Tuberculin Reactivity and the Booster Response in Staff and Residents of a Nursing Home

by

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A Thesis
Submitted to the Faculty of Graduate Studies
in Partial Fulfilment of the Requirements
for The Degree of

Master of Science

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ISBN 0-315-77826-1

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ACKNOWLEDGEMENTS

I would like to express my gratitude to my advisors, Drs. Jure Manfreda and Earl Hershfield, for the countless hours that they spent helping me with this project, their patience dealing with a (stubborn) novice and their continued interest and support throughout. Thanks to my other committee members, Drs. David Fish and Margaret Fast, for their fresh look at the thesis and useful advice, and to my program director Dr. Sharon McDonald for allowing me the flexibility during my residency, to complete this thesis.

Joanne MacMorran, Director of TB Nursing was terrific in sharing her wealth of field experience, getting the study off the ground and supervising the study nurses. Thanks to Barb Bennett for the many hours spent "making it happen" in the nursing home. Anne, Gloria and Sonia from the TB Registry were invaluable in digging up older statistics and liaising with the nursing home. Thanks to Dr.Connelly, Sr.Celestine, Therese Dubowec, Jack Kisil, and staff and residents of the nursing home for their enthusiasm and participation in this research. Without these people this project would not be possible.

The Manitoba Lung Association and Manitoba Medical Foundation gave financial support for the presentation of these results at the ALA/ATS annual meeting in Miami Florida in May 1992.

Finally, to Liza, Priya and Zacharias, for their patience, love and support during the many hours I spent down in the dungeon working on this project.

ABSTRACT

This study examined the prevalence and determinants of tuberculin reactors and the booster response in 272 (97%) residents and 218 (69%) staff of an urban nursing home where a case of miliary TB was being investigated. Many subjects were foreign-born (56%) and 15% had a history of BCG vaccination (34% of staff). Testing was done with 5 TU PPD-S (Connaught). Those with <10mm of induration at 48 hours were retested at one week. Test sizes >9mm were classified positive (reactors). A questionnaire was given to collect information on risk factors for a positive test. Results showed that 28% (36% staff and 22% of residents) of subjects were reactors at the initial test, 6% at the booster test (staff=residents) and 32% at either test(40% staff and 26% residents). BCG (OR=4.8) and Foreign-Birth (OR=1.7) were significantly associated with total reactors. The association with foreign-birth was inversely related to the time since immigration. Only BCG was associated with a positive booster test (OR=6.7). Seventy-two percent of positive tuberculin reactions in individuals with a history of BCG was attributed to the vaccine. Conclusions: 1. staff as well as residents should be two-step tested when retesting for converters is anticipated; 2. the prevalence of tuberculin reactors is highly related to the prevalence of BCG vaccinees and foreign-birth;
3. chemoprophylaxis is probably not indicated for isolated tuberculin reactors with a history of BCG.

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LIST OF ABBREVIATIONS

ATS	American Thoracic Society
BCG	Bacille Calmette Guerin
CDC	Centre for Disease Control (United States)
CI	confidence interval
HIV	Human Immunodeficiency Virus
INH	Isoniazid
LCDC	Laboratory Centre for Disease Control (Canada)
M.	Mycobacterium
MHSC	Manitoba Health Services Commission
ml	milliltre
mm	millimetre
MOTT	mycobacteria other than tuberculosis
N	number of subjects
OR	odds ratio
p	probability of Type I error
PPD	purified protein derivative (of tuberculin)
PPD-S	international standard of PPD
SD	standard deviation
TB	tuberculosis
TU	Tuberculin Units

Chapter One

INTRODUCTION

Although the prevalence of tuberculosis (TB) has dramatically declined during this century (Comstock and O'Brien 1991), it is the eighth most commonly reported communicable disease in Canada (Laboratory Centre for Disease Control [LCDC] 1989). After consideration of the morbidity, mortality, treatability and other factors, the Canadian Advisory Committee on Epidemiology ranked TB as the second most important communicable disease to include in a national surveillance system (LCDC 1988). The United States has targeted TB for a national elimination campaign (Centre for Disease Control [CDC] 1989).

Twenty-seven percent of all cases of TB in Canada occur in the elderly population (persons aged 65 years and older) and they have the highest annual age specific incidence rate of 18/100,000 (Statistics Canada 1991). Although only 5.6% of the elderly population of Manitoba live in nursing homes (Manitoba Health Services Commission [MHSC] 1991), these institutions have all the necessary elements for the transmission of TB (Stead et al. 1985): a reservoir of old infection in elderly residents (Stead and To 1987); staff immigrating from high prevalence countries; delayed diagnosis

due to atypical presentation, non-specificity of symptoms or residents unable to communicate their symptoms (Borowitz 1982, Kim 1990, Morris and Nell 1988, Morris 1990, Yoshikawa 1992); prolonged close contact; and a pool of susceptible hosts (Stead 1981, Stead et al. 1985, Narain JP et al. 1985).

A number of outbreaks of TB in nursing homes have been reported (CDC 1979, CDC 1980, Stead 1981, CDC 1983, Morris and Nell 1988) leading to recommendations for special surveillance in this setting (CDC 1990a), including tuberculin testing all residents and staff at nursing home entry.

The study reported in this thesis was part of the public health investigation of an isolated case of miliary TB, diagnosed at autopsy, in a resident of a large urban nursing home[1].

The initial objectives for the public health investigation of a reported communicable disease include determining whether transmission has occurred and if there is an epidemic (Evans 1991). An epidemic is loosely defined as occurring when the observed frequency of events is greater than the usual or expected frequency (Last 1988). Any transmission of tuberculous infection to previously uninfected people is

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[1] The reader is referred to Section 3.1, p.37, for a more complete description of the case.

evidence for an epidemic of TB (Benenson 1990). The most direct evidence of transmission is the documentation of tuberculin skin test conversion from negative to positive (discussed in 2.2).

Two problems arose while planning the public health investigation of this case. The first problem was the absence of baseline tuberculin status in staff and residents, as well as the lack of data on the normal prevalence of tuberculin reactors in Manitoba nursing homes. Without baseline tuberculin status it is uncertain whether positive test results in individuals reflect new or remote infection. In the absence of this information, an indicator of possible TB transmission could be the demonstration of a higher than expected prevalence of tuberculin reactors among residents and staff. No data currently exist on the normal prevalence of tuberculin reactors among staff and residents of Manitoba nursing homes. The absence of these data deferred the possibility of identifying TB transmission by three months when tuberculin testing was repeated for converters.

The second problem arose from the current policy of only two-step testing individuals older than 65 years. Two-step testing involves repeating the tuberculin test at one week (well short of the incubation period for test conversion after new infection, Benenson 1990) on initially negative

individuals. This is done because some individuals with remote infection (as opposed to new infection) will only become positive after a second test. This is called a booster response (Comstock and O'Brien 1991). It is important to distinguish converters from boosters because converters are at higher risk of developing clinical disease and are managed differently (CDC 1990). Therefore, the identification of boosters by retesting people at one week, would avoid unnecessary chemoprophylaxis of individuals, with its attendant costs and side effects. It would also reduce false evidence of disease transmission, simplifying the work of infection control personnel.

As the prevalence of boosters has been related to increasing age (Thompson et al. 1979), two-step testing in Manitoba is only done on the elderly. Review of data from two previous case investigations in Manitoba nursing homes revealed that staff had unexplained higher rates of conversion than nursing home residents (Manitoba TB Registry 1985 and 1987, unpublished). This led to the hypothesis that some converters among nursing home staff were really boosters.

Therefore, there were two major objectives for this study:

1. To describe the prevalence and determinants of tuberculin reactors among staff and residents of a nursing home.

2. To determine whether nursing home residents have a higher prevalence of boosting compared to staff.

Chapter Two

LITERATURE REVIEW

This literature review will focus on three areas relevant to the questions under study. The first section (2.1) will cover the epidemiology of tuberculosis in North America with emphasis on the elderly population. The second section (2.2) will review the tuberculin test and booster response. The final (2.3) section will examine the application of tuberculin testing in the nursing home setting.

2.1 The Epidemiology of Tuberculosis

2.1.1 Pathogenesis, Natural History and Risk Factors for Infection and Disease

Material for this section has been taken from excellent recent reviews by Benenson (1990) and Comstock and O'Brien (1991).

Tuberculosis (TB) is a communicable disease caused by Mycobacterium tuberculosis. The main reservoir of M. *tuberculosis* is man. Although it also replicates in cattle, zoonotic spread does not contribute to the burden of disease in the human population. Disease in cattle is well controlled in North America and pulmonary disease in humans is rarely

acquired from ingestion of contaminated milk. Without pulmonary infection there is no portal of exit to maintain the cycle of infection.

Therefore, TB in N. America is transmitted from person to person almost entirely by airborne spread. Infectious particles are released into the air from an infectious source by coughing, sneezing and singing. Inhaled droplet nuclei less than 5 microns in size, containing tubercle bacilli, penetrate the alveoli where they can establish a primary infection. These nuclei can also remain suspended in the air for long periods of time, leading to indirect spread of infection by people inhaling contaminated air. Ultraviolet light and good ventilation can prevent indirect airborne transmission.

After primary infection, the bacilli are transported intracellularly by macrophages to the regional lymph nodes. Future disease is a function of the initial dose and the host's cell mediated immune response. Three possibilities exist. First, the tubercle bacilli can be killed in the alveolus thus terminating the infection. Second, the bacilli can be walled off by sensitized lymphocytes and macrophages and held in check, preventing replication and disease. A unique feature of the tubercle bacillus is its ability to survive indefinitely in infected hosts. Third, the bacilli

can continue to replicate and disseminate from the lymphatics and blood to other areas of the lung or any organ in the body. It is only by secondary spread to other regions of the lung that the bacilli can establish a portal of exit through the bronchi, where they can be coughed up, completing the cycle of infection. Although TB can infect any organ in the body, it usually causes pulmonary disease. In Canada, 85% of reported cases involve the lungs (Statistics Canada 1991).

Most individuals infected with M. *tuberculosis* never develop disease. The risk of disease after childhood infection is estimated to be 5%-10% over a lifetime (Rouillon et al. 1976, Styblo 1981, Reider et al. 1989, Comstock and O'Brien 1991). The highest risk (5%-8%) is in the first 2 years after the initial infection, with a very small annual risk of disease thereafter. Late progression to clinical disease, at least two years after the initial infection, is typically called reactivation. This is the meaning for reactivation that will be used in this paper. It should be noted that Statistics Canada (1991) defines reactivation administratively, as reoccurrence of disease in the same individual, after six months of inactivity following the initial case report.

In order to understand the risk factors for a communicable disease, the process of infection must be distinguished from the development of disease. This is particularly important

for TB for which there is only a small risk of disease after infection.

Epidemiologic data has consistently shown that infection with the tubercle bacillus is the product of factors exogenous to the host: the infectious dose and the proximity and duration of contact (Rouillon et al. 1976, Styblo 1980, Reider et al. 1989). The following gradient for the infectious potential of cases has consistently been demonstrated: sputum smear positive cases are more infectious than smear negative/culture positive cases, who are more infectious than culture negative cases. The other determinant of infection is proximity and duration of contact. The relationship of these two variables is described by Styblo (1980) in a review of TB contacts aged 0-14 years in Rotterdam from 1967-1969: 50% of household contacts of smear positive cases were positive tuberculin reactors compared to 5% of casual contacts of similar cases. For household contacts of smear negative/culture positive cases, 6% were reactors compared to 1% of the same age group among the general population. In 1985, in the United States, 29% of close contacts of all ages were positive reactors compared to 16% of other contacts (CDC 1986).

Thus, factors which lead to delayed diagnosis (increasing the chance of a case progressing to smear positivity) and prolonged close contact with a case increase the risk of

infection with TB in contacts. This situation is commonly encountered in individuals of lower socioeconomic status who may have limited access to health care and live in crowded conditions.

Infection with the tubercle bacillus is a necessary but not sufficient step for the development of clinical disease. The following variables have been identified as risk factors for disease in infected individuals. These include:

1. Infectious dose - It has been demonstrated that newly infected individuals (converters) whose sources are highly infectious cases of TB, have higher relative risks of progressing to clinical disease, than converters who are contacts of less infectious cases (Reider et al. 1989).

2. Age - Early childhood, adolescence and old age have been shown to be high risk periods after initial infection for progression to clinical disease (Grzybowski and Allen 1964, Reider et al. 1989). The exact mechanism for a differential age related risk is uncertain (Reider et al. 1989).

3. Host immunity - Factors reducing local and systemic cell mediated immunity have been shown to influence the risk of disease. These include: malnutrition, human immunodeficiency virus (HIV) infection, cancer, substance abuse, diabetes, silicosis, gastrectomy and other unusual medical conditions (Reider et al. 1989; Comstock and O'Brien 1991).

4. Infection with drug resistant organisms - Newly infected

individuals, with INH resistant bacteria, who are given INH are at greater risk of disease progression (Benenson 1990).

Knowledge of these risk factors for infection and disease, contributes to an understanding of the pattern of disease in the population.

2.1.2 The Pattern of Disease in North America - Tuberculosis in Decline

In discussing the distribution of TB in a population, it is necessary to distinguish tuberculous infection (reactors[2]), from tuberculous disease (tuberculosis). The prevalence of infected individuals will be called prevalence of reactors, incidence of new reactors will be called infection rates and the incidence of reported disease will be called case rates. It should be noted that data on the prevalence of reactors and infection rates are not routinely collected. They are estimated from age specific prevalence rates obtained from various population surveys and adjusted for cross-reacting infections and secular trends in disease rates. The methods for these projections are reviewed by Reider et al.(1989) and

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[2]Tuberculous infection is identified by a hypersensitivity reaction elicited by a tuberculin skin test (discussed in 2.2). Therefore, infected individuals are called reactors.

Comstock and O'Brien (1991)

The 1989 Canadian annual case rate for TB was 7.8/100,000 (Statistics Canada 1990). The 1986 United States annual rates (per 100,000 population) for TB cases was 9.0 and mortality was 0.7 (Reider et al. 1989). For the same year, the annual infection rate in the United States population was estimated to be 8/100,000 (Reider et al. 1989). Therefore it appears that both the current risks of infection and disease are low.

The morbidity, mortality and infection rates of TB have dramatically declined during this century. These changes have been largely attributed to improvement in living conditions (Comstock and O'Brien 1991). Less crowding and improved lighting and ventilation at home and work have reduced transmission. Similarly, improved nutrition and overall health status may have reduced the likelihood of disease after infection. Data indicate that this decline began in the last century but has accelerated since the advent and availability of chemotherapy: streptomycin in 1946 and INH in 1952. Chemotherapy quickly renders cases non infectious and prevents reactors from progressing to disease (Ferebee 1970, Rouillon et al. 1976).

