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THE UNIVERSITY OF ALBERTA

TUBERCULOSIS AMONGST INSTITUTIONALIZED ELDERLY

BY

COLIN MACARTHUR

A THESIS

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Colin Macarthur

(Student's signature)

2E3.31 Walter C. Mackenzie
Health Sciences Centre
University of Alberta
Edmonton, Alberta T6G 2B7

Date: Sept 01 1989

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled Tuberculosis Amongst Institutionalized Elderly submitted by Colin Macarthur in partial fulfilment of the requirements for the degree of Master of Science in Experimental Medicine.

Donald A Enarson
(Supervisor)
J.K. Rieksaitis
Stephen Newman

Date: 1989 Sep 11

Abstract

In Canada, morbidity and mortality rates for tuberculosis have declined steadily over the last 100 years. A change in the age-specific incidence of tuberculosis has accompanied this decline. At the turn of the century, tuberculosis was a disease of young persons. Today tuberculosis is a disease of the elderly. Cohort studies have shown that the high rates in old age are the residuals of high rates of infection experienced in earlier life. In 1981, 28% of new active cases occurred in persons aged 65 years or over. Recent studies have suggested that elderly persons resident in nursing homes are at increased risk of tuberculosis disease, with nosocomial spread and epidemic outbreaks of tuberculosis occurring amongst the elderly residents of such facilities.

The registry-based study described herein determined the incidence rates of tuberculosis amongst the nursing home and non-nursing home elderly in Alberta for the years 1979-83 inclusive. Provincial notification rates were used to represent tuberculosis incidence. Based on previous studies and surveillance guidelines, a relative risk of four or more was determined an important difference

Over five years, 1074 cases of tuberculosis occurred in Alberta with 210 (19.6%) occurring amongst persons aged 65

years or over. Of these 210, 12 cases occurred amongst the nursing home elderly, giving a case rate of $37.2/10^5$ persons/year (py). The remaining 198 cases gave a non-nursing home case rate of $25.2/10^5$p/y. The relative risk (that is, risk of tuberculosis associated with residence in a nursing home) was equal to 1.47 (95% confidence interval: 0.65-2.29). The risk estimate was nonsignificant with the upper 95% confidence limit less than four. The data had 99.9% power to detect a relative risk of four or more. The crude relative risk was marginally confounded by the variables age and sex (in the direction of overestimation) and by the variable ethnic status (in the direction of underestimation). Surveillance bias was considered unlikely as both study groups had similar (and high) proportions of bacillary cases.

In conclusion neither residence in a nursing home nor institutionalization *per se* appeared to be a risk factor for tuberculosis amongst the elderly.

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BACKGROUND AND LITERATURE REVIEW

1.1 History and Epidemiology

Tuberculosis has plagued human populations for eons. Hippocrates, around 400 B.C., described tuberculosis, "number thirteen of the epidemics - as the greatest and most dangerous disease, proving fatal to the greatest number" (1). Over two thousand years later, tuberculosis remains a leading contender for the number one cause of disability and death worldwide. According to W.H.O. estimates approximately 10 million new cases of tuberculosis occur each year - almost half being advanced, infectious cases - resulting in 2-3 million deaths annually (2,3).

Tuberculosis is however, unevenly distributed throughout the world. The differential rates between countries (essentially between developed and developing countries) is firstly a function of disparate socioeconomic conditions - tuberculosis is a sensitive indicator of poverty. In addition, the distribution of tuberculosis in populations is influenced by the phase of the 'epidemic' occurring in that population. Unlike other communicable diseases with acute and finite epidemics, the time-course of the phases of a tuberculosis epidemic is not measured in weeks, but in decades. In North America, the peak of the tuberculosis

epidemic is thought to have occurred around 1890 (4). In Canada, the epidemiological characteristics of tuberculosis today suggest the decline phase in the epidemic.

The characteristics of the different phases of the tuberculosis epidemic are shown in table 1.

Table 1. Characteristics of different phases of the tuberculosis epidemic.

CHARACTERISTIC	PEAK	DECLINE
Overall rates	Very high	Lower, and steadily decreasing
Specific rates (age- and sex-)	Highest in young adults, often women	Highest in elderly, particularly men
High-risk groups	Absent	Present
Most common cause of disease	Recent infection	Remote infection
Reversions of tuberculin reaction	Uncommon	Common

At the height of the epidemic, tuberculosis is primarily a disease of young people. Two peaks of incidence occur, one in infants and one in young adults (particularly females) (5-7). This was the situation in Canada at the end of last century. However, since then, morbidity and mortality rates from tuberculosis have been steadily declining. This

declining incidence has changed the pattern of tuberculosis distribution, with tuberculosis nowadays a disease of the elderly (8).

