenomenon) should be done between 1 and 4 weeks later. It cannot be done less than one-week after the first test is administered and every effort should be made to do it no later than 4 weeks after the first. However, it can be done later although the booster effect may be reduced slightly, but of greater importance, introduce the real possibility of true conversions because of exposure in between.

Testing Materials

The PPD material should be from Connaught laboratories. The PPD used throughout will be 5 tuberculin units, which is equivalent to 0.1 mL. The syringes used will be tuberculin syringes with 26 or 27 gage needles.

Testing Technique

PPD material can be drawn up into the syringe beforehand if testing will be done in batches. It is important that this is done no more than 30 minutes before testing.

The subject should be seated comfortable with their arm resting on a table. The tester should be seated facing the subject. PPD-T1 should be done on the right arm and PPD-T2 should be done on the left arm.

The volar (inside) aspect of the forearm should be used.

Avoid areas with rash, eczema, or significant scarring such as from a burn or skin graft.

Wipe the area with an alcohol swab and let it dry for a few seconds (less pain).

The needle should be lying flat on the skin with the bevel upward. The easiest way to inject the needle intradermally is to actually pull the skin onto the needle.

The material should be injected slowly but steadily, i.e. over 2-5 seconds. As it is injected there should be resistance and a small wheal or papule should be seen. If a small amount runs out onto the skin during or after injection that is okay. If no papule appears and most of it seems to run out onto the skin then repeat the injection

at least 2 inches away from the first site. Record the fact that two injections were given.

If the injection is too deep and appears to be subcutaneous please record but do not repeat the injection.

If there is any bleeding use a dry gauze. Do not apply band-aids.

If the subject is feeling faint or dizzy have them sit with their head down. If you are in a crowded place try to get them off to one side. Don't let them return to work until you are absolutely certain they are feeling 100% fine.

At the time of testing, the time, date and place of reading should be agreed upon between the study personnel and the physician.

Technique of Reading

All reading should be done between 24 and 48 hours after testing. In occasional circumstances readings will be done after 72 hours. If this occurs, the exact interval should be recorded.

At the time of the reading the subject and the reader should be seated.

The subject should be seated with the arm resting in a relaxed position.

First the site of injection should be inspected for any redness, erythema, and blistering. Erythema should not be recorded; the presence of blistering should be recorded.

The site should be palpated to detect if there is any induration.

If there is any induration the ballpoint technique should be used to define the limits. The transverse diameter of induration is measured.

The ballpoint technique consists of holding a ballpoint pen and pushing it along the skin, starting from the outside of the reaction and moving towards the center. Where the ballpoint pen encounters resistance and stops is to be taken as the edge of induration. The ballpoint pen should be approached on several occasions from each side of the arm, where it stops consistently should be marked on each side and the distance between measured with machinists calipers.

The result should be recorded in millimetres. If no induration is felt, then this is recorded as zero millimetres.

The physician should be given a tuberculin skin testing record card at the time of the tuberculin skin test reading. The record card should record both test results in the case of a two-step test.

If a physician cannot be seen, but contacted and says there is absolutely no reaction this can be taken as a negative reading. However, every effort must be made to meet them and read them, even up to one week later. In general, positive reactions will remain for as long as one week and completely negative will of course remain negative throughout.

Again, in exceptional circumstances, arrangements can be made that someone else reads the test somewhere else. In general this should be done only if the physicians realized after been given the test that they won't be available for reading.

If a physician considers a test positive, every effort must be made to see the physicians and obtain a reading.

* This protocol is based on the tuberculin skin testing protocol developed by Dr. R. Menzies for the Canadian Study of TB in Health Care Workers (Study Protocol Manual, Chapter 6, 1996)

Appendix 5:
Notice to Physicians with Positive Mantoux Tests

Name:_____ Date:_____

Your tuberculin skin test measures _____ mm. This is considered to be a positive reaction which indicates that, at some point in time, you have been exposed to tuberculosis. Because this is your first recorded positive skin test, it is advised that you:

1. Have a chest X-ray if you have not had one in the past year.
2. See a physician if you suffer from tuberculosis symptoms, including persistent cough, weight loss, night sweats, fever.
3. Submit sputum for TB culture if you have a productive cough.
4. Consider INH chemoprophylaxis.
5. Notify Occupational Health.