In their review of the epidemiology of TB in the United States, Reider et al.(1989) note that, from 1953 (when a

uniform system of national reporting was instituted) until 1980, the infection rate in the US population had been dropping by 8% per year and the case rate had been declining by 5%-6% annually. Grzybowski and Allen (1964) reported similar findings in their population based study of the epidemiology of TB in Ontario from 1958-1962. They noted a large decline in the prevalence of TB in the population from previous decades. They characterized four features of what they called tuberculosis in decline. These included:

1. A shift to a majority of reported cases arising from reactivation of old infection, rather than from recent transmission of tubercle bacilli. Currently it is estimated that 80-90% of cases in North America result from reactivation of remote infection.(Reider et al. 1989)

2. A decline in the population infection rate. The prevalence of tuberculin reactors was 18% of the entire population and annual incidence of new infection was 1.5%, in their study. This was lower than rates from previous decades. Conversely, they noted a large pool of uninfected susceptible individuals in the population.

3. Instability of tuberculin skin reactions characterized by reversion of positive tuberculin reactions to negative reactions by 8% annually.

4. Decreased utility of mass tuberculin testing in case finding because of low case detection rates and false positive tests. Despite intensive efforts, they found no cases linked

to isolated converters. In addition they estimated that 10% of positive tuberculin tests were caused by atypical mycobacteria other than M.*tuberculosis*.

The CDC reports that 1986 was the first year in this century in which the annual incidence of tuberculosis increased in the United States (CDC 1990b). This has been attributed to reactivation of disease in young adults caused by the HIV epidemic (Reider et al. 1989).

With the changing epidemiology of TB and reduction of the pool of tuberculous infection in the general population, identifiable high risk groups have emerged. These include: persons of lower socioeconomic status, such as blacks and hispanics (CDC 1990 b), aboriginals (Enarson and Grzybowski 1986) and the homeless (Nardell et al. 1986); immigrants from high prevalence countries (Reider et al. 1989, Orr et al. 1990); individuals infected with HIV (WHO 1989, CDC 1990b); and the elderly (CDC 1990b). In the United States in 1988, 66% of cases occurred in ethnic and racial minorities, 20% among immigrants and 27% in the elderly (Reider et al. 1989). Knowledge of these risk groups facilitates targeting of TB prevention programs.

2.1.3 The Epidemiology of Tuberculosis in the Elderly

Twenty-seven percent of all cases of TB in Canada and the United States occur in the elderly (65 years of age and older) population. They have the highest annual age specific case rate of 18/100,000 (Statistics Canada 1991), prevalence of reactors and case fatality ratios (Reider et al. 1989).

It has been suggested that the incidence of tuberculosis is increasing in the elderly population (Stead and Lofgren 1983). Although TB has been declining in all age groups, the rate of decline has been slower for the elderly. The secular trends for age specific case rates in the United States were reviewed by Powell and Farer (1980). They show higher overall case rates for the elderly and a slower rate of decline in this group. It is suggested that the reason for the slower rate of decline is that a greater proportion of cases in the elderly result from reactivation of remote infection rather than recent disease transmission (Powell and Farer 1980, Reider et al. 1989). Therefore, the impact of a reduction in transmission rates will affect the incidence in younger age groups more appreciably. This is supported by the fact that only 5% of reported cases in the elderly are primary TB reflecting recent infection, compared to 15% in the rest of the population (Statistics Canada 1991).

The slower rate of decline of TB among the elderly and aging of the general population have contributed to the rising percentage of cases attributed to the elderly. The percentage of all cases arising from the population over 65 years old had increased from 14% in 1953 to 29% in 1979 (Powell and Farer 1980). The higher percentage in the elderly is used in TB surveillance as an indicator that population transmission is declining and a measure of success for TB control programs (Reider et al. 1989, Powell and Farrer 1980).

The rise in the percentage of tuberculosis cases attributed to the elderly should not be confused with a rising incidence rate. Higher incidence reflects higher risk of disease, either by increased infection or reactivation. Stead and Lofgren (1983) describe rising incidence rates over time for the over 80 age group in Arkansas, in contrast to the rest of the US population. Their findings may be an artifact of recent intensive case surveillance among the elderly population compared to the rest of the population of that state, causing an ascertainment bias. They also note that access to medical care has increased for the elderly, relative to the rest of the population over the last few decades. This could also result in more intensive diagnostic efforts thus inflating reported rates.

Therefore, although there does not appear to be convincing

evidence of an epidemic of TB among the elderly of North America, higher case rates may be expected in the future. This could be due to a combination of higher case rates among the very elderly over 80 and the projected aging of the over 65 age group as a whole. This is in contrast to changing intensity of risk factors for infection or reactivation.

The prevalence of reactors and incidence of disease are not randomly distributed within the elderly population. These rates appear to be related to age, sex, ethnicity, and other factors.

The prevalence of tuberculin reactors in the United States population rises until the ages of 60-69 years and declines thereafter (Stead and Lofgren 1983). For 1981, it was estimated that 18% of this age group would have a positive tuberculin test (Stead and Lofgren 1983). The higher risk of infection with increasing age results from a combination of cumulative exposure over time, as well as a birth cohort effect from higher population infection rates earlier in the century. The levelling off and decline of reactor rates after age 70, may reflect survivorship, death of residual bacilli in the host, or diminished immunocompetence with age (Stead and To 1987).

Males have higher infection rates after age 25 (Reider et al.

1989). The infection rates for females decline after age 54, compared to infection rates for males in whom no decline is noted until after age 65. The differences between the sexes are thought to reflect different survival patterns for women infected earlier in the century compared to males. At that time females, who were infected as young adults, had a 3:2 mortality ratio for tuberculosis.

The age specific case rates for the 1987 US population by sex and ethnicity are reviewed by Reider et al.(1989). For white males and females, they note a steady increase in case rates with age, without the levelling off at age 69 observed for infection rates. In contrast, rates for non-whites also increase with age but show a small peak in the very young, a second peak from ages 35-55, and a steady increase thereafter. This age distribution is characteristic of higher prevalence populations (Styblo 1980). For both groups, males have higher case rates than females for all ages after 20 years. Elderly males have twice the annual TB incidence of elderly females.

2.1.4 The Epidemiology of Tuberculosis in Nursing Homes

Stead and To (1987) studied the prevalence of tuberculin reactors and the risk of reactivation in Arkansas nursing homes. They reported the results of tests on 50,000 residents

from 227 nursing homes. They found that 15-20% of residents were positive reactors at nursing home entry of whom 2-3% developed TB over a mean time period of two years. Males had higher rates of positive reactions compared to females and these rates declined with age. They also found that the prevalence of reactors was double the rate at admission, when the population was retested 6 months after nursing home entry. They attributed this to the death of initial entrants who were anergic and dying, improvement in health and re-establishment of immunocompetence in other residents, and the possibility of nosocomial transmission.

In Manitoba, 5.6% of the elderly population live in nursing homes (MHSC 1991). Less than 5% of the annual incident TB cases among the elderly of Manitoba occur in the nursing home population (Manitoba TB Registry 1990, unpublished). In Arkansas, Stead and Lofgren (1983) reported that 20% of all cases of TB in the elderly occur among nursing home residents. They estimated that nursing home residents have four times the annual case rate of community dwelling elderly. The higher case rates in US nursing home residents may be partially attributed to the ascertainment bias discussed previously. Many of these institutions have active surveillance programs in contrast to standard case finding in the community.

Despite the low contribution of nursing home residents to the

incidence of disease in the elderly population, these institutions have all the necessary elements for the epidemic transmission of tuberculosis (Stead et al. 1985). These include:

1. A reservoir of infection which may reactivate in elderly residents (Stead and To 1987).

2. Infected staff from high prevalence countries may also reactivate.

3. Delayed diagnosis due to atypical presentation, non-specificity of symptoms or residents' inability to communicate their symptoms (Borowitz 1982, Kim 1990, Morris and Nell 1988, Morris 1990, Yoshikawa 1992). This may result in a reactivated case transmitting infection for a prolonged period of time or a newly infected individual progressing from non infectious primary to infectious post primary disease (Rouillon et al. 1976).

4. Prolonged close contact (Stead 1981, Stead et al. 1985, Narain JP et al. 1985). Many residents do not leave their ward. In addition, hallways may be dark and there may be high recirculation of the air during the winter and summer when heating and airconditioning units are in operation.

5. A pool of uninfected susceptible hosts. In addition, nursing home residents being older and in poorer health, may have a higher risk of developing disease after infection (Stead and To 1987).

Several outbreaks in nursing homes have been reported in the literature, confirming this potential for epidemic spread (CDC 1979, CDC 1980, Stead 1981, CDC 1983, Morris and Nell 1988). Attack rates of infection as high as 80% have been reported among susceptible residents, and 50% among staff. In addition, numerous cases of active disease have occurred in residents, staff as well as visitors and family members from the community. Manitoba had an outbreak in a 60 bed nursing home from 1983-85, where one infectious resident may have caused seven (5/7 in staff) new cases of disease. Two cases were unrecognized until after exploratory surgery by thoracotomy and laparotomy (Manitoba TB Registry 1985, unpublished).

Reports of outbreaks in the United States have led to recommendations for special surveillance in the nursing home setting including tuberculin testing all residents and staff at entry (CDC 1990a).

2.2 The Tuberculin Test

2.2.1 Biology and Test Description

Information for this section is taken from reviews by the American Thoracic Society (ATS) 1981, Musial and Roberts (1987), and Comstock and O'Brien (1991).

The tuberculin test is the only practical method for identifying tuberculous infection. It is based on the fact that infected individuals become sensitized to tuberculous antigens contained in culture extracts called tuberculins. Purified protein derivative (PPD) is a precipitate obtained from filtrates of tuberculin. The current tuberculin used, PPD-S, is derived from an international standard produced in 1939 by Seibert (ATS 1981). Injection of tuberculin intradermally produces a characteristically cell mediated immune response (ATS 1981): delayed onset, usually after 24 hours; induration reflecting cellular infiltration; and occasional necrosis. Thus, infected individuals can be detected by the characteristic induration elicited after a tuberculin test.

Individuals will develop hypersensitivity to the tubercle bacillus 2-12 weeks after infection, with a skin reaction that can be detected by a tuberculin test. The change in test

results from negative to positive after infection is called conversion (ATS 1981).

There are two methods of tuberculin testing, the Mantoux and multipuncture techniques. The Mantoux method involves injecting tuberculin contained in 0.1 ml of diluent intradermally into the forearm of the subject. The test is read at 48-72 hours, the time of peak induration, when the size of induration in millimeters (mm) is measured and recorded. It has been well standardized and is therefore the method of choice for diagnosis and surveys. The multipuncture method is associated with many false positive readings, due to variation of dose delivered. It is also subject to greater observer variation and is of limited value. It is used primarily for testing children or individuals fearful of needles (Comstock and O'Brien 1991).

Four factors complicate the interpretation of results from tuberculin surveys: false positive results caused by cross reactions; false negative results caused by procedural errors and host anergy; false positive converters caused by boosting; and reversion of test results from positive to negative over time.

2.2.2 False positive Tests - Cross Reactions with Mycobacteria other than Tuberculosis (MOTT) and Bacille Calmette-Guerin (BCG)

The distribution of tuberculin reaction sizes from individuals with culture positive tuberculosis is roughly symmetric with the mean centred around 16mm (Palmer et al. 1959). Mycobacteria other than tuberculosis (MOTT) can cross react with PPD-S producing induration after testing. Rust and Thomas (1975) reported a bimodal distribution of reaction sizes in a population of navy recruits with household contact to TB. A higher peak centred around 16mm was similar to the distribution for tuberculosis, and a smaller peak of reaction sizes less than 8mm, represented infection with MOTT. The prevalence of MOTT infections varies widely in North America. It can be estimated in a population by simultaneously testing people with a second PPD (PPD-Battey or PPD-Gause) which is specific to MOTT (Grzybowski and Allen 1964, Grzybowski et al. 1969 and Thompson et al. 1979). In epidemiologic studies Grzybowski estimated that 10% (1964) of positive tuberculin reactions in Ontario and 25% (1969) in British Columbia are caused by MOTT. He noted that there was considerable variation within provinces. Less than 2% of the Manitoba population is estimated to be infected with MOTT (E.S. Hershfield 1992, personal communication).

Bacille Calmette-Guerin (BCG) is derived from an attenuated strain of M. bovis (CDC 1988). It is used for vaccination against tuberculosis. It is used universally in many high prevalence countries and has been given to selected high risk groups in some parts of the US and Canada, such as the aboriginal population and health care workers (Comstock and O'Brien 1991). Vaccination with BCG can also elicit a tuberculin skin reaction indistinguishable from true infection with TB (Snyder 1985, ATS 1990).

Different cutoffs have been proposed (CDC 1990c) for the interpretation of positive tuberculin tests in individuals. These cutoffs are based on the probability of true infection, the risks of disease, and the likelihood of a false positive test result. Age is also considered when chemoprophylaxis is being contemplated. This is because the risk of side effects increases with age. A 5mm cutoff has been proposed for individuals with a high risk of infection and disease, such as recent contacts of cases, people with HIV or radiologic findings consistent with inactive TB. In individuals with intermediate risks of disease, such as isolated recent test conversion or immigrants from high prevalence groups, a 10mm cutoff has been proposed. In individuals with a low risk of disease, such as isolated reactors with no risk factors, a 15mm cutoff has been proposed. Epidemiologic studies to estimate the prevalence of reactors in a population generally

use 10+mm as an arbitrary cutoff to define a positive test (Comstock and O'Brien 1991).

By delaying the reading of the skin tests to 48-72 hours, the peak time for delayed hypersensitivity, false positive readings caused by immediate hypersensitivity reactions to the needle, stabilizer or diluent are avoided. The latter reactions occur soon after injection and subside within 24 hours (ATS 1981).

2.2.3 False Negative Tests - Procedural Errors and Anergy

A tuberculin test may be falsely negative in infected individuals, for a variety of factors which are procedural or host related. A complete list of these factors is presented by the ATS (1981).

Procedural errors relate to problems with the antigen, the method of administration, and the accuracy of test reading. These errors can be largely avoided by standardization, proper training and measures taken for quality assurance.