The decline in tuberculosis morbidity and mortality *ante-dated* both isolation of cases and specific chemotherapy, indicating that factors other than medical intervention influenced the downward trend (9).

Social changes around this time which led to improved living standards, such as improved housing, hygiene and ventilation probably contributed to the declining incidence of tuberculosis (10,11). In addition to the social changes, the medical manoeuvres that hastened the decline in tuberculosis incidence were the isolation of infectious cases in the sanatoria and the introduction of specific drug therapy. Isolation of active cases in the sanatoria in the early part of the century, removed infectious cases from the community, thus reducing the likelihood of transmission (12). Chemotherapy, when introduced, reduced transmission of tuberculosis by rendering infectious cases, non-infectious relatively quickly (13,14).

The declining incidence of tuberculosis infection is demonstrated in tuberculin surveys. European studies toward the end of last century showed that more than 90% of children were infected by five years of age (6,15). Tuberculin surveys of pre-school children in Ottawa showed

that 52% of children were infected in 1922 (16). By 1963, this figure had fallen to less than 5% (17).

The key event in the decline in tuberculosis mortality was the introduction of specific chemotherapy in the 1940s. This heralded a marked acceleration in the rate of decline in mortality (18,19). At the turn of the century, the mortality rate for tuberculosis was 100/100,000/year for the general population (20). Since 1950, the mortality rate has decreased by approximately 50% every five years, with a present day tuberculosis mortality rate of approximately 0.5/100,000/year (21).

The trend in tuberculosis incidence and mortality in Canada from 1965-83 is shown in figure 1.

The impact of the declining incidence on the pattern of tuberculosis distribution is seen when age-and sex-specific rates are calculated. The age-and sex-specific rates for Canada, 1981 are shown in figure 2.

From figure 2 it is seen that tuberculosis incidence rises progressively with age in men. For women, the rates are similar to those for men up to age 30 years, then rise more slowly. The two peaks of incidence noted at the turn of the century (infancy and young adult life) have now all but disappeared (5).