Please feel free to call Dr. Anne Fanning at 492-6455, if you have any questions or concerns.

Appendix 6:
Informed Consent Form

TUBERCULOSIS (TB) INFECTION PREVALENCE AND DETERMINANTS OF INFECTION AMONG PHYSICIANS

Principal Investigators: Dr. E. A. Fanning, Dr. C. L. Soskolne

Background: Physicians, like other health care workers, are at a high risk for tuberculosis exposure. The increase in global TB rates, the mounting problems with drug resistant TB, and increased immigration to Canada from countries where TB is endemic are all factors which increase the danger to physicians as they are exposed to known and unknown TB cases.

Purpose: The purpose of this study is to determine a baseline prevalence rate of tuberculosis infection among physicians and to gain a better understanding of the risk factors for infection.

Procedures: Participating in the study will involve:

1) Filling out a questionnaire (15 minutes) about your practice, as well as past TB exposure, previous skin tests, and vaccinations. This questionnaire is strictly CONFIDENTIAL and will only be used for the study.

2) "Two-step" tuberculin skin testing for those physicians who have not had a test within the last year. This means you will receive an initial PPD (purified protein derivative) skin test. If the first test is negative, the skin test will be repeated 1-4 weeks later. If the test is positive, a chest x-ray and further medical evaluation will be recommended.

Possible Benefits: Indicate if you have been infected with tuberculosis, and improve our understanding of modes of TB transmission.

Possible Risks: The tuberculin skin test is virtually painless and without risk. However, strong positive reactions can cause a sore arm for a couple of days.

Confidentiality: Personal records relating to this study will be kept confidential. Only the study investigators will have access to your records. Any report published as a result of this study will not identify you by name.

Please See Over

Tuberculosis (TB) Infection Prevalence and Determinants of Infection Among Physicians

I agree to take part in this study, and therefore, if necessary, undergo the "two-step" tuberculin skin test:

YES ☐ NO ☐

Signature of Participant:_____ Date:_____

Printed Name:_____

Signature of Witness:_____ Date:_____

Printed Name:_____

Signature of Principal Investigator: _____

Please contact one of the individuals identified below if you have any questions or concerns:

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Appendix 7:
Grouping of Specialties according to Clinical Considerations

SPECIALTY GROUPING ACCORDING TO CLINICAL CONSIDERATIONS

SPECIALTY (n)	TOTAL
1. FAMILY MEDICINE (152) - Occupational Medicine/Community Medicine (6)	158
2. MEDICINE - Cardiology (15) - Dermatology (13) - Emergency Medicine (5) - Endocrinology (6) - Gastroenterology (14) - Geriatric Medicine (6) - Infectious Disease (14) - Internal Medicine (25) - Medical Oncology (11) - Nephrology (5) - Neurology (10) - Ophthalmology (13) - Physical Med and Rehab (6) - Rheumatology (7)	150
3. SURGERY - General Surgery (20) - Plastic Surgery (8) - Orthopedic Surgery (15) - Otolaryngology (7) - Urology (12)	62
4. RESPIRATORY MEDICINE	18
5. PATHOLOGY/LAB MEDICINE	20
6. ANESTHESIA	33
7. DIAGNOSTIC RADIOLOGY	32
8. O&G (21) PEDS (37)	58
9. PSYCHIATRY	29

Appendix 8:
Logistic Regression
Variables and Model Building Steps

VARIABLES USED IN LOGISTIC REGRESSION ANALYSIS

TUBERCULIN SKIN TEST RESULT (tstreg) on:

ADMITTING PRIVILEGES (hospadm)	0- No	1- Yes	
AGE (age2) - continuous -> dichotomous	0 <45years	1 >45 years	
BCG (bcg)	0- No	1- Yes	
CHARLES CAMPSELL HOSPITAL (cch)	0- No	1- Yes	
FOREIGN BIRTH (cobcbfb)	0- No	1- Yes	
FOREIGN MEDICAL SCHOOL (loccbfb)	0-No	1- Yes	
FOREIGN PRACTICE (forprac)	0- No	1- Yes	
GENDER	0-male	1-female	
GI PROCEDURES (gi2)	0 < 10%	1 > 10%	
NORTH WEST TERRITORIES/YUKON (nwt)	0- No	1- Yes	
PERCENTAGE TIME IN HOSPITAL (perc3)	1 < 10%	2 – 10-90%	3 >90%
PREVIOUS CONTACT (contact)	0- No	1- Yes	
TIME SINCE GRADUATION (gradyrs) - continuous			