On the other hand, factors that transiently or permanently affect the host immune response are much more difficult to control or quantify. It has been estimated that 10% of cases of TB who are older than 65 years will not react to tuberculin

(Stead and To 1987, Battershill 1980). Absence of a delayed hypersensitivity response after skin testing with a variety of antigens is called anergy (CDC 1991). This can be a marker for impairment in a person's cell mediated immunity. Currently there is no practical screen for anergy that could be applied widely for tuberculin testing (CDC 1991). Only three antigens besides tuberculin have been sufficiently standardized for use by a Mantoux type procedure. These include histoplasmin, coccidioidin, and mumps. Hypersensitivity to the first two antigens is rare outside endemic regions of the United States (CDC 1991). Other antigens such as candida and trychophyton have not been well standardized. Many younger and elderly individuals that are anergic to these antigens will still react to tuberculin (Morse et al. 1985, Burstin et al. 1986, Alvarez et al. 1987, Barry et al.1987, Dorken et al. 1987).

2.2.4 False Positive Converters - Procedural Error, Subject Variation, and the Booster Response

Periodic testing is done on individuals to detect recent infection with its higher associated risk of disease and to offer converters chemoprophylaxis. Repeated testing is done in populations to estimate current levels of disease transmission.

As noted in the previous section, transient anergy and procedural errors can lead to initial negative test results. Subsequent positive test results in these individuals may be misinterpreted as representing conversion. Even with fastidious technique, there is a 6mm error level in tuberculin tests in the same individual (Nissen et al. 1951). In order to avoid this error the ATS (1981) has not only defined conversion as going from less than 10mm to greater than or equal 10mm, but have also added that the test size must increase by 6mm. In this way the incidence of false positive convertors can be reduced.

There is still a group of individuals with remote infection who only react after a second tuberculin test. Despite proper technique these people will only increase their reaction size by 6mm after a second test. This has been referred to as the booster response (Thompson et al. 1979). The biologic basis of this response is believed to reflect an anamnestic (delayed immune recall) immune response from remote infection (ATS 1981).

The importance of the booster response was brought into epidemiologic and clinical focus by a report from Ferebee and Mount (1964) during INH chemoprophylactic trials. At that time they observed an inexplicably high rate of apparent converters retested one year after an initial tuberculin test.

They hypothesized that these individuals were not newly infected. They tested their hypothesis by successively administering second tests at closer intervals, finding the peak booster effect at 1-5 weeks and persisting for a year after the initial test. They also administered diluent to controls and found no evidence of boosting in that group. Retesting at one week (well short of the range of incubation for TB, Benenson 1990) can distinguish a booster response from new infection.

The booster response has been associated with age, cross reactions with MOTT and BCG, and borderline initial reaction sizes. Thompson et al. (1979), studied 1500 hospital employees in different regions of the United States and found a positive booster response in 6% of initial tuberculin negative subjects. In their study boosting was related to increasing age and caused by either sensitization with TB or MOTT in areas endemic for the latter. The relation to age was thought to be on the basis of a waning immune response due to increasing remoteness from initial infection. Others (Morse et al. 1985) have found high rates of boosting (21-31%) in young South East Asian refugees in the United States. Therefore, age may only be a marker of distance in time from the initial infection.

Previous vaccination with BCG may also elicit a booster

response. In fact, the booster response was initially described when serial tests were done following BCG vaccination in guinea pigs (Tolderlund et al. 1960). The relationship of a history of BCG vaccination to a positive booster test has recently been reported by Sepulveda et al. (1990). In their study of 208 first year health care students in Chile, they found that 26% of subjects with BCG scars had a positive booster response compared to 6% of subjects without BCG scars.

The booster response has also been related to initial reaction sizes. A number of authors have found that subjects with initial reaction sizes of 5-9mm had higher rates of boosting than subjects with 0-4mm. These findings suggest that the second test enhances a weak baseline level of tuberculin sensitivity.

Recent studies have shown that some individuals will only boost after a third or fourth successive tuberculin test. Van den Brande and Demedts (1992) studied the continuation of boosting in 223 elderly residents of a geriatric hospital, by performing successive tests on negative reactors at weekly intervals. They found that 20% of initially negative subjects boosted at the second test, 18% boosted at the third test and 7% boosted at the fourth test. Overall 57% of their subjects were positive reactors; only 29% would have been identified

after the first test. They also reported that continuation of boosting was related to age. They attributed the high rate of boosting in their subjects to the high prevalence of TB infection in Europe during the war. A lower prevalence of TB, may explain the lower rates of boosting after a third test in the US (Gordin et al. 1988 and Burstin et al. 1986). They reported boosting rates of 8.7% and 3.7% respectively, after third sequential tests administered to residents of chronic care institutions. This observation of continued boosting has also been described in young South East Asian refugees (Morse et al. 1985) and the Chilean students (Sepulveda et al. 1990) previously mentioned.

2.2.5 Tuberculin Test Reversion

Grzybowski and Allen (1964) reported that 8.5% of tuberculin reactors will become negative each year and that this rate of reversion is even higher in younger individuals. Perez-Stable et al.(1988) reported a similar rate of test reversion for nursing home residents studied prospectively in the United States. They observed that persons with a positive booster response were more likely to revert to a negative test over time compared to persons who were initial reactors. It is thought that reversion represents the death of any surviving tubercle bacilli in the host. The booster response may reflect an intermediate stage in the waning of host immunity.

If reversion reflects loss of immunity, these individuals may be susceptible to reinfection.

2.3 The Role of Tuberculin Testing in Nursing Homes

The primary objective of TB control in any setting is to identify all active cases and newly infected contacts who would be eligible for treatment or chemoprophylaxis[3]. In this way, immediate morbidity is reduced and future generations of infection and disease are avoided. Tuberculin testing is the cornerstone of all control efforts. If TB is suspected in an individual, tuberculin testing will identify infection and direct the course of further investigative manouevers.

Due to the potential for epidemic spread of TB in the nursing home setting, special surveillance programs have been recommended (CDC 1990a). These include tuberculin testing all residents and staff at entry routinely. Tuberculin testing used in this way has four potential advantages:

1. It can lead to the identification and treatment of active cases at the time of entry into the nursing home, preventing spread of infection;

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[3] Treatment refers to the administration of antituberculous drugs to cases of TB. Chemoprophylaxis refers to administration of antituberculous drugs to individuals with a positive tuberculin test, in whom no evidence of disease is detected (Canadian Lung Association 1988).

2. It can identify the pool of old inactive infection among staff and residents who are at risk of reactivation. This can lead to their treatment with INH chemoprophylaxis, preventing future reactivation and potential transmission of TB in the nursing home;

3. Screening for occult transmission. Occult transmission can be identified if tuberculin negative individuals are retested at specified intervals and clusters of converters are found. Investigation of these clusters may reveal previously unidentified casesof TB who can be treated.

4. It can expedite future case investigations. Baseline testing can identify potential sources of disease (positive reactors), as well as susceptible individuals at risk of new infection. In this manner, converters can be rapidly identified and treated, secondary cases prevented and the chain of infection broken.

As some tuberculin reactors will only be detected after repeat testing (i.e. boosters), two-step baseline testing has been recommended for these surveillance programs (CDC 1990a). This strategy has the advantage of reducing the misclassification of boosters (with a low risk of disease) as converters (with a high risk of developing TB) during repeat testing. This would avoid unnecessary chemoprophylaxis of individuals with

its attendant costs and side effects. It also reduces false evidence of disease transmission, simplifying the work of infection control personnel. After the introduction of two-step baseline testing in their institution, Bass and Serio (1981) described a decline in the annual rate of converters from 8.7% to 2.9% detected during screening. Welty et al.(1985) reported similar findings: after introduction of two-step baseline testing, the annual rate of converters dropped from 12% to 4.7% in a chronic care institution.

Other authors have questioned the cost effectiveness of two-step testing in populations with a low prevalence of boosters (Valenti et al. 1982). Rates of boosting among initially tuberculin negative subjects are 3%-14% of elderly residents and 0%-12% of staff of chronic care institutions (Thompson et al. 1979, Bass and Serio 1981, Valenti 1982, Simon et al. 1983, Welty et al. 1985, Burstyn et al. 1986, Barry et al. 1987, Gordin et al. 1988, Aronow and Bloom 1989 and Van Den Brande and Demedts 1992).

2.4 Conclusion

As tuberculosis declines in North America, it is receding into well defined risk groups. One of these risk groups is the elderly population over the age of 65 years. There is no convincing evidence of increased incidence of infection or disease among the elderly. Despite this, their relative contribution to the burden of TB in the population will likely increase as the population ages.

A minority of TB cases among the elderly in North America occur in nursing home residents. Nevertheless, epidemic nosocomial transmission has been reported in these institutions, leading to cases among residents, staff and community members. These outbreaks have prompted calls for intensive TB surveillance in nursing homes including mass tuberculin testing of residents and staff.

Tuberculin testing requires a high level of quality assurance to avoid false negative results and careful interpretation of positive findings because of cross reacting infections with MOTT and BCG. In addition, many reactors will only be detected after one or more successive tests (boosters). The prevalence of boosting varies from setting to setting and appears to be related to initial reaction sizes, age (or possibly time since initial infection) and infection with

cross reacting mycobacteria.

Routine two-step testing of individuals, when periodic testing is anticipated, has been shown to reduce reported rates of converters during surveillance. This avoids unnecessary and possibly harmful chemoprophylaxis of individuals, as well as exhaustive searches for infectious sources of TB. Others have questioned the cost effectiveness of routinely adding a second test in populations with a low prevalence of boosters.

This review of the literature points to a number of implications for this study. First, it suggests that a meaningful estimation of the prevalence of tuberculin reactors should measure and control for risk factors for TB, as well as cross reactions with BCG and MOTT. Therefore, in addition to age and status as staff or resident, data was collected on sex, place of birth, history of TB, history of a positive tuberculin test, and history of vaccination with BCG.

Aboriginal status was not included because preliminary data indicated that only three individuals in the nursing home were aboriginal. Data was not collected on HIV status because of issues surrounding confidentiality and the estimated low prevalence of infection in the Manitoba population (Manitoba Health 1990). Similarly, testing was not done for MOTT because of the low prevalence of infection with MOTT estimated in Manitoba (ES Hershfield, personal communication 1992) and the added costs of testing.

Chapter Three

METHODS

3.1 Subjects

Subjects included residents (N=280) and staff (N=316) of a large urban nursing home, serving predominately an ethnic East European population. This study began as part of the public health investigation of a reported case of TB. A case of miliary TB was diagnosed in a resident at autopsy in August 1990. This resident had shown a steady decline in health after a fractured hip in 1988 and had not left her single room in the three months prior to death. She had no record of cough or respiratory symptoms in the 18 months prior to her death. Scarring in her lung was noted upon admission to the nursing home in the early 1980's and on a chest x-ray at the time of her hip fracture. No specimens were obtained for TB bacteriology and tuberculin testing was not done while she was in the nursing home.

The nursing home is located in Winnipeg, Manitoba, Canada. A nursing home in Manitoba refers to a facility for individuals requiring at least 0.5 hours of nursing care per day (Shapiro and Tate 1988).

3.2 Tuberculin Testing

Testing was initially done September 17-24, 1990, on residents and staff from the ward of the index case. The investigation was expanded to include the remaining residents and staff on January 28-February 4, 1991 (residents) and February 11-18, 1991 (staff). A team of trained nurses, following a standardized protocol performed two-step testing (ATS 1981). For each test, subjects were injected intradermally with 5 TU (0.1ml) of PPD-S (Tubersol@, CT68 Connaught) on the volar surface of the upper forearm, using standard tuberculin syringes. On all occasions reactions were read at 48 hours, at which time the size of induration in millimeters (mm) was recorded. Only individuals with less than 10mm of induration at the first test were eligible for the second test one week later.

Subjects with greater than 9mm of induration for the first test were classified as initial reactors. Reaction sizes greater than 9mm for the second test were classified as boosters. Reaction sizes greater than 9mm for either test were classified as total reactors.

3.3 Test for Inter-observer Variability

Testing for inter-observer variability was done on two

separate days of reaction size reading. At these times, a sample of reactions was read simultaneously by the author, as well as by the study nurses. Both observers were blinded to each other's readings.

3.4 Questionnaire

A self administered questionnaire (Appendix 1) was completed by staff and residents who were able to provide a history. A chart review was performed for the remainder of residents. The questionnaire was distributed at the time of the first reading. The questionnaire gathered information on age, sex, country of birth and year of arrival in Canada if foreign-born, location in the NH and occupation (for staff only). A self reported past history of clinical TB, previous positive tuberculin reactions and history of BCG vaccination were also included as questions. Questions pertaining to the risk of reactivation and symptoms of TB were asked as part of the public health investigation for transmission, but were not included in this study.

3.5 Examination for BCG Scars

Subjects were asked about prior BCG vaccination. Their arms and backs were inspected for scars >4mm in size, which could be compatible with BCG vaccination. This was done by the

study nurses.

3.6 Follow Up

Positive reactors on either test had a chest x-ray done to rule out current active disease. Chest x-rays were read by a physician with training and experience in reading radiographs from tuberculosis surveys, who was blind to information recorded on the questionnaire. Three consecutive first morning sputum samples for bacteriology were obtained if subjects had symptoms or chest x-ray abnormalities compatible with active TB. Gastric washings were performed if these individuals were unable to provide a sufficient sputum sample. Bacteriologic analysis included Ziehl-Neelsen staining and standard methods for culture and sensitivity (Musial and Roberts 1987).

3.7 Statistical Analysis

All data were coded by the author. Data were entered into a computerized database by a data entry operator. All entries were verified a second time for transcription errors.

Chi Squared tests were used to compare categorical variables. Two sided group t and paired t tests were used for continuous

ones. Odds ratios and 95% confidence levels were calculated as tests of association. Multiple logistic regression was used to estimated adjusted odds ratios and their 95% confidence intervals (Kahn and Sempos 1989). Calculations of population attributable risk are shown in Appendix 2. The correlation coefficient and the Kappa statistic (Kramer and Feinstein 1981) was calculated for reproducibility tests. Cross classifications between observer readings for test accuracy, were tabulated according to methods in described in Fletcher, Fletcher and Wagner (1988). A 5% alpha error defined the significance level.

Chapter Four

RESULTS

4.1 Subjects

Eighty-two percent (490 of 596) of eligible subjects were studied. This included 272 of 280 (97%) residents and 218 of 316 (69%) staff. Eighty-one of the 316 staff (26%) were excluded from the present analysis because they had had one-step tuberculin testing done 3 months prior to the study. The remaining 17 staff were not tested because they were on Workman's Compensation, holiday, or refused to participate. Eight residents were not tested because they were either transferred to another health facility or died during the period of the survey.