Cohort studies, in which a group of people born in the

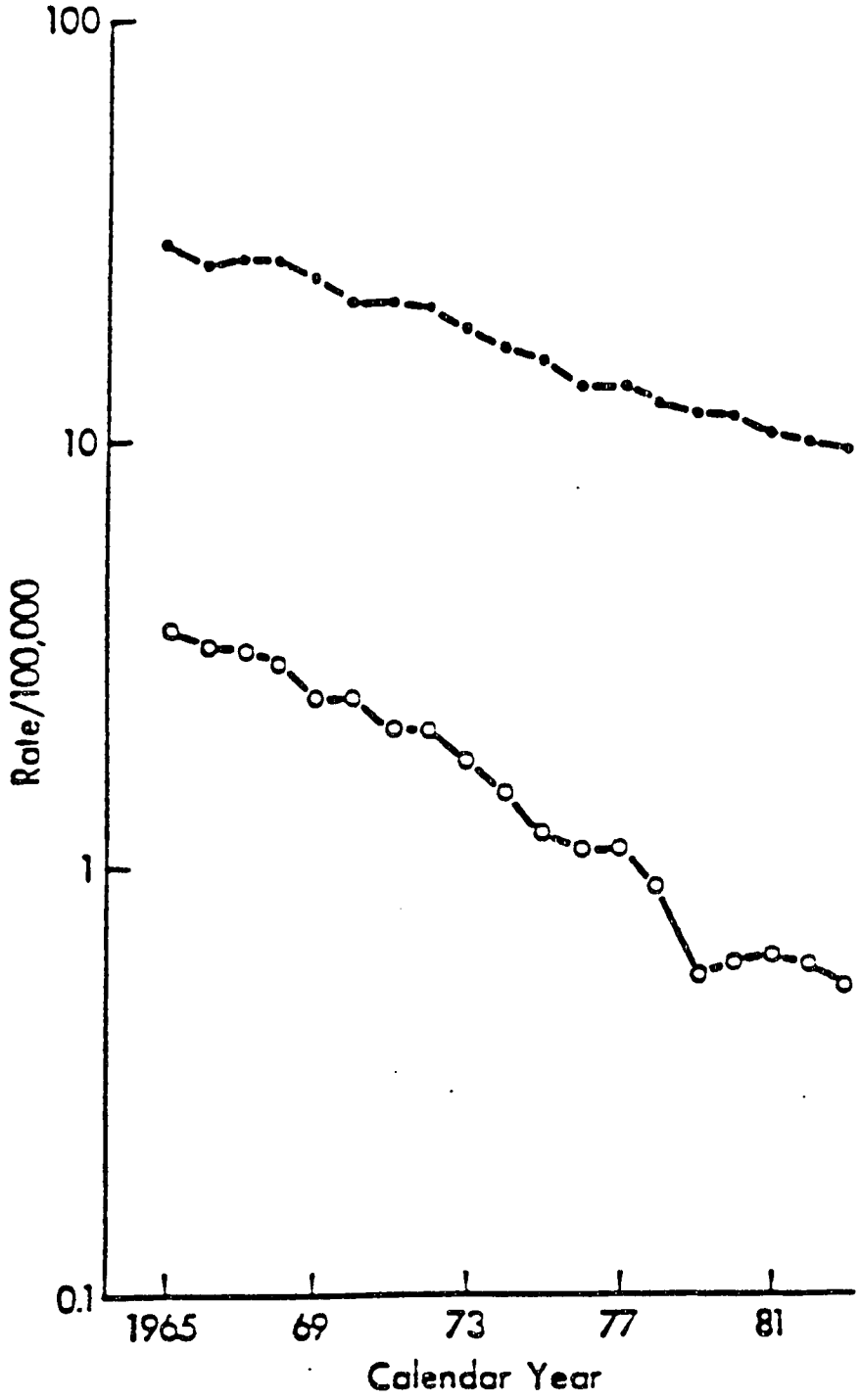
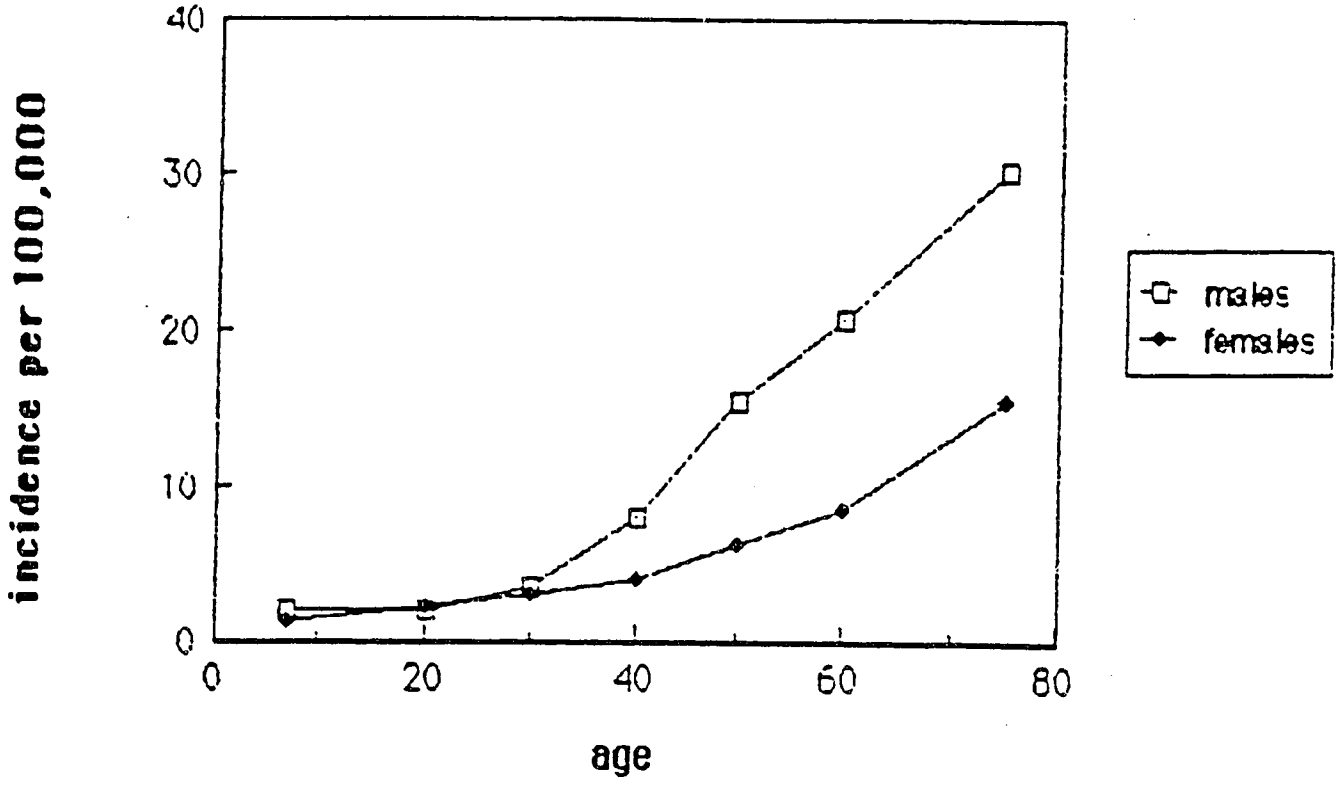


Figure 1. Trend in tuberculosis incidence and mortality in Canada 1965-83. Closed circles indicate annual incidence, open circles, annual mortality.