Patient Population Variables

FOREIGN BORN (for2)	0 < 10%	1>10%	
ABORIGINAL (aborig2)	0 < 10%	1>10%	
ELDERLY (eld3)	0 <10%	1 - 10-50%	2 >50%

CONDITIONAL LOGISTIC REGRESSION: Model Building Steps

Step One:

Iteration 0: Log Likelihood =-227.35647

Conditional (fixed-effects) logistic regression — Number of obs = 456; chi2(7) = 167.37; Prob > chi2 = 0.0000; Log Likelihood = -175.28973; Pseudo R2 = 0.3231

tstreg	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age2	2.670642	.6987904	3.754	0.000	1.599166	4.460032
bcg	4.555112	1.134939	6.086	0.000	2.795221	7.423046
cobcbfb	4.684767	1.200626	6.026	0.000	2.834911	7.741703
forprac	4.40032	1.878228	3.471	0.001	1.906155	10.15805
Ield3_1	.9092409	.2943346	-0.294	0.769	.4820949	1.714847
Ield3_2	.4974443	.2567036	-1.353	0.176	.1809199	1.367737
hospadm	.5583677	.175118	-1.858	0.063	.301969	1.032472

Step Two:

Conditional (fixed-effects) logistic regression — Number of obs = 456; chi2(5) = 165.35; Prob > chi2 = 0.0000; Log Likelihood = -176.29775; Pseudo R2 = 0.3192

tstreg	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age2	2.66476	.6939433	3.764	0.000	1.59953	4.439394
bcg	4.559054	1.129612	6.123	0.000	2.805238	7.409344
cobcbfb	4.524177	1.146642	5.956	0.000	2.752989	7.434891
forprac	4.294549	1.830502	3.419	0.001	1.862528	9.902216
hospadm	.5388244	.1646636	-2.023	0.043	.2960205	.9807824

likelihood-ratio test — chi2(2) = 2.02; Prob > chi2 = 0.3649

Step Three:

Conditional (fixed-effects) logistic regression — Number of obs = 456; chi2(4) = 161.20; Prob > chi2 = 0.0000; Log Likelihood = -178.37542; Pseudo R2 = 0.3112

tstreg	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age2	2.759703	.7123443	3.933	0.000	1.663976	4.576964
bcg	4.330514	1.058887	5.994	0.000	2.681672	6.993156
cobcbfb	4.561058	1.152743	6.005	0.000	2.779307	7.485051
forprac	4.040737	1.700346	3.318	0.001	1.771226	9.218221

Clogit: likelihood-ratio test — chi2(1) = 4.16; Prob > chi2 = 0.0415

UNCONDITIONAL LOGISTIC REGRESSION: Model Building Steps

*bold type identifies variables to be removed.

Step One:

Logit Estimates — Number of obs = 470; chi2(10) = 193.34; Prob > chi2 = 0.0000; Log Likelihood = -225.99888; Pseudo R2 = 0.2996

tstreg	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age2	2.80295	.7148481	4.041	0.000	1.700317	4.620627
bcg	4.971797	1.181427	6.749	0.000	3.120656	7.921015
cobcbfb	4.592057	1.118044	6.261	0.000	2.849459	7.400349
contact	**1.093105**	**.2788777**	**0.349**	**0.727**	**.6629793**	**1.802288**
forprac	4.319177	1.707526	3.701	0.000	1.990172	9.37371
gender	1.217602	.3576247	0.670	0.503	.684695	2.165279
gi210	1.875141	.655748	1.798	0.072	.9448517	3.721382
perc3_2	.6624706	.1876727	-1.454	0.146	.3802139	1.154264
perc3_3	.9228054	.31086	-0.238	0.812	.4768381	1.785868
resm	5.887565	4.464111	2.338	0.019	1.332084	26.02195