Table 1 identifies the characteristics of subjects. The mean age ($\pm$ standard deviation) of all subjects was 66$\pm$24 years and 76% were female. The mean age of residents was 85$\pm$8 years and 189 (70%) were female compared to staff whose average age was 41$\pm$13 years, 184 (84%) being female. The average length of stay in the nursing home for residents was 4$\pm$5 years. For staff, the mean duration of employment in the nursing home was 9$\pm$6 years.

TABLE 1. Characteristics of Subjects

Variable	Residents (N=272)	Staff (N=218)	Total (N=490)
Age	85 ± 8*	41 ± 13	66 ± 24
Female	189 (70%)	184 (84%)	373 (76%)
Male	83 (30%)	34 (16%)	117 (24%)
Foreign-Born	183 (67%)	92 (42%)	275 (56%)
Canadian-Born	89 (33%)	126 (58%)	215 (44%)
Years in Canada	60 ± 18	19 ± 13	44 ± 26
History of TB	4 (0.2%)	1 (0.5%)	5 (1%)
History of Positive Tuberculin Test	1 (0.4%)	19 (9%)	20 (4%)
History of BCG	0 (0%)	74 (34%)	74 (15%)
BCG Scar	0 (0%)	59 (27%)	59 (12%)
Years in Nursing Home	4 ± 5	9 ± 6	6 ± 6

* Refers to mean ± standard deviation.

Not one of the residents reported a past history of BCG vaccination, in contrast to 74 (34%) staff members. Scars were observed for 59 (80%) of this BCG vaccinated group. Most (82%, N=61) of the BCG vaccinated staff were involved in direct resident care (defined as nurses, orderlies and aides), compared to 60 (42%) of the other staff. The average age for the BCG vaccinated group, 42±10 years, was similar to the mean age of remaining staff (41±14 years).

Four residents and one staff member reported a past history of TB. A small number of subjects (N=20, 4%), most of whom were staff (N=19), reported a history of a positive tuberculin test.

More than half (N=275, 56%) of all subjects were foreign-born. The average number of years in Canada for this group was 44±26 years. Two thirds (N=183) of residents were foreign-born compared to 42% (N=92) of staff. The average duration since arrival in Canada was 60±18 years for residents and 19±13 years for staff. Eastern Europe was listed as the region of origin for 201 (73%) of these subjects. Figures 1 and 2 illustrate the breakdown of countries of birth for foreign-born residents and staff respectively. Overall, 155 (85%) of foreign-born residents originated in Eastern Europe compared to 46 (50%) of staff. The second most frequent country of origin for foreign-born staff was the Philippines (36%, N=33).

FIGURE 1. Country of Birth for Foreign-Born Residents (N=183)

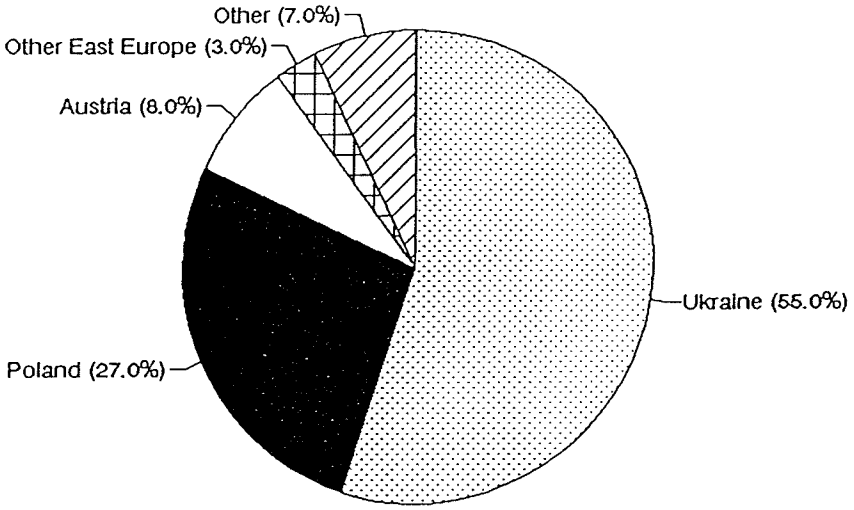
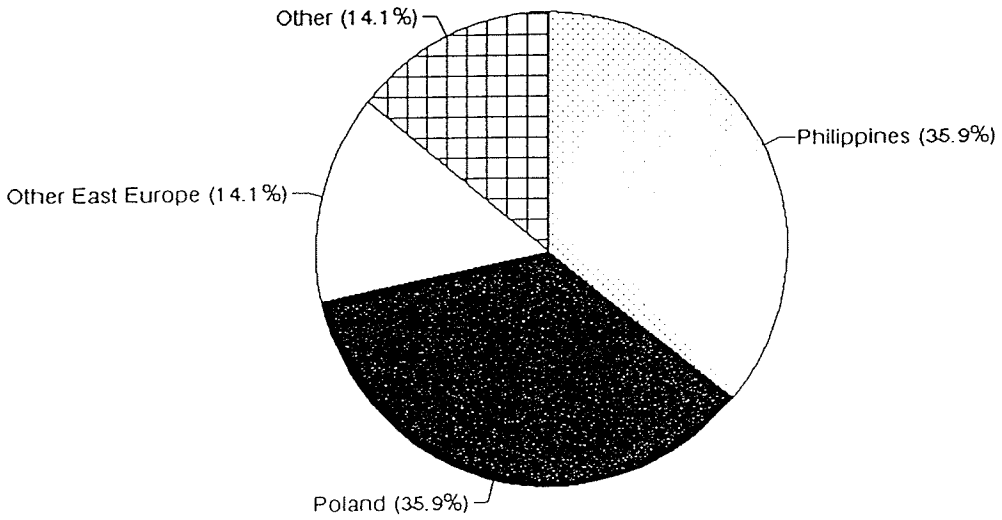


FIGURE 2. Country of Birth for Foreign-Born Staff (N=92)



4.2 Inter-observer Variability

Sixteen percent (N=132) of all reactions were read by a second blinded observer. The average difference in readings was 0.4± 2.4mm. The correlation coefficient between readers was 0.95 ($p<.0001$).

Table 2 shows the cross classification by observer, for all readings dichotomized into reactors (>9mm) and non reactors(<9mm). By arbitrarily using the outside observer as the "gold standard" it reveals a test sensitivity of 88%, specificity of 99%, positive predictive value of 96% and negative predictive value of 97%. The test accuracy was 97%. Therefore, 12% of true positive and 1% of true negative reactions were misclassified. The Kappa statistic was 0.88 indicating a high concordance between observers.

TABLE 2. Interobserver Variability - Cross Classification of Tuberculin Test Results for Each Observer

		Observer #1		
	Result	Positive	Negative	Total
Observer #2	Positive	21	1	22
	Negative	3	107	110
	Total	24	108	132

Sensitivity - 21/ 24 = 88%
Specificity - 107/108 = 99%

Positive Predictive Value - 21/ 22 = 96%

Negative Predictive Value - 107/110 = 97%

Accuracy - 128/132 = 97%

Observer #1 is the outside observer (the author).
Observer #2 is the study nurse.

4.3 Initial Test

Figures 3 and 4 illustrate the distribution of reactions by size, for the 490 subjects who had an initial tuberculin test. The majority (N=333; 68%) of individuals had 0mm of induration, 137 (28%) had positive initial reactions (>9mm) and 20 (4%) had reaction sizes of 1-9mm. The mean and median reaction size for individuals with greater than 0mm induration was 15±7mm.

FIGURE 3. Distribution of Initial Tuberculin Reactions by Size for All Subjects (N=490)

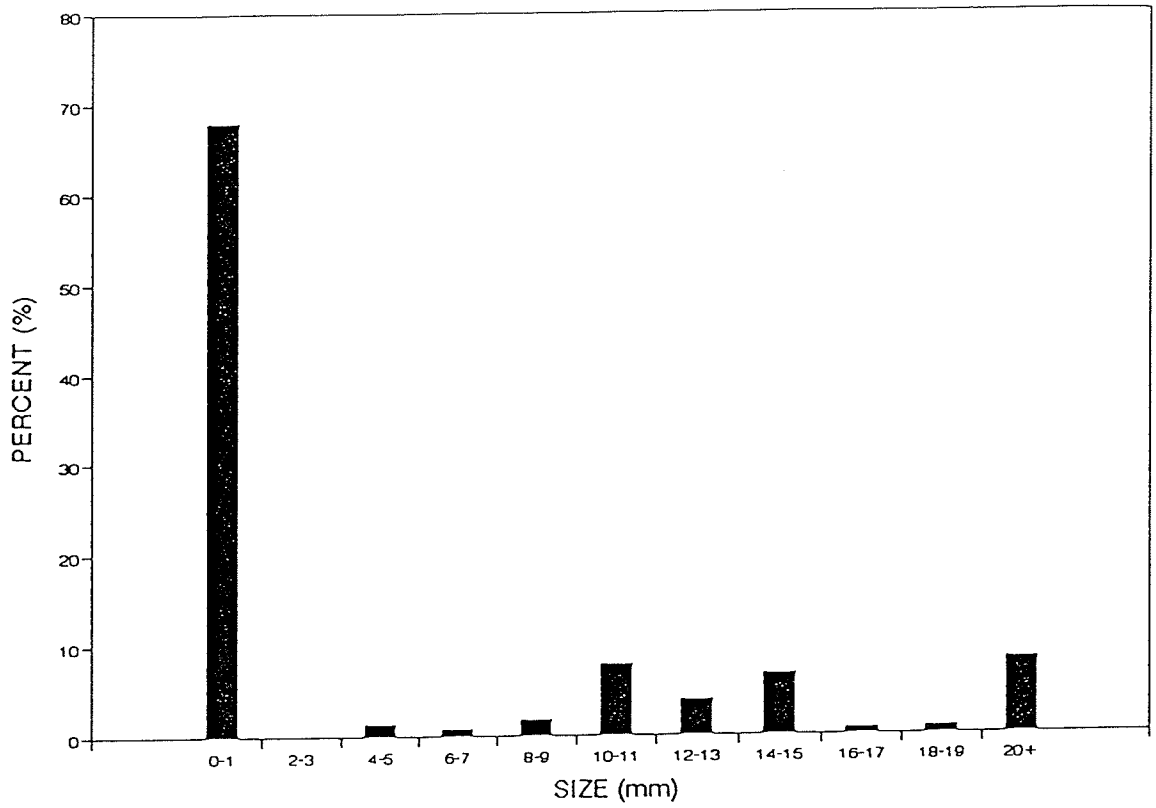
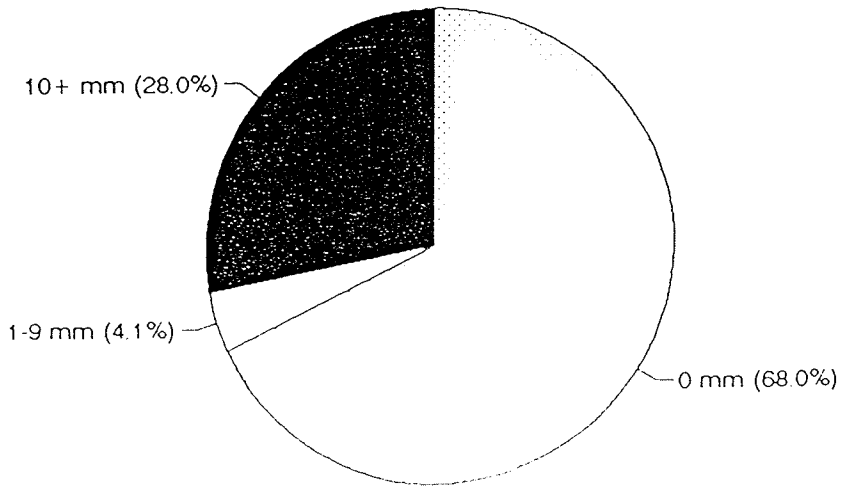


FIGURE 4. Breakdown of Initial Tuberculin Reactions by Size for All Subjects (N=490)



Four variables were found to be significantly associated with a positive initial tuberculin test: age, BCG, foreign-birth and staff (compared to residents). These variables will be examined individually. The results of the categorical analysis of these variables are presented in Table 3.

Figure 5 illustrates the distribution of initial reactors by 15 year age groups. It demonstrates the highest percentage (46%) for the 35-49 age group with a steady decline in percentages for the other groups. The percentage of reactors differs significantly by age group ($p<.001$).