Source: Statistics Canada

Figure 2.

INCIDENCE OF TB BY AGE AND SEX, CANADA 1981



Source: Statistics Canada

same period are followed over their lifetimes for the development of tuberculosis explain this phenomenon (5,22,23). Each cohort is seen to experience the same age and sex-specific pattern of incidence (two peaks, one in infancy, one in early adult life). However, for each successive cohort, the incidence rate, over all ages, decreases. Thus the peaks are seen to flatten out and ultimately disappear. This was shown in Frost's landmark cohort study of tuberculosis mortality in Massachusetts during the early part of the century (5).

As Frost explained, "the present day peak of incidence in the elderly, does not represent postponement of maximum risk into old age, but rather indicates, that the present high rates in old age are the residuals of higher rates in earlier life".

This is further demonstrated if disease rates are calculated, not amongst the whole population, but only amongst the infected population. Tuberculosis can again be shown to be a disease predominantly affecting young adults (24).

This shift in maximum incidence of tuberculosis from young to old age groups, in the declining phase of the tuberculosis epidemic, has been more recently demonstrated in the Inuit of northern Canada (24) and in populations of other developed countries (3,25).

This age-shift phenomenon, therefore, reflects both the enduring viability of the mycobacterium bacillus in the human host and the steadily diminishing risk of tuberculosis infection.

For any communicable disease with decreasing incidence of infection, such as tuberculosis, the epidemiological and clinical characteristics of the disease become particularly influenced by those remotely infected (26). Certainly today's elderly have lived through an era of endemic, untreated tuberculosis and were likely exposed and infected (27).

Thus the changing pattern of tuberculosis incidence has identified today's elderly as the largest reservoir of infected individuals (28). This pool of infected persons is thought to be the major source of new active cases of tuberculosis, as a result of recrudescence of remote, dormant infection (29-35). Although many advanced countries are under the misapprehension that tuberculosis is no longer a problem (2), tuberculosis in the elderly has become and will remain for some time a definite problem. This segment of the population is responsible for a disproportionate number of new active cases each year. In Canada in 1981, approximately 28% of new cases arose in persons 65 years of age or over, an age-group constituting only 9.7% of the total population (36).

1.2 Clinical

Tuberculosis is an infectious disease with a long and indefinite incubation period (37). In this regard, the dynamics of the disease are best understood by considering the pathogenesis as a two-stage process:

1) acquisition of infection
2) development of disease after infection

Infection is a state in which the tubercle bacillus has become established in the human host, but there are no symptoms, no roentgenographic abnormalities compatible with tuberculosis, and bacteriologic studies (if done) are negative (38). Infection is usually determined by demonstration of a significant reaction to a tuberculin skin test (39).

The risk factors for infection are essentially extrinsic and relate to the likelihood of coming into contact with an infectious case of tuberculosis (40). The most important determinant is the degree of infectiousness of the source case (41-49). Degree of crowding and intimacy of exposure are also important (44). Other risk factors for becoming infected with Mycobacterium tuberculosis - age (adolescents and young adults), sex (male), urban residence, country of

origin, socio-economic status, race - all appear to be related to the likelihood of coming into contact with an infectious case (45,46). Intrinsic risk factors, for example, breathing patterns or efficiency of respiratory clearing systems, are as yet unidentified.

Factors that increase the probability of transmission of Mycobacterium tuberculosis are detailed in table 2.

Table 2. Factors associated with increased likelihood of transmission of Mycobacterium tuberculosis

FACTORS	CHARACTERISTICS
source cases	smear-and culture-positive sputum pulmonary cavities tuberculous laryngitis inadequate or no chemotherapy coughing, singing, shouting
environmental air factors	inadequate ventilation recirculation of air
contact risk factors	proximity to source case prolonged exposure to source case

Mycobacterium tuberculosis is, however, much less contagious than, for example, the usual communicable diseases of childhood. During the 1930s only 51% of children aged 5-19 of household contacts were infected by the time the source case was diagnosed (48). Thus, most infections only occur after prolonged exposure. One

experimental study has estimated that a person exposed to an untreated case of tuberculosis would have to breathe contaminated air for an average of 600 to 800 hours to become infected (49).