Step Two:

Logit Estimates — Number of obs = 470; chi2(9) = 193.22; Prob > chi2 = 0.0000; Log Likelihood = -226.05976; Pseudo R2 = 0.2994

tstreg	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age2	2.832689	.7175989	4.110	0.000	1.724114	4.65406
bcg	4.965931	1.179411	6.748	0.000	3.117741	7.909726
cobcbfb	4.589665	1.11729	6.260	0.000	2.848182	7.395952
forprac	4.390726	1.722558	3.771	0.000	2.035144	9.472781
gender	**1.212347**	**.3553338**	**0.657**	**0.511**	**.6825636**	**2.15333**
gi210	1.89578	.6608279	1.835	0.067	.9573648	3.754036
perc3_2	.6659335	.1883984	-1.437	0.151	.3824886	1.159426
perc3_3	.9231901	.3110104	-0.237	0.812	.4770158	1.786692
resm	6.052864	4.567327	2.386	0.017	1.379328	26.56162

Logistic: likelihood-ratio test — chi2(1) = 0.12; Prob > chi2 = 0.7271

Step Three:

Logit Estimates

Number of obs = 470
chi2(8) = 192.79
Prob > chi2 = 0.0000
Log Likelihood = -226.27603 Pseudo R2 = 0.2987

tstreg	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age2	2.711275	.6611791	4.090	0.000	1.681114	4.372703
bcg	4.964481	1.178519	6.750	0.000	3.117504	7.905706
cobcbfb	4.57172	1.111419	6.252	0.000	2.838875	7.362291
forprac	4.355414	1.709755	3.748	0.000	2.017822	9.401041
gi210	1.853609	.6399627	1.787	0.074	.9421905	3.646678
perc3_2	.6451792	.1798366	-1.572	0.116	.373609	1.114149
perc3_3	.9078234	.3050432	-0.288	0.773	.4698768	1.753956
resm	5.916929	4.473457	2.351	0.019	1.344469	26.04006

Logistic: likelihood-ratio test chi2(2) = 0.55
Prob > chi2 = 0.7579

Step Four:

Logit Estimates

Number of obs = 470
chi2(6) = 189.89
Prob > chi2 = 0.0000
Log Likelihood = -227.72434 Pseudo R2 = 0.2943

tstreg	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age2	2.759942	.6644424	4.217	0.000	1.721779	4.424075
bcg	4.814146	1.13236	6.681	0.000	3.036013	7.633695
cobcbfb	4.537239	1.095648	6.263	0.000	2.82647	7.28348
forprac	4.191593	1.616908	3.715	0.000	1.968012	8.927509
gi210	1.761635	.5901637	1.690	0.091	.9135989	3.396848
resm	6.456183	4.800939	2.508	0.012	1.503164	27.72971

Logistic: likelihood-ratio test chi2(2) = 2.90
Prob > chi2 = 0.2350

Step Five:

Logit Estimates

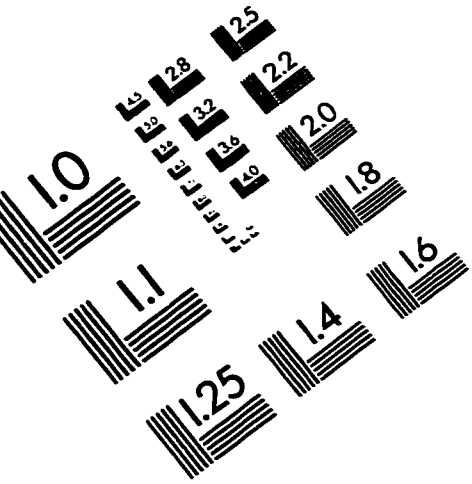
Number of obs =	470
chi2(5) =	187.01
Prob > chi2 =	0.0000
Log Likelihood = -229.16534	Pseudo R2 = 0.2898