FIGURE 5. Distribution of Initial Tuberculin Reactors by Age

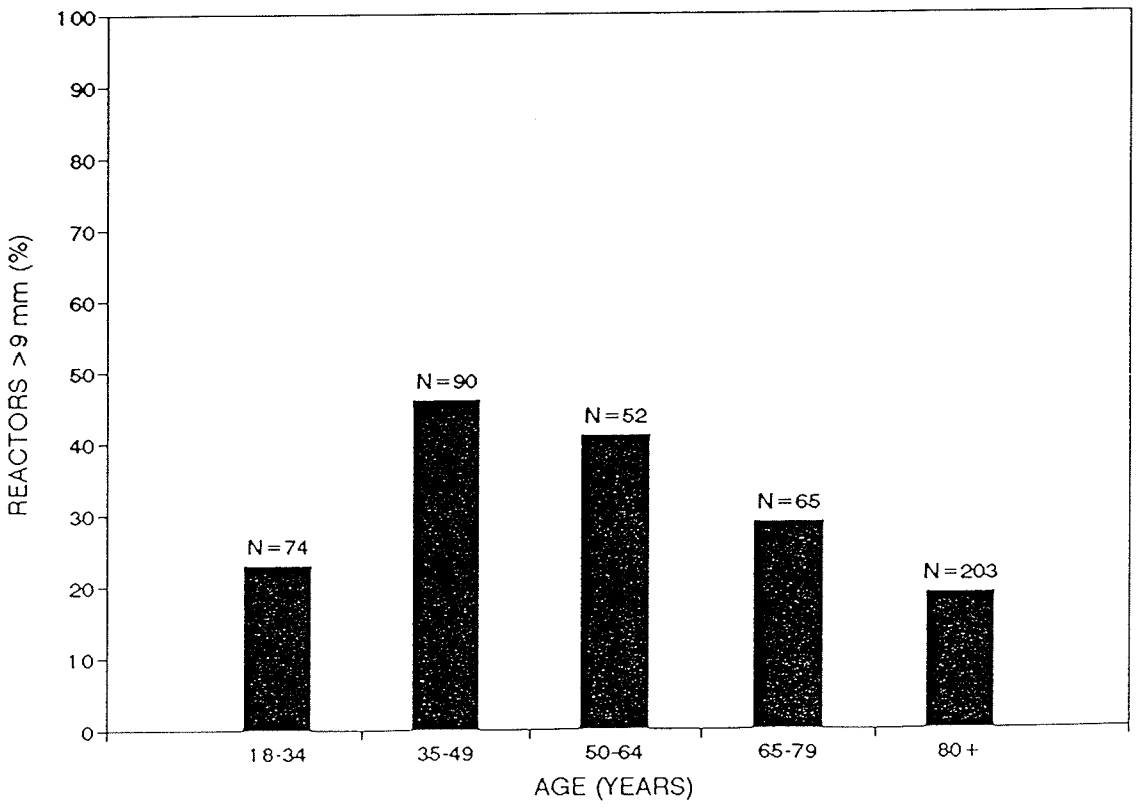
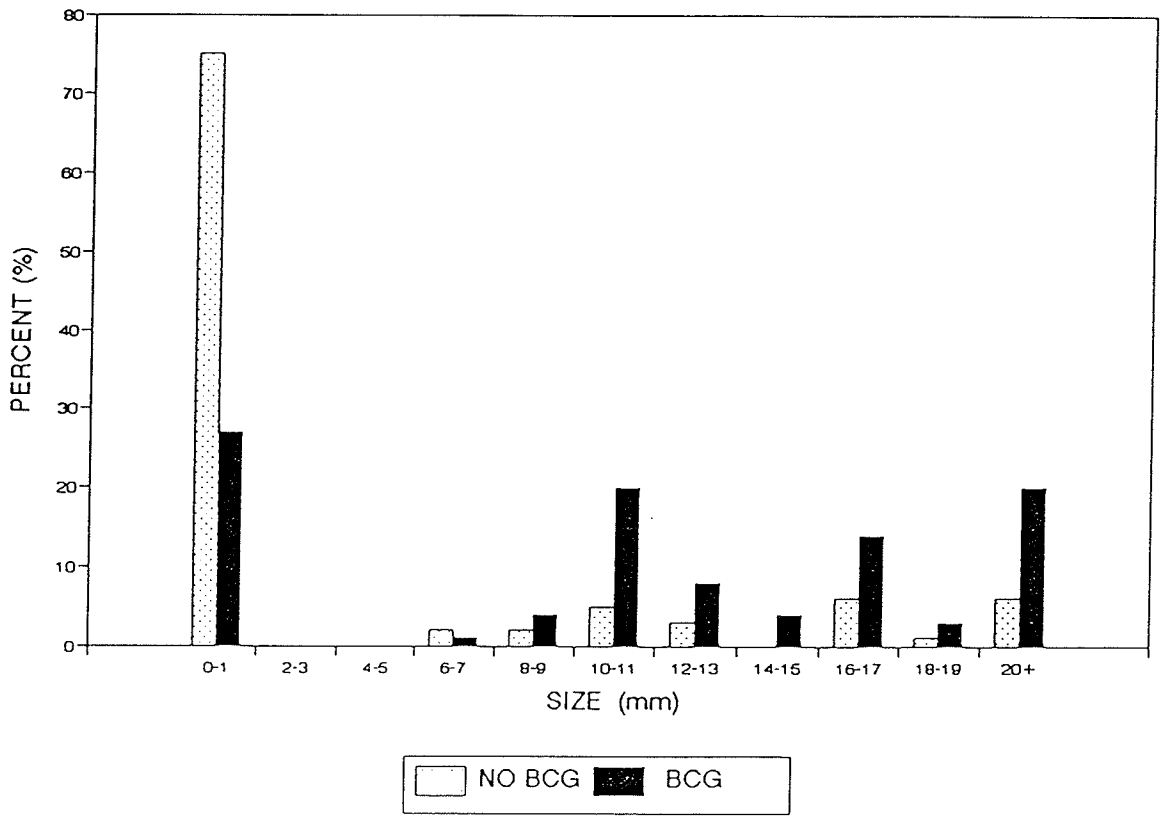


Figure 6 shows the distribution of reaction sizes for the BCG vaccinated subjects compared to those without a history of BCG. It demonstrates a smaller percentage of 0mm reactions (27% vs 75%) for the BCG group. The mean size of reactions greater than 0mm was 15±7mm for each group.

FIGURE 6. Distribution of Initial Tuberculin Reactions by Size, for Subjects with (N=74) and Without (N=416) a History of BCG Vaccination



There were 50 (68%) initial reactors in the BCG vaccinated group compared to 87 (21%) in the other group. A history of BCG was the variable most strongly associated (OR = 7.8) with a positive initial reaction (Table 3).

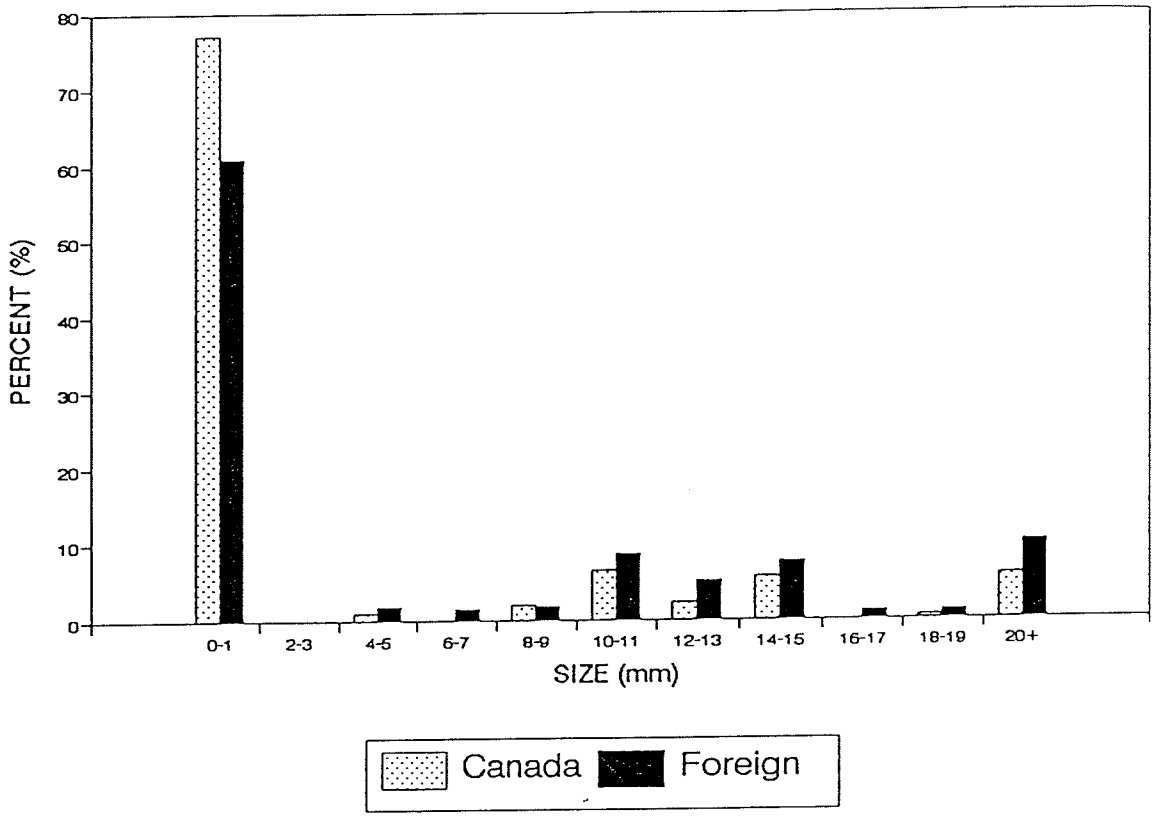
TABLE 3. Number and Percent of Subjects with a Positive Initial Tuberculin Reaction - Univariate Analysis

Variable		Tested	Positive	%	OR+	95% CI*
Total		490	137	28		
Sex						
	Female	373	107	29	1.2	0.7-1.9
	Male	117	30	26		
Birth						
	Foreign	275	93	34	2.0	1.3-3.0
	Canadian	215	44	20		
Status						
	Staff	218	78	36	2.0	1.3-3.0
	Residents	272	59	22		
History:						
	TB +	5	2	40	1.7	0.3-2.3
	-	485	135	28		
	Positive Tuberculin Test +	20	9	45	1.7	0.4-1.7
	-	470	128	27		
	BCG +	74	50	68	7.8	4.6-13.5
	-	416	87	21		

+ Refers to Odds Ratio
* Refers to 95% Confidence Interval

Figure 7 illustrates the distribution of initial reaction sizes by place of birth. The foreign-born group has a smaller percentage of 0mm reactions (61% vs 77%) compared to Canadian-born subjects. The mean size of reactions >0mm was 15±7mm for each group.

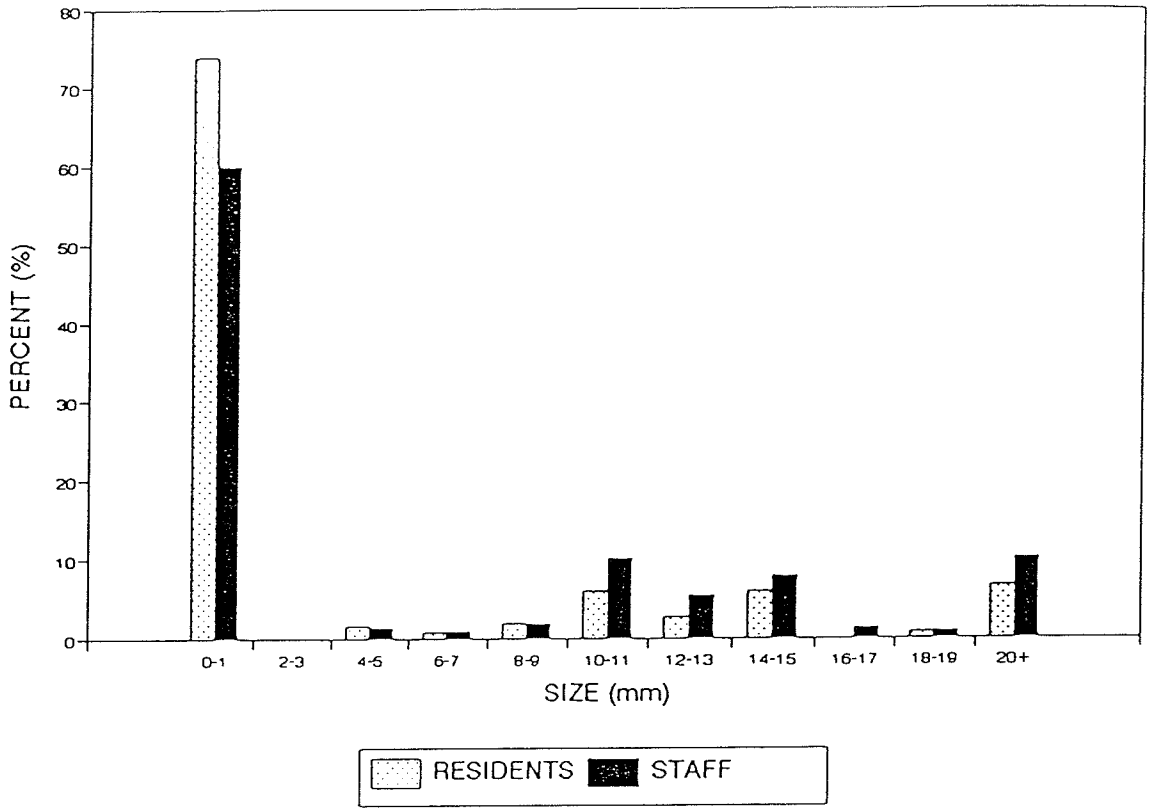
FIGURE 7. Distribution of Initial Tuberculin Reactions by Size, for Canadian (N=215) and Foreign-Born (N=275) Subjects



There were 93 (34%) foreign-born subjects with positive initial reactions compared to 44 (20%) of Canadian-born subjects. The odds ratio for this association was 2.0 (Table 3).

The distribution of reaction sizes for staff compared to residents is shown in Figure 8. Staff had a smaller percentage of 0mm reactions (60% vs 74%). The mean reaction size for each group was 15±7mm.

FIGURE 8. Distribution of Initial Tuberculin Reactions by Size, for Residents (N=272) and Staff (N=218)



There were 78 (36%) staff who were initial reactors compared to 59 (22%) residents. The odds ratio for this association was 2.0 (Table 3).

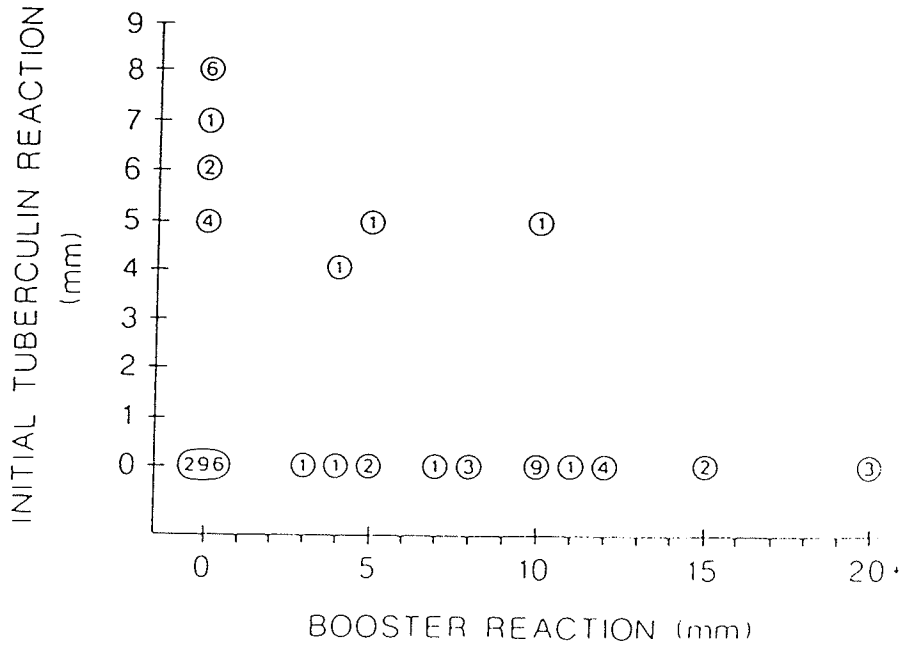
Neither sex, a history of a positive tuberculin reaction nor a history of clinical TB were significantly related to a positive initial test (Table 3).