Tuberculosis disease indicates a state in which an infected person has a disease process involving one or more of the organs of the body (38). Definitive diagnosis of tuberculosis disease requires culture of Mycobacterium tuberculosis bacilli from the patients' tissues or secretions. The presence of acid-fast bacilli on smear, or evidence of caseating granulomata on biopsy are only presumptive evidence (50). Smear and culture techniques are obviously complementary in the diagnosis of tuberculosis disease. The close correlation of the positivity of sputum smears with infectiousness of a case makes this technique valuable from a public health standpoint (51,52).

Culturing Mycobacterium tuberculosis is more expensive and time-consuming than acid-fast staining procedures. However, culture is considerably the more sensitive of the two methods for detecting the presence of mycobacteria (53). Culture is also essential for distinguishing Mycobacterium tuberculosis from other mycobacteria and for testing drug susceptibility.

Only 5-15% of those infected with Mycobacterium tuberculosis ever become ill with tuberculosis (54). Disease

may develop within weeks after the initial infection or many years later. The risk of active disease appears to be greatest in the first one or two years following infection: thereafter, the risk diminishes as the time from infection lengthens (55, 56). However, for the untreated, infected person, if no intervention takes place, the risk of developing disease can be considered to be lifelong.

The risk of disease following infection appears mainly to be related to the intrinsic characteristics of the individual:

a) Age. Risk of disease is highest in infants and adolescents and young adults (57,58).

b) Sex. Female reactors have slightly higher rates than male reactors during the childbearing ages (58,59).

c) Body Build. Lean, underweight tuberculin reactors are at increased risk of disease compared to persons above or at ideal body weight (60-64).

d) Possibly inherited susceptibility. Genetic susceptibility to tuberculosis has been studied in twins (65) and analysis of Human Leukocyte Antigen (HLA) phenotype has shown an association with HLA-BW 15 (66). However, there are few data that race is a significant risk factor.

Other risk factors for development of disease following infection include: intercurrent illness/immunosuppression including: diabetes mellitus (67-69), silicosis (70,71), cancer (72,74), HIV infection (75-77), chronic renal failure (78,79), prolonged corticosteroid therapy (80,81), and organ transplant patients on immunosuppressive therapy (82,83). Malnourished persons and persons having undergone gastrectomy or intestinal by-pass are also considered to be at increased risk of disease (84-87). Lastly, socioeconomic factors such as low socio-economic status (88,89) and alcohol/drug abuse (90-92) are thought to contribute to an increased risk of disease.

1.3 Diagnosis of Tuberculosis in the Elderly

Diagnosis of tuberculosis disease in the elderly may be difficult for several reasons.

First, with the introduction of chemotherapy which rendered patients non-infectious in a relatively short period of time, the necessity for long-term sanatorium care was virtually eliminated (13,14). As a result, tuberculosis returned to the main stream of medicine, and became the responsibility of physicians practising in community hospitals (93). With the decreasing incidence of tuberculosis, physicians have become less aware of the

disease, with a subsequent low index of suspicion (94). Urban hospital studies have shown that up to 50% of patients with culture-positive pulmonary tuberculosis are misdiagnosed at the time of admission (95,96). The resultant delay in diagnosis - approximately two weeks as found in most studies - contributes unnecessarily to morbidity and mortality from tuberculosis (97-100). This is an important issue, as, without treatment, approximately 25% of patients die from tuberculosis within the first two years, and 50% of persons who die from tuberculosis in Canada, do so because they were not diagnosed and thus not treated (101,102).

Secondly, physician error in diagnosis of tuberculosis is often compounded by the characteristics of the disease in the elderly. The classic symptomatology of pulmonary tuberculosis - cough, sputum production, night sweats - are often absent in the elderly (103). The disease often presents in an insidious and atypical fashion, with a paucity of respiratory symptoms (104). In addition, tuberculosis often coexists with significant concurrent illness in the elderly (105).

In summary, the non-specificity of symptoms (often dismissed by both patient and physician as part of the phenomenon of aging); the presence of concurrent illness and the already low index of suspicion all contribute to physician failure in the diagnosis of tuberculosis in the

elderly.

In addition to the general problems of clinical diagnosis, the specific diagnostic procedures for tuberculosis also exhibit limitations when used in the elderly.