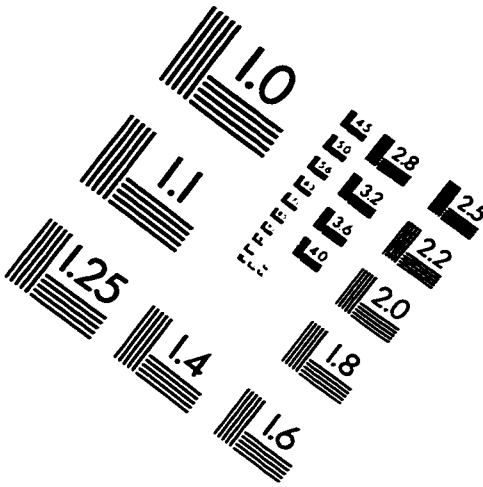
tstreg	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age2	2.633988	.6263184	4.073	0.000	1.65277	4.197738
bcg	4.758705	1.113865	6.665	0.000	3.0078	7.528848
cobcbfb	4.467219	1.074006	6.226	0.000	2.788637	7.156201
forprac	4.371649	1.687007	3.823	0.000	2.051961	9.313684
resm	7.576749	5.774186	2.657	0.008	1.701329	33.74252

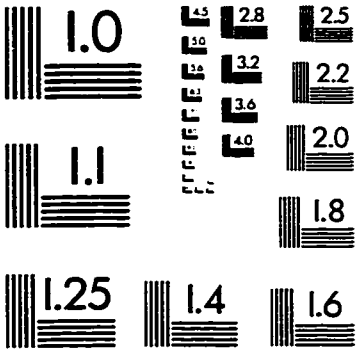
Logistic: likelihood-ratio test

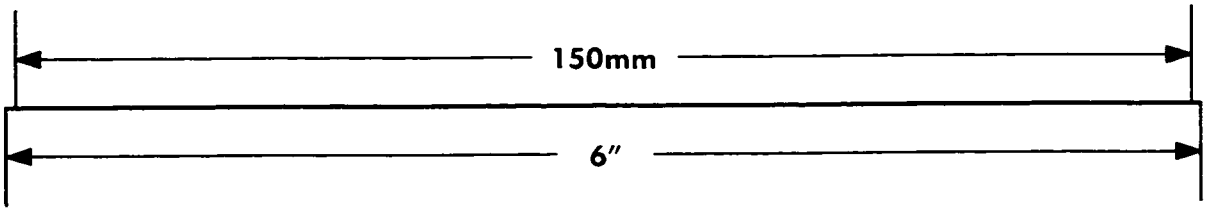
chi2(1) =	2.88
Prob > chi2 =	0.0896

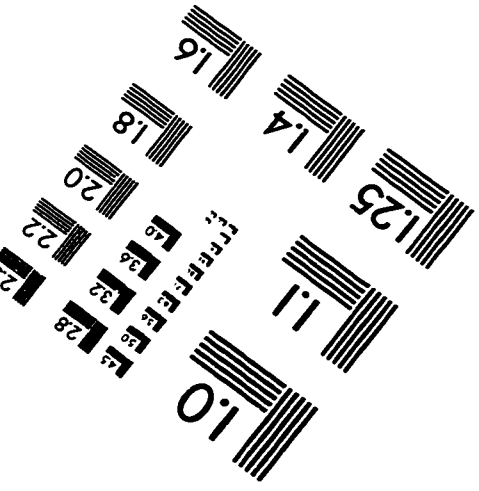
IMAGE EVALUATION
TEST TARGET (QA-3)

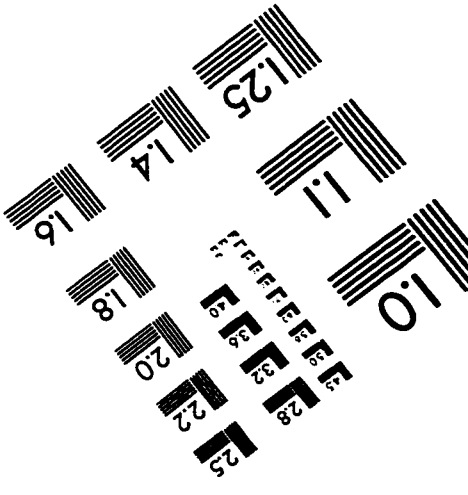












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