4.4 Booster Test

There were 339 subjects with initial reaction sizes <10mm who had a second tuberculin test. This included all residents who were initially negative (N=213) and 89% (N=126) of eligible staff.

Figure 9 illustrates the relationship of the initial and booster test sizes for these subjects.

FIGURE 9. Comparison of Booster and Initial Reaction Sizes, for Subjects with an Initial Reaction Size of <10mm who were Retested (N=339)



Numbers in circles represent the number of individuals at each point.

Two groups are identified. The first group (N=323) had 0mm

induration on the initial test. At the second test, most of these subjects (92%, N=296) remained at 0mm, 6% (N=19) boosted over 9mm and 2% (N=8) had 1-9mm of induration. The second group (N=16) had initial reactions sizes of 1-9mm. For this group, 13 (80%) subjects regressed to 0mm, one (6%) subject boosted and two (13%) stayed at 1-9mm. In summary, most subjects (88%, N=296) have 0mm on both tests, most with initial reaction sizes 1-9mm regress to 0mm and both groups have an equal chance of boosting.

Figure 10 shows the classification of reaction sizes for all 339 subjects who had a booster test. Most subjects (N=309, 91%) had 0mm induration, 20 (6%) were boosters (>9mm) and 10 (3%) had reactions of 1-9mm. The average increase in size for boosters was 13±5 mm.

FIGURE 10. Breakdown of Booster Tuberculin Reactions by Size (N= 339)

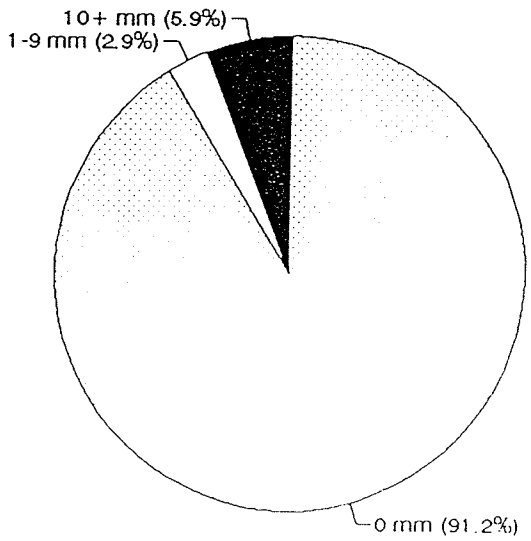


Table 4 shows the results of univariate analysis for the booster test. Only a history of BCG was significantly associated with a positive booster reaction. The average increase in reaction size for persons who were BCG vaccinated and positive boosters was 10±1 mm. There were 5 (25%) boosters among BCG vaccinated subjects compared to 15 (5%) among the other subjects. The odds ratio for this association was 6.7. Neither foreign birth, staff, age, sex, history of positive tuberculin test, nor history of clinical TB were significantly associated with a positive booster response.

TABLE 4. Number and Percent of Subjects with a Positive Booster Reaction - Univariate Analysis

Variable		Tested	Positive	%	OR+	95% CI*
Total		339	20	6		
Sex						
Female		253	17	7	2.0	0.6-6.9
Male		86	3	4		
Birth						
Foreign		177	10	6	0.9	0.4-2.7
Canadian		162	10	6		
Status						
Staff		126	8	6	1.1	0.5-3.3
Residents		213	12	6		
History:						
TB	+	3	1	33	8.3	0.7-96.0
	-	336	19	6		
Positive Tuberculin Test	+	9	0	0		
	-	330	20	6	-	-
BCG	+	20	5	25	6.7	2.1-21.0
	-	319	15	5		

+ Refers to Odds Ratio
* Refers to 95% Confidence Interval

The group of subjects with 1-9mm reaction sizes for the booster test was examined by BCG status. One subject (5%) with a history of BCG vaccination had a reaction size of 1-9mm compared to 9 (3%) of the non-vaccinated. These differences were not significant.

4.5 Multivariate Analysis for all Tuberculin Reactors.

A positive tuberculin reaction for either test was recorded for 157 of 490 (32%) subjects in this study. These subjects are defined as total reactors. The initial test detected 137 (87%) reactors and the booster test detected 20 (13%) reactors.

Table 5. examines the association of a positive reaction with a history of BCG vaccination, stratifying by place of birth. It clearly demonstrates the relationship of BCG to a positive tuberculin reaction, independent of place of birth. For Canadian-born subjects, the odds ratio for a positive test for BCG vaccinated compared to nonvaccinated individuals was 8.4. Similarly, for foreign-born subjects, the odds ratio of a positive test for BCG vaccinated compared to non-vaccinated individuals was 9.1.

TABLE 5. Percentage of Reactors* and Odds Ratios By BCG Status For Canadian and Foreign-Born Subjects

Status	Tested	Positive	%	OR$	95% CI+
Canadian Born:					
BCG	27	18	67	8.4	3.7 - 18.9
No BCG	188	36	19		
Foreign Born:					
BCG	47	37	79	9.1	4.6 - 18.0
No BCG	228	66	29		
Total	490	157	32		

* Reactor means >9mm induration on either tuberculin test
+ Refers to 95% Confidence Interval
$ Refers to Odds Ratio

Table 6. examines the association of a positive tuberculin test with foreign-birth, stratifying by status as staff or residents, for subjects without a history of BCG vaccination. An interaction between foreign birth and status is observed. Foreign birth is not significantly associated with being a reactor for the residents (OR=0.9). In contrast, a positive association is shown for foreign-born staff, compared to Canadian-born staff (OR=5.3)

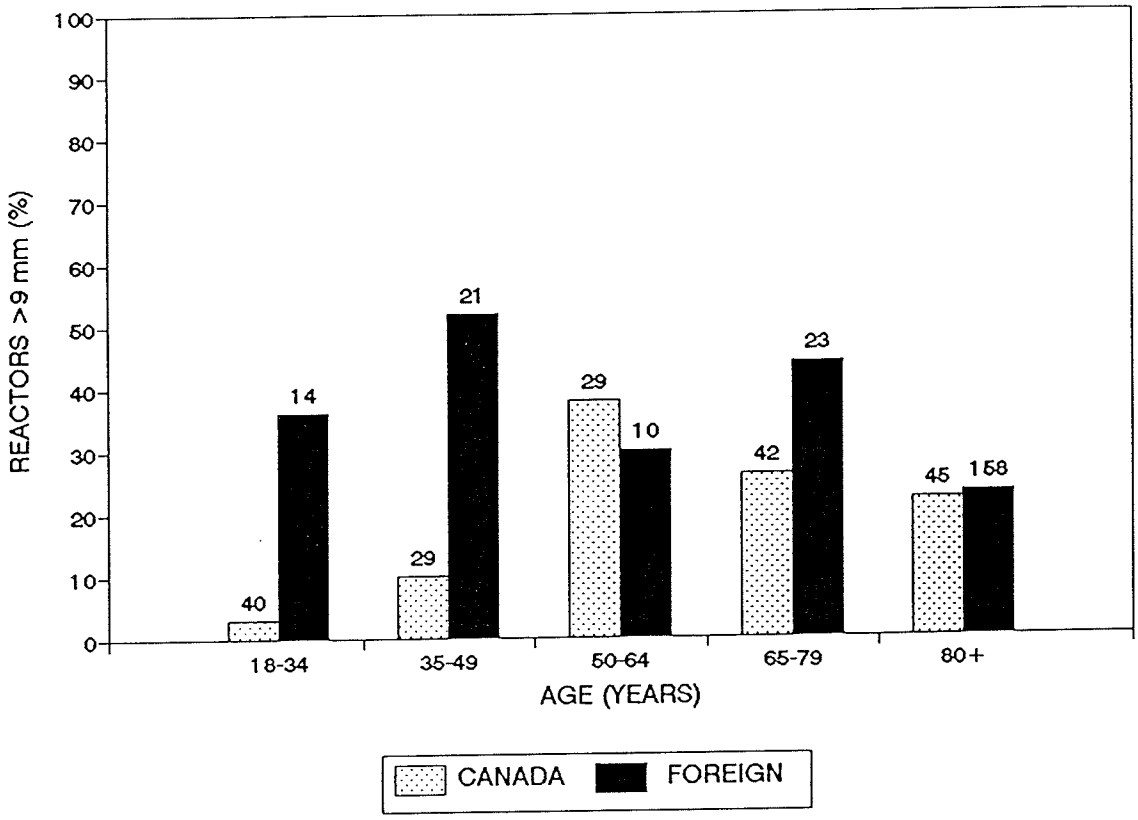
TABLE 6. Percentages of Reactors* and Odds Ratios By Place of Birth, for Residents and Staff without a History of BCG

Status	Tested	Positive	%	OR$	95% CI+
Residents:					
Foreign	183	47	26	0.9	0.6 - 1.6
Canadian	89	24	27		
Staff:					
Foreign	45	19	42	5.3	2.5 - 11.4
Canadian	99	12	12		
Total	416	102	25		

* Reactor means >9mm induration on either tuberculin test
+ Refers to 95% Confidence Interval
$ Refers to Odds Ratio

Figure 11 shows the distributions of reactors by age for Canadian and foreign-born subjects without a history of BCG vaccination. A bimodal distribution is observed for foreign-born subjects. Peaks are identified at ages 35-49 and 65-79 years. In contrast, a single peak is observed for Canadian-born subjects, at ages 50-64 years. The largest differences between foreign and Canadian-born subjects, for prevalence of reactors is noted in the younger age groups. There is no difference in prevalence of reactors by place of birth after the age of 80 years.

FIGURE 11. Distribution of Total Tuberculin Reactors by Age, for Canadian and Foreign-Born Subjects without a History of BCG Vaccination (N= 416)



Total Reactor means >9mm induration on either test

Using stepwise multiple logistic regression, the following variables were entered into a model: age, sex, resident/staff, place of birth, history of BCG, history of TB, history of a positive tuberculin test, and years in the nursing home. Only BCG (adjusted OR=4.8) and foreign birth (adjusted OR=1.7) were significantly associated with a positive tuberculin reaction (Table 7). When years since arrival in Canada were added to

was added to the model, foreign-birth was dropped for the latter i.e. only BCG and years in Canada were significant variables. The association with a positive tuberculin test was inversely related to the time since arrival in Canada. The adjusted odds ratio was 0.98 per year since arrival in Canada (95% confidence interval=0.97-0.99).

TABLE 7. Adjusted Odds Ratio for a Positive Tuberculin Test - Multiple Logistic Regression+

Variable	Odds Ratio	95% CI*
BCG	4.8	2.1 - 11.3
Foreign-Birth	1.7	1.1 - 2.6

* Refers to 95% Confidence Interval
+ Model included: Age, sex, history of TB, history of positive tuberculin test, years in NH, Resident/Staff and place in the nursing home

After adjusting for foreign birth, 72% of positive tuberculin tests among BCG vaccinated individuals were attributed to the effect of the vaccine (Appendix 2).

4.6 Follow Up

All positive reactors and symptomatic individuals were investigated for active tuberculosis. A case of apical pulmonary tuberculosis was identified in a separate building and could not be linked to the index case. This resident had an abnormal chest x-ray and was smear-negative, but culture positive for specimens obtained by gastric washings. One asymptomatic staff member had evidence of unchanging apical scarring on repeat chest x-ray and was bacteriologically negative.

Chapter Five

DISCUSSION

5.1 Overview

Forty percent of staff and 26% of nursing home residents who were found to be tuberculin reactors after two-step testing. The prevalence of reactors is in the intermediate range [11-43%] for residents (Welty et al. 1985, Burstin et al.1986, Dorken et al. 1987, Barry et al.1987, Stead and To 1987, Gordin et al.1988, Morris et al.1988, Aronow and Bloom 1987, Van den Brande and Demedts 1992) and high range [3-47%] for staff (Thompson et al.1979, Bass and Serio 1981, Valenti et al.1982, Simon et al.1983 and Barry et al.1987) reported from other investigations. Despite the consistency with other reports, these rates cannot be considered to be representative of all Manitoba nursing homes. The institution reported on in this study was not randomly selected from all Manitoba nursing homes. In addition, a number of variables were found to be significantly related to a positive test. If these risk factors are not randomly distributed in the population, the prevalence of reactors can also be expected to vary.

A history of BCG vaccination was the variable most strongly associated with a positive initial tuberculin reaction (Table 3). This was the only variable related to a positive

booster response (Table 4). Aside from a smaller percentage of 0mm readings, there was no characteristic distribution of reaction sizes or peaks for the BCG vaccinated subjects compared to the rest of the subjects. Therefore, this data does not support a distinction between BCG vaccinated reactors and other reactors, based on reaction size.

It is unlikely that the observed association between BCG vaccination and a positive tuberculin test is confounded by underlying infection with M. tuberculosis for three reasons. First, the association was independent of foreign birth. The association was almost as strong for Canadian-born subjects in whom TB infection rates are low (Reider et al. 1989), as for foreign-born subjects (Table 6). After adjustment for foreign-birth, the odds ratio for BCG remained significant (Table 7). Second, although it is possible that BCG vaccinated staff had higher cumulative exposure to occult TB infection in the nursing home (a larger proportion with BCG vaccination were involved in direct resident care), this is unlikely to completely explain the association. This is because increased age and duration of employment, both indicators of increased exposure to TB, were not significantly associated with a positive reaction. Third, there was no convincing evidence of transmission of TB identified. Both cases, were of very low infectious potential (Styblo 1980, Reider et al. 1989) and reactors were randomly distributed among wards and buildings

(Table 7).

Self report of BCG vaccination appears to be a valid measure, as 80% with such a history had a BCG scar (Table 1). To our knowledge, this is the first report examining the relationship of BCG to positive tuberculin reactions in staff and residents of a nursing home.

The association of BCG with a positive tuberculin test is consistent with a study of 208, 19 year old, first year medical and health care students in Chile (Sepulveda et al. 1990). The investigators reported similar results of 67% (68% in this study) of subjects with BCG scars having a positive initial reaction, compared to 12% of the group with no scars. Similarly, they found that 26% (25% in this study) of the vaccinated group had a positive booster response. They reported that the initial reaction size was related to the number of BCG scars a subject had on their arm, suggesting a dose-response relationship.