As outlined in section 1.2, definitive diagnosis of tuberculosis requires culture of Mycobacterium tuberculosis. However, the frail elderly are often not capable of sufficient sputum production for examination. One study of nursing home residents demonstrated that only 60% of the residents were able to provide a 'decent' sputum specimen (106). Without proof of culture, diagnosis by other means - usually by clinical history or radiographic findings - is presumptive. In addition, both these methods for diagnosis of tuberculosis are particularly unreliable in the elderly. For example, older persons are often less able to provide an accurate account of their symptoms. Contributing factors (more common in the aged) include poor memory, mental confusion, deafness and impairment of speech (104). Diagnosis of tuberculosis in the elderly by chest x-ray is limited by both technical and interpretive problems. X-ray films of 'poor' quality are more likely in ill, frail patients unable to cooperate fully. Scoliosis, more common in the elderly, may obscure lung apices, hindering the diagnosis of tuberculosis. In addition, the classic chest x-ray of pulmonary tuberculosis - involving the apices and

posterior segments of the upper lobes (107) - is often not seen in the elderly. Atypical chest x-ray findings have been been reported in 8-29% of adult patients with active tuberculosis (108-110). For those aged over 60 years, in one study, unusual roentgenographic findings were noted in 35% of cases and were implicated in the failure to diagnose tuberculosis (110). Miliary tuberculosis - once a disease of childhood nowadays increasingly a disease of the elderly - may be missed on chest x-ray, as the pulmonary nodules may not be large enough to cast a radiographic shadow (111). The presence of concurrent illness (again more common in the aged) is also seen to delay the diagnosis of miliary tuberculosis (105,111).

1.4 Aging - Demographics and Risk of Institutionalization

Although arbitrary, by definition, old age begins at 65 years. Since the turn of the century, a marked increase in the proportion of the population aged 65 years or over has occurred. In Canada in 1901, just over a quarter of a million persons were 65 years of age or over, accounting for approximately 5% of the total population. By 1951, the number of elderly had quadrupled, and by 1981, 2.4 million persons, or 9.7% of the total population, were aged 65 years or over. This trend is expected to continue. By 2031, when the 'baby boom' (post-war births) generation reaches old

age, 20% of the total population is expected to be 65 years of age or over. (See table 3).

Table 3. Population 65 + in Canada 1901 - 2031.

Year	Canada	
	Number	Per cent
1901	271,201	5.0
1931	576,076	5.6
1951	1,086,237	7.8
1981	2,360,975	9.7
2031 (projection)	6,240,000	20.2

Sources: Statistics Canada 1921 Census of Canada Vol 2, 1961 Census of Canada Catalogue 92-542, 1981 Census of Canada Catalogue 92-901.

Factors influencing the development of this trend are fertility, longevity and immigration. The main factor in the aging of the population has been the decline in fertility (112). The average number of births per woman in Canada in the early 1900s was 3.6. By 1976, this number had declined to 1.7 (113). Therefore, with fewer young, the proportion of elderly in the total population increased. Life expectancy at all ages has also increased, with a subsequent increase in the proportion of old elderly. In 1951, those persons 75 years and older accounted for 31% of

the elderly population. By 1981, 37% of the elderly population was 75 years or older.

Another characteristic of old age in Canada is the sex-distribution. (See table 4.)

Table 4. Population 65 + in Canada by Sex 1901-1981.

Year	Per cent	
	Male	Female
1901	51.2	48.2
1931	51.1	48.9
1951	50.8	49.2
1981	42.8	57.2

Sources: Statistics Canada 1921 Census of Canada Vol 2, 1961 Census of Canada Catalogue 92-542, 1981 Census of Canada Catalogue 92-901.

At the turn of the century, men outnumbered women in the elderly population, but since 1961, females have outnumbered males. Consequently, this ratio of males to females in the over 65s has been decreasing steadily and is expected to continue to decrease. This sex-difference is even more marked amongst the old 'elderly' (those aged 75+). This change in sex composition in the elderly population is best explained by the differential mortality between males and females which is observed throughout the age span, but is

especially evident in the extremes of the age distribution. Whether females have a longer life expectancy because of biologic (genetic superiority) or environmental (lifestyle) differences remains unclear.

The impact of aging on health care utilization has been well documented. A disproportionate fraction of health care dollars are spent on those aged 65 years or over (114).

As elderly persons are more likely to suffer from chronic disease and resultant disability, in parallel with the aging of the population has been the creation of an extensive nursing home industry. Given that aging is characterized by the convergence of multiple dysfunctions, it is not surprising that almost all nursing home days are accounted for by persons aged 65 years or over (115).