The Chilean findings and our results are at variance with the ATS/CDC statements regarding BCG (ATS 1981, Snider 1985, CDC 1988 and ATS 1990). They maintain that BCG vaccination may not cause conversion, that reaction sizes are small and that if a positive reaction occurs it is usually not sustained. Although we did not record the time of vaccination, it is

likely that most individuals had probably been immunized at least 20 years in the past (as the mean age of vaccinated subjects was 42). This discrepancy may be due to CDC/ATS recommendations being based on older studies, using different batches of BCG, administered by different routes and doses (Hershfield 1990/91). Subjects may also have been younger or less healthy at the time of vaccination in older studies. It has recently been shown that the immune response to BCG is lower for children receiving vaccine in the neonatal period compared to those receiving it after 9 months (Pabst et al. 1989). Many health care workers may not have been vaccinated until job entry. Therefore it is likely that young health care workers receiving BCG in adolescence or pre-employment may have positive reactions which are sustained over time. This is in contrast to infants and children in developing countries, who may be malnourished or chronically ill and lose their reaction. Alternatively, it is possible that vaccinated individuals have their tuberculin reactions maintained by continued exposure to TB. One would need a large prospective study of a healthy group of individuals vaccinated after infancy to resolve this issue.

The other variable significantly associated with a positive tuberculin test was foreign-birth. The association with foreign-birth probably represents old infection with M.tuberculosis acquired in high prevalence countries (Figures

1 and 2). It is impossible to say how much of this association could be confounded by cross reaction with MOTT in those countries. The large mean reaction size (15±7mm) of foreign born reactors makes cross reaction with MOTT less likely (Rust and Thomas 1975).

The relationship of a positive tuberculin reaction to foreign birth was inversely related to the duration of time elapsed since arrival in Canada. The longer the time since emigration from the country of origin (and presumably the site of infection), the smaller the probability of having a positive tuberculin test. The inverse relation with time, likely represents either waning immune memory or death of any residual tubercle bacilli from remote infection (Chaparas 1982, Stead and To 1987). This is consistent with the findings of reversion of positive tuberculin tests to negative over time (Grzybowski and Allen 1964, Perez-Stable et al. 1988). This likely explains the lack of association of foreign birth with a positive test for residents (Table 5) and the loss of association with increased age (Figure 11). By age 80 there is no difference between foreign and Canadian-born subjects.

The lack of a direct association between a history of TB and a positive tuberculin test is probably due to the small number of subjects (N=5, Table 1) reporting past disease.

Neither age, sex, status as staff nor resident and duration in the nursing home were significantly associated with a positive test using multivariate analysis (Table 7). In North America, the percentage of reactors has been shown to increase with age, declining after 70 (Grzybowski and Allen 1964, Stead and To 1987, Reider et al. 1989). The mixed nature of the study population, including immigrants from high prevalence countries and BCG vaccinated staff, demonstrates that a typical age distribution for reactors may not be generalizable to the nursing home settings. Even after BCG vaccinated staff are removed, one observes two very distinct distributions of reactors by age (Figure 11). Canadian-born subjects approximate the typical distribution of tuberculin reactors with very low percentages of reactors for people under 50 (<10%), a peak at 64 (40%) and a decline thereafter. In contrast foreign-born subjects have high percentages in the groups under 50 (38% and 52%) and 65-79 years (44%). The lower percentage among individuals aged 50-64 years, may be due to the small numbers (N=10) in this group and random error.

The finding of no association between male sex and a positive test is difficult to explain. Most surveys (Grzybowski and Allen 1964, Dorken et al. 1987, Stead and To 1987 Reider et al. 1989) show that males have higher infection rates and case rates than females at all ages after 20 years. The high percentage of females in the study population (76%, Table 1)

does not reflect the sex distribution in the general population (MHSC 1991). The mixed nature of the population with BCG vaccinees and foreign-born subjects may be concealing an association. There are insufficient numbers in this study to perform meaningful subgroup analysis by age and sex.

A self reported history of a positive tuberculin test was not significantly associated with being a reactor. Only 45% of subjects with a past positive tuberculin test were currently positive after two-step testing (Tables 3 and 4). This could be due to previous false positive multipuncture tests (ATS 1981, Comstock and O'Brien 1991), errors in subject recall or waning immunity. It could also be due to the small number of individuals (Table 1) reporting a past positive tuberculin test. It is highly unlikely that only one resident ever had a tuberculin test during their lifetime.

The booster response was detected in 6% of initial tuberculin negative staff and residents. These findings are consistent with other studies reporting rates of boosting in the range of 3-14% for elderly residents, and 0-12% for staff of long term care institutions (Thompson et al. 1979, Bass and Serio 1981, Valenti 1982, Simon et al. 1983, Welty et al. 1985, Burstin et al. 1986, Barry et al. 1987, Gordin et al. 1988, Aronow and Bloom 1989 and Van Den Brande and Demedts 1992).

The only variable significantly associated with boosting was

a history of BCG vaccination. Neither age, history of TB or initial reaction size was related to a positive booster response (Table 4).

Age was not significantly associated with boosting in contrast to other reports (Thompson et al. 1979). This may reflect the mixed nature of the study population as discussed previously. It is interesting to note that high rates of boosting (21%-31%) were reported among young adult South East Asian refugees in the United States (Morse et al. 1985). Therefore age may be a marker of time elapsed since initial infection (the refugees having high infection rates in early life), rather than only reflecting senescence of the immune system. It appears that in a nursing home with a mixed population of staff who were either infected with TB in high prevalence countries or received BCG vaccination, age may not be a reliable marker of the likelihood of boosting. The small number of individuals reporting a past history of TB (N=5) may preclude the identification of a significant association for this variable.

The results from this study indicate that the booster response is neither a random finding reflecting subject or observer variation, nor merely the "top up" of a weakly positive initial test. Almost all of the boosters had 0mm induration for the initial test (Figure 9). Conversely, those

individuals with small amounts of induration (1-9mm) on the initial test regressed to 0mm after the second test.

Subjects with 0mm or 1-9 mm initial reaction sizes had equal rates of boosting (Figure 9). The results suggest that it is unlikely that these two groups are distinct. This contrasts with other studies from chronic care institutions, which report rates of boosting ranging from 32%-62% for subjects with 5-9mm initial reaction sizes, compared to lower rates for subjects with 0-4mm (Thompson et al. 1979, Simon et al. 1983, Welty et al. 1985, Alvarez et al. 1987 and Barry et al. 1987). It is unlikely that the difference in our findings are due to methodologic errors as we used standard antigens and had a low level of interobserver variability (Table 2). We also had similar percentages of initial 1-9mm reaction sizes as the studies cited (Figure 4). This makes a measurement bias in the form of ignoring small reaction sizes unlikely. Perhaps this discrepancy is due to random error, differences in age, a smaller overall prevalence of tuberculous infection or lower exposure to atypical mycobacterial infection in our subjects.

This study did not examine the phenomenon of continued boosting among tuberculin negative staff and residents. As part of the public health case investigation, staff and residents were retested three months after the two-step test to ascertain the possibility of disease transmission. Nine

(4.4%) two-step tuberculin negative residents and one (1.5%) staff converted to a positive test. These converters were randomly distributed among six of eight wards in both buildings, and most could not be linked to the two cases identified (Manitoba TB Registry 1991, unpublished). The small percentage of converters is consistent with reports of continued boosting after a third tuberculin test in residents of chronic care institutions (18% found by Van den Brande and Demedts 1992, 8.7% by Gordin et al. 1988 and 3.7% by Burstin et al. 1986) and young South East Asian refugees (21%, Morse et al. 1985). Further study is needed to determine the prevalence and determinants of continued boosting in the Manitoba nursing home population.

5.2 Implications for Tuberculosis Control in Manitoba Nursing Homes

This results of this study raise questions about the broader issues of the need, effectiveness and efficiency of mass tuberculin testing in long term care institutions. If interpreted cautiously, the results from this study may have implications for the future investigation of cases and for planning TB control programs in the nursing home setting.

5.2.1 The Estimation of Tuberculin Reactors in Manitoba Nursing Homes

One of the objectives of this study was to document the baseline level of tuberculin reactors in a nursing home. This information is useful during the investigation of a case of TB, since it provides a reference point for the expected number of reactors in staff and residents. If the observed number of reactors found during an investigation is significantly higher than expected, transmission can be suspected.

The percentage of reactors in this study is consistent with results from other jurisdictions. Nevertheless, considering the high prevalence of foreign-born staff and residents, the number of BCG vaccinees, and the cases of TB, caution must be

used before generalizing these results to all Manitoba nursing homes. More nursing homes must be surveyed to determine the generalizability of these results.

5.2.2 Technical Issues with Tuberculin Testing

The results of this study highlight a number of technical issues if tuberculin testing is planned. Despite 97% accuracy, there were 12% of positive reactions randomly misclassified as negative, during the variability check (Table 2). Misclassifications may be higher in less controlled circumstances. False positive test results were infrequent. This emphasizes the need for a high level of quality assurance if mass tuberculin testing is anticipated.

The findings of this study also show that a self reported history of a positive tuberculin test may be unreliable. The majority who report a history of a positive test were not reactors on two-step testing and therefore are susceptible to new infection (Stead 1981 and Chaparas 1982). Failure to test this group during an investigation may miss converters and evidence of TB transmission. It may also result in the withholding of chemoprophylaxis, which is indicated for recent converters (Canadian Lung Association 1988 and CDC 1990). Further research would have to be done to confirm this

finding.

Six percent of subjects boosted after a second test. This percentage is consistent with other studies. Therefore it can be estimated that, during a case investigation, 17 contacts (the recipricol of 6%) would have to have a booster test to prevent the identification and treatment of one booster, falsely labelled as a converter. At less than one dollar per test (Connaught 1989), the direct costs of two-step testing may be less than the costs of drugs, clinic visits and lab tests associated with chemoprophylaxis.

A positive booster reaction does not appear to be related to age in this setting and, even if it is, the impact may be marginal. Therefore, if repeat testing is anticipated and resources permit, all subjects (staff and residents) should have two-step testing. This will avoid unnecessary chemoprophylaxis of staff and intensive searches by public health officials for occult sources of infection.

The findings of this study suggest that tuberculin surveillance may not be useful in a BCG vaccinated population, as 75% may be reactors. After adjusting for foreign birth, 72% of positive tuberculin tests among vaccinated staff can be attributed to BCG (Appendix 2). Therefore, chemoprophylaxis is probably not indicated for isolated BCG vaccinated

reactors, unless they can be linked to a known infectious case of TB. Otherwise it would appear that old BCG infection is being treated, rather than remote TB. More information on the prevalence of BCG vaccination among staff and residents of Manitoba nursing homes is needed. In addition further research is needed to confirm the association and to estimate the population attributable risk fraction.

5.2.3 Issues Surrounding the Need for Mass Tuberculin Testing in a Nursing Home

The demonstration of a mixed population of reactors and uninfected (susceptible) individuals in a closed environment highlights the potential for epidemic nosocomial spread of TB in a nursing home. Manitoba does not experience the same incidence of tuberculosis that is reported in United States nursing homes (Stead and Lofgren 1983, Stead and To 1987). From 1983-1990, the average number(range 0-3) of cases reported annually from Manitoba nursing homes was one (Manitoba TB Registry 1990, unpublished). This represents 1% of all cases reported in the province and 4% among the elderly in Manitoba (Manitoba TB Registry 1990, unpublished).

It may be that many cases are being missed in nursing homes. This is supported by the incidental finding of active

tuberculosis in a resident during this study, as well as the unanticipated diagnosis of miliary TB in the index case at autopsy. Both of these residents were frail and died. It is uncertain if tuberculosis was the cause of their demise or merely a marker of the dying process. It is also uncertain what the infective potential is for this subset of cases who reactivate at the end of their lives. Although it is possible that residents and staff were infected by these cases at some indeterminate point in the past, we could find no convincing evidence of new infection in this study population. It is likely that these cases do not lead to high rates of new infection or disease. Stead and To (1987) noted the consistency of finding only 6 convertors for each new case of TB identified in Arkansas nursing homes. This number is consistent with other studies (Rouillon et al. 1976). If one assumes that only 5-10% of newly infected individuals will develop disease in the first two years after infection (Rouillon et al. 1976, Stead and To 1987 and Reider et al. 1989), then it can be estimated that 10-20 (1/.05 or 1/.1) individuals will have to be infected to produce a new case. One would require double that number of converters to propagate the epidemic, if it is assumed that primary TB is not infectious and that new cases have only a 50% chance of progressing to smear positivity (Rouillon et al. 1976). Therefore, the individual or public health significance of reactivated cases detected by intensive surveillance in a

nursing home is uncertain. The small number of convertors, low risk of disease associated with infection, as well as shorter life span for residents probably prevent the occurrence of more epidemics in this setting.

This discussion does not intend to imply that highly infectious cases of tuberculosis do not occur among staff and residents in nursing homes. Reports from the literature and our experience in Manitoba confirms that infectious cases with resultant epidemics do occur (CDC 1979, CDC 1980, Stead 1981, CDC 1983, Morris and Nell 1988). Three questions remain from different perspectives. For the elderly resident, is reactivation a cause of death or a marker for the dying process? From the public health perspective, how frequently do these cases lead to new infection? Is the magnitude of transmission from these cases sufficient to lead to new tuberculosis and propagation of an epidemic.

5.2.4 Issues Surrounding the Effectiveness and Efficiency of Mass Tuberculin Testing

Different program alternatives are possible for TB control, in addition to the investigation of reported cases and contacts. One option could involve mass tuberculin testing of all residents and staff at nursing home entry with or without retesting at regular intervals.

As discussed in Section 2.3 of this thesis there are three potential advantages of mass tuberculin testing residents and staff at nursing home entry: identification and treatment of active cases, identification and treatment of reactors (preventing future reactivation), and obtaining baseline tuberculin status for future case investigations or screening programs for occult converters.

Tuberculin testing for the purpose of case finding is unlikely to avert most outbreaks, as the majority of infected individuals will be inactive at entry, yet may still reactivate well after admission (Stead and To 1987, Narain JP et al. 1985, CDC 1979, CDC 1980, CDC 1983). In view of the low probability of finding active TB at nursing home entry it seems doubtful that many new cases will be picked up with one test at entry. In addition, many jurisdictions require mandatory chest x-rays of prospective residents. A tuberculin test used for case finding in this circumstance would be redundant.