Of importance, therefore, are potential risk factors for institutionalization amongst the elderly (116). Two independent prospective studies of elderly populations in Manitoba and Massachusetts identified similar predictors of long-term care facility use by the elderly (117,118). High-risk elderly included those:

a) of advanced age (persons aged 85+ years had a 7-times increased risk, and those aged 75-84 had 3-times increased risk compared to those aged

65-74.)

b) social characteristics

1) living alone (without spouse or relative)

2) living in senior citizen housing.

Both variables increased the risk of institutionalization by approximately two and one half times.

c) health-related risk factors included:

1) admission to hospital in the previous year

2) problems with one or more basic ADL's (activities of daily living)

The key socio-demographic characteristics were found to be better predictors of admission than health and physical functioning characteristics.

An estimated 20% of persons aged 65 years and over will spend some time in an extended care facility. However, at any one time only approximately 5% of persons aged 65 years or over reside in nursing home facilities (119).

1.5 Tuberculosis and the Institutionalized Elderly

One characteristic of the epidemic in decline is the emergence of 'high risk' groups.

Groups at high risk of tuberculosis in Canada are listed in Table 5.

Table 5. Risk of active tuberculosis by demographic group in Canada.

Group	rate/100,000	rate ratio	reference
*HIV infected	12,000	----	(120)
Contacts	875	62.5	(121)
Untreated inactive TB	530	37.9	(122)
Urban poor Vancouver	370	26.4	(123)
Indochinese refugees	350	25.0	(124)
Inuit	215	15.4	(125)
Canadians born in Philippines	220	15.7	(126)
Canadians born in China, Hong Kong	191	13.6	(126)
Canadian Indians	168	12.0	(127)
Other Canadians born outside Canada	20	1.4	(21)
Born in Canada, not Indians/Inuit	14	1.0	(126)

*San Francisco population based study.

The issue is whether elderly persons, residing in nursing home facilities constitute a 'high risk' group for development and spread of tuberculosis. That is, is the incidence rate of tuberculosis amongst elderly residents of nursing homes significantly greater than that for the non-nursing home elderly?

Research, primarily by Stead and his colleagues, has led them to believe that tuberculosis is an endemic and even nosocomial infection amongst the elderly residing in nursing homes (128-133).

In 1979, Stead *et al* were the first to document and study an 'outbreak' of tuberculosis occurring in a single nursing

home (128). Following identification of a smear positive case of pulmonary tuberculosis in an elderly resident, residents and staff in the facility were surveyed for tuberculosis infection using the tuberculin skin test with five tuberculin units (TU) of purified protein derivative (PPD). Those with significant reactions ($\geq$ 10 mm) had further tests: chest x-ray and sputum culture. Two further cases (on chest x-ray evidence) were identified at this time. Six months later, two more cases of pulmonary tuberculosis were diagnosed amongst the residents in the facility. One smear- positive case occurred in a resident with concurrent chronic lymphatic leukemia. One smear-negative, culture positive diagnosis was made at *post-mortem* in a resident with antibiotic-unresponsive pneumonia. All residents were retested with 5 TU PPD at this time.

Of the 228 residents, 47 (21%) had a previous record (before identification of the index case) of a 'positive' tuberculin skin test. Fifty of the remaining 181 residents had 'converted' from a negative (< 10 mm) to 'positive' ($\geq$ 10 mm) skin test. These findings were interpreted as evidence of nosocomial spread of tuberculosis amongst the residents.

Eight of the fifty residents who 'converted', developed clinical tuberculosis (five cases detailed above plus three

other 'converters'). Thus 16% of 'converters' developed clinical tuberculosis within a two-year time-frame. Only three of the eight cases (38%) were culture-proven for Mycobacterium tuberculosis. On chest x-ray evidence, five of the eight cases amongst the residents were labelled as progressive primary disease. That is, the radiographic findings were typical of exogenous re-infection not recrudescence of old infection.

Of the 138 employees, 21 (15%) showed evidence of tuberculous infection on skin testing. One employee (39 year-old cook) developed active (smear and culture positive) pulmonary disease.

One visitor to the facility underwent surgery during this time-frame for removal of a lung lesion that was discovered to be tuberculous.

Two other outbreaks of tuberculosis occurring in nursing home facilities in Oklahoma and Washington were reported in 1980 and 1983 (129,130). In the Oklahoma facility, residents were surveyed with skin testing (5 TU PPD) and chest x-ray following discovery of a smear and culture-positive case of tuberculosis in an elderly resident. Five further cases of tuberculosis (none culture-proven) were identified and treated.