The other potential advantage of mass screening is to identify the pool of reactors among staff and residents, who are at risk of reactivation. This can lead to their treatment with INH chemoprophylaxis, preventing future reactivation and potential transmission of TB in the nursing home. There are two problems with this strategy. First, an unknown percentage

of positive tuberculin reactions may be caused by infection with BCG or MOTT (ATS 1981, Sepulveda et al. 1990). Our data suggests that 72% of positive reactions among BCG vaccinated staff are due to the vaccine rather than TB (Appendix 2). Grzybowski and Allen (1964), and Rust and Thomas (1975) expressed concern about an increasing proportion of false positive tuberculin reactions caused by MOTT as the prevalence of TB infection declines in the population.

Second, chemoprophylaxis is associated with its own morbidity. INH can cause hepatitis, the risk of which increases with age. Most isolated reactors in a nursing home would exceed the age limit for safe INH treatment (Taylor et al. 1981, Comstock 1986, Canadian Lung Association 1988, and CDC 1990). Based on these criteria, only 22% (34 out of 157 total reactors were under 35 years old) of reactors in our study would be eligible for chemoprophylaxis. If one did not treat the BCG vaccinees in this group (N=17) this percentage would drop to 11% (17/157). Therefore, mass screening to identify reactors for chemoprophylaxis would have a low impact on preventing reactivation of TB in a nursing home. This is exclusive of problems related to low compliance with chemoprophylaxis (CDC 1989 and Glassroth et al. 1990). If safer and more acceptable chemoprophylaxis becomes available in the future, active screening to find and treat old infection in this setting may be worthwhile to eliminate the reservoir of TB.

It appears that at present the greatest use of tuberculin testing is in obtaining baseline information for future case investigations, or in screening (for occult converters) programs. Baseline testing would avoid the 3 month delay in identifying recent converters and reduce the ambiguity in interpreting a positive tuberculin test found in the presence of a case of tuberculosis. In this manner, outbreaks can be detected early, secondary cases can be avoided by rapidly identifying and treating converters, and the chain of infection broken.

The resource needs of alternative programs (excluding administrative and start up costs) can be estimated, using data from this study and rates of new admissions. Each year, Manitoba reports one case of TB in nursing homes and admits approximately 1850 new residents (personal communication, Juanita, Office of Long Term Care, Manitoba Health July 1992). If mass testing was done in Manitoba, 3646 tuberculin tests[4] and 516 chest x-rays[5] would be performed annually on new nursing home admissions. This does not include the testing of an indeterminate number of new staff.

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[4]This assumes 1850 initial tests + 1443 booster tests(on 78% of people-Table 3) + 353 repeat tests during the investigation of one nursing home per year.

[5] This assumes that 26% of new admissions are reactors and that 10% of tuberculin negative individuals in a home with a case will convert.

This could be compared to the "gold standard" investigation of a case of TB in a 280 bed home performed once a year. This would include intensive surveillance of the whole nursing home during the 2 year incubation period for disease. In this situation one would perform at least 1176 tuberculin tests[6] and 314 x-rays[7]. This would be higher if one included all new residents and staff entering the nursing home during this period.

Therefore, one would have to do at least an additional 2500 tuberculin tests and 200 chest x-rays in order to identify and treat 35 new converters, perhaps preventing 1-2 secondary cases of TB.

This is a very imprecise estimate. It is intended to be a starting point in identifying issues relevant to public health policy. Some of the assumptions based on the results of this study need to be replicated before they can be deemed valid. Also, the resource expenditure may be much greater with a screening program: new staff have not been counted (data not readily available); most case investigations would be smaller (87 of 114 nursing homes in Manitoba have less than 100

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[6] This assumes 490 initial tests + 353 boosters tests + 333 two-step negative individuals retested at 3 and 18 months for conversion.

[7] This assumes 157 reactors x-rayed initially and at one year for the presence or development of disease.

residents, MHSC Annual Report 1991); and a screening program would have start up and administrative costs. Similarly the benefits in the number of converters treated and cases prevented may be smaller. In addition, this analysis does not consider anergic cases missed by tuberculin testing and reverters who become newly infected but are not retested because of previous positive results. In contrast, savings accrued by avoiding the treatment of secondary cases which are prevented by a screening program, must also be considered.

Therefore, policy analysts would have to decide if the potential benefits in converters treated and secondary cases prevented are worth the added costs of screening and how this compares to other priorities for TB control in the Manitoba population. It is not difficult to envisage that, if the number of annual case investigations in nursing homes increased (eg. two large homes), a threshold would be rapidly reached where a screening program may be more efficient.

The other purpose of baseline testing would be to identify occult TB transmission. If tuberculin negative individuals are routinely retested for conversion at specified intervals, occult transmission may be detected. The possibility of continued boosting after a second test and false positive converters would limit the use of this strategy of disease control, in nursing homes without reported cases. Other

problems with repeat screening for conversion, surround the lack of an effective response when clusters of converters are detected. Stead (1981) and the CDC (1983) report delayed and inadequate investigations of occult converters in nursing homes, resulting in second generations of cases.

Other less direct advantages of tuberculin surveillance in nursing homes exist. Currently, there is no routine tuberculin surveillance in the province. Therefore, data from nursing home surveillance can be used to estimate the trends for TB infection in the Manitoba population, as well as among the immigrant population.

Chapter Six

CONCLUSIONS

6.1 Study Objectives

The first objective of this study was to estimate the distribution and determinants of tuberculin reactors among staff and residents of a nursing home. It was felt that this data may be useful in estimating the expected number of reactors during future case investigations, as well as for estimating the need, logistics and impact of a mass tuberculin surveillance program in provincial nursing homes. The findings of this study show that the prevalence of reactors is significantly related to foreign birth and a history of BCG vaccination in subjects tested. Therefore, it is not possible to estimate the percentage of tuberculin reactors in nursing homes, without knowledge of the prevalence of these risk factors in this setting.

The second objective of this study was to determine if nursing home residents had higher rates of boosting compared to staff. This was addressed, because of questions surrounding the current policy of only two-step testing people aged 65 years and older. That policy is based on reports that the prevalence of boosting increases with age (Thompson et al. 1979).

In this study, the booster response was found to be equally distributed among staff and residents, and unrelated to age. The only variable associated with a positive booster response was a history of BCG vaccination. These findings are consistent with reports of high rates of boosting among young refugees (Morse et al. 1985) and health workers (Sepulveda et al. 1990). Nevertheless, it is possible that the lack of association of a booster response with age may be due to insufficient sample size.

Therefore, until further data is available, two-step testing should be administered to both groups when repeat testing is anticipated. This would prevent the unnecessary treatment of individuals falsely labelled as converters, as well as fruitless public health investigations searching for occult sources of tuberculosis.

6.2 Other Findings

Five other findings may have relevance to case investigations and planning TB control strategies. These include:

1. Most subjects with a self reported history of a positive tuberculin test were negative during this study. Therefore these individuals should be retested when a case is investigated. Failure to do so may miss new infection in this

group, and result in withholding indicated chemoprophylaxis.

2. From these results, it is estimated that 72% of positive tuberculin reactions among BCG vaccinated staff are attributed to BCG, rather than infection with M.tuberculosis. Therefore chemoprophylaxis of isolated tuberculin reactors with a history of BCG may not be warranted.

3. Mass testing to identify isolated reactors eligible for chemoprophylaxis would have a limited effect in preventing reactivation of TB in a nursing home setting. In this study population, only 21% of isolated reactors would be eligible for chemoprophylaxis based on age criteria. If BCG vaccinees were excluded, only 11% would be eligible.

4. The mixed population of reactors and susceptible individuals, as well as the incidental finding of a case of tuberculosis, highlights the potential for epidemics of tuberculosis in nursing homes.

5. This study showed that even under controlled situations 12% of reactors can be randomly misclassified as negative. These people would falsely be called converters on retesting. This emphasizes the need for a high level of quality assurance for tuberculin testing.

6.3 Future Research

A number of issues surrounding tuberculin surveillance in nursing homes meriting further research, arise from the review of the literature and findings of this study. Five areas for future study are identified.

1. This study should be replicated on a larger and more representative sample of staff and residents in Manitoba nursing homes. This can confirm or refute the associations found in this study, examine other associations such as among aboriginal people and other risk groups, estimate the distribution of these risk factors in the Manitoba nursing home population and estimate the overall prevalence of tuberculin reactors and boosters in this setting. The association of a positive tuberculin test with BCG vaccination, could also be studied in new hospital employees who are routinely being screened.

2. The prevalence of continued boosting with third and fourth consecutive tuberculin tests was not measured in this study. Expected rates of continued boosting would be useful in deciding if converters found during an investigation of a case with low infectious potential, reflect new transmission or old infection. High rates may impact on tuberculin testing policies. Therefore, estimation of the prevalence and

determinants of continued boosting should be a priority for future research.

3. Knowledge of the rate of reversion from a positive to a negative tuberculin test over time, may be useful if mass testing is undertaken. Reverters may be at risk of new infection and disease upon later exposure to TB and would not be tested for conversion because of baseline positive results. Findings of a substantial percentage of reactors reverting to negative within five years (the average length of stay for residents in this study), may mitigate any advantages derived from baseline tuberculin testing in a nursing home setting. Further studies are needed to look at reversion rates among staff and residents of nursing homes and estimate the impact of reversion on surveillance strategies.

4. Research should be done to examine the prevalence and significance of smear negative cases detected during intensive investigation and surveillance. Their individual risk could be examined through survival analysis after diagnosis. The public health significance could be examined by a case control study examining tuberculin reactors (representing new and old infection) in homes with these occult cases compared to homes without cases, while controlling for other risk factors for a positive tuberculin test such as foreign birth and BCG.

5. Further health services research is necessary to determine the optimal strategy for TB prevention in Manitoba nursing homes. The routine testing of all staff and residents at nursing home entry is currently being recommended in the United States. Our findings suggest that mass tuberculin testing would require both training and ongoing quality assurance to maintain a reasonable level of test accuracy. The effect of mass testing is uncertain. It appears that the major impact of such a strategy would be in the simplification of case investigations and the possible prevention of a small number of secondary cases of tuberculosis. If many nursing homes are reporting cases each year, routine baseline testing may be more efficient than extended and intensive surveillance during the incubation period for disease. Mass screening used for early detection of cases or to reduce the pool of reactors through chemoprophylaxis are likely to have a marginal effect on the prevention of TB in nursing homes. A more detailed analysis is required to estimate the cost effectiveness of routine tuberculin screening in Manitoba nursing homes. This analysis would help make rational choices between various TB control strategies and other programs to improve the health of the nursing home population.

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Appendix 1

QUESTIONNAIRE

NAME_____ STATUS - STAFF/RESIDENT/VOLUNTEER_____

MHSC_____ ADDRESS_____ PHONE_____

DOB (M/D/Y)_____ SEX (M/F)_____

COUNTRY OF BIRTH_____YEAR OF ARRIVAL_____ABORIGINAL (Y/N)_____

BCG (Y/N)___SCAR (Y/N)___HISTORY OF TB (Y/N)___TREATMENT (Y/N)___
PAST POSITIVE MANTOUX (Y/N)___ FAMILY HISTORY OF TB (Y/N)_____

DATE ADMITTED/EMPLOYED (M/D/Y)_____

FOR RESIDENT - ROOM_____ WARD___ EAT DININGROOM (Y/N)____
ATTEND ACTIVITY ROOM (Y/N)___ WALK (Y/N)___ WHEELCHAIR (Y/N)____ BEDRIDDEN (Y/N)___
LEVEL OF CARE____

FOR STAFF - CONTACT WITH INDEX (Y/N)___ JOB_____FULL TIME (Y/N)_____
CONTACT OTHER CASE(S) (Y/N)___ WHO?_____

STERIODS/CHEMO/RADIORX (Y/N)____ CANCER/IMMUND. (Y/N)____ DIABETES (Y/N)____
GASTRECTOMY (Y/N)____SILICOSIS (Y/N)___

ANY OF THESE SYMPTOMS IN LAST YEAR:
HEMOPTYSIS (Y/N)___FEVER 2 WEEK DURATION (Y/N)___COUGH 3 WEEK DURATION (Y/N)___
WEIGHT LOSS (Y/N)____GASTRECTOMY (Y/N)___

TUBERCULIN TEST:
TEST 1 (M/D/Y)_____ SIZE____ BOOSTER DONE (Y/N)____ DATE (M/D/Y)_____ SIZE_____
TEST 3 (M/D/Y)_____ SIZE____ TEST 4 (M/D/Y)_____ SIZE_____

CXR1(M/D/Y)_____NORMAL(Y/N)__ABN SECONDARY(Y/N)__PRIMARY(Y/N)__STABLE(Y/N)__
CXR2(M/D/Y)_____NORMAL(Y/N)__ABN SECONDARY(Y/N)__PRIMARY(Y/N)__STABLE(Y/N)__
CXR3(M/D/Y)_____NORMAL(Y/N)__ABN SECONDARY(Y/N)__PRIMARY(Y/N)__STABLE(Y/N)__

BACTERIOLOGY (3 CONSECUTIVE SAMPLE = 1 SPECIMEN)
SPEC 1 (M/D/Y)_____SOURCE____SMEARPOS (Y/N)____C + SPOS (Y/N)____ PHAGE#____
SPEC 2 (M/D/Y)_____SOURCE____SMEARPOS (Y/N)____C + SPOS (Y/N)____ PHAGE#____
SPEC 3 (M/D/Y)_____SOURCE____SMEARPOS (Y/N)____C + SPOS (Y/N)____ PHAGE#____
SPEC 4 (M/D/Y)_____SOURCE____SMEARPOS (Y/N)____C + SPOS (Y/N)____ PHAGE#____

DIAGNOSIS NORMAL (Y/N)___REACTOR (Y/N)___CONVERTER (Y/N)____(M/D/Y)_____
CASE (Y/N)___(M/D/Y)_____ ICD_____

Appendix 2

CALCULATION OF POPULATION ATTRIBUTABLE RISK FRACTION

The population attributable risk fraction (PAR) was calculated according to methods described in Kahn and Semplos(1989). The following formula was used:

PAR = p(OR-1)/1+p(OR-1)

Where p = the prevalence of exposure

OR = Odds Ratio (as an estimate of Relative Risk)

PAR= Population attributable risk fraction, also known as the etiologic fraction.

In this study, the prevalence of BCG vaccination among staff was 34%. For staff only, the Mantel-Haenszel odds ratio for BCG vaccinated tuberculin reactors compared to those unvaccinated, adjusted for foreign-birth was calculated to be 8.4.

Therefore, the PAR was calculated as follows:

0.34(8.4-1)/1 + 0.34(8.4-1)

= 0.72

Multiplication by 100 will convert this figure to a percentage.