The Washington outbreak occurred in a skilled nursing care

facility, where a smear and culture-positive case occurred in an elderly resident. Residents, visitors and staff were surveyed for tuberculosis infection and disease. Eleven further cases - 7 residents, 1 employee, 3 visitors - all bacteriologically proven, were identified.

A retrospective cohort study in a single nursing home appeared to confirm nosocomial spread of tuberculous infection amongst nursing home residents (131). Of 714 residents admitted between 1972 and 1981, 226 had undergone at least two tuberculin skin tests and thus were included in the study. On admission, 13% of residents had a 'positive' tuberculin test ($\geq$ 10 mm). On follow-up, 38 of 226 residents (17%) 'converted' to a 'positive' skin test. All were treated prophylactically with INH. These 'conversions' were interpreted as evidence of nosocomial spread of tuberculosis infection.

These findings prompted Stead *et al* to survey all nursing home residents in Arkansas, in an effort to determine the occurrence and spread of tuberculosis in the entire population of nursing home elderly (132). Initially a cross-sectional tuberculin survey was performed on 95% of all permanent and newly admitted nursing home residents, with a second test performed two to three weeks later on 59%. These residents were then followed prospectively over the next three years for the development of tuberculosis

infection and/or active disease. Only 12% of newly admitted residents had 'positive' tuberculin reactions ($\geq$ 10 mm), whereas 21% of residents in whom the skin test was delayed more than one month after admission (mean thirty months) had 'positive' tuberculin tests. These findings were interpreted as evidence of nosocomial spread of tuberculosis infection within nursing homes. Additional evidence provided, was that those not reactive on initial testing, were more likely to convert their skin test to 'positive' if they resided in a nursing home with a previously documented case of tuberculosis. Those residents with documented 'conversion' of their skin tests and given prophylactic INH appeared to be afforded significantly increased protection from active tuberculosis when compared to residents with skin test conversion, not given INH therapy.

For the years 1981-1983 in Arkansas, the case-rate for tuberculosis in those aged 65 years or over living at home was approximately 60/100,000/year. For those aged 65 years or over residing in a nursing home, the case-rate was almost four times greater at 234/100,000/year.

Stead *et al* interpreted these findings as suggesting that tuberculosis was an endemic and nosocomial infection amongst nursing home residents. The pathogenesis of transmission and occurrence of disease in these elderly was explained as follows. Only a small percentage (12%) of elderly admitted

to nursing homes had previously been infected with tuberculosis (as indicated by skin test results). Reactivation occurred in these elderly as a result of concurrent degenerative changes associated with aging. Unsuspected transmission of tuberculosis infection from these cases then occurred amongst the nursing home residents. For the vast majority of residents (90%) this represented primary infection, with the subsequent development in 5 - 10% of progressive primary tuberculosis.

Another U.S. State, Tennessee, reported a similar discrepancy with tuberculosis case rates for those aged 65 years or over (133). For Tennessee in 1982, the tuberculosis case-rate for nursing home residents was approximately 184/100,000/year, two and a half times that for persons aged 65 years or over, not residing in nursing homes.

For Alberta, in 1976, the director of TB Services surveyed the residents of a single nursing home facility using tuberculin skin testing, with chest x-rays for reactors and sputum examinations for those with abnormal x-rays. From this survey, a policy for tuberculosis surveillance in residential facilities in Alberta was developed. All nursing home facilities received a copy of this surveillance policy and, in addition, the registrar for the tuberculosis case-registry visited approximately 75% of all such facilities to provide in-service education with regard to

tuberculosis surveillance and treatment. Therefore, in Alberta from 1976 onwards, TB Services had made a priority of the issue of tuberculosis in nursing homes.

The objective of this retrospective registry-based study was to determine and compare the incidence rate of active tuberculosis amongst the nursing home and non-nursing home elderly in Alberta for the years 1979-1983 inclusive. The study hypothesis was that the incidence rate of tuberculosis amongst the nursing home elderly in Alberta was not four (or more) times the incidence rate of tuberculosis amongst the non-nursing home elderly.

CHAPTER TWO

MATERIALS AND METHODS

2.1 Research Proposal

2.1.1 General Objectives

In Canada, morbidity and mortality rates for tuberculosis have declined steadily over the last 100 years. The downward trend in incidence has been attributed to social, public health and specific medical measures. Specifically, improved living standards (better housing, hygeine, ventilation), isolation of cases in sanatoria, and introduction of specific chemotherapy, all aided in reducing transmission of tuberculosis.

A change in the age-specific incidence of tuberculosis has accompanied this decline. At the turn of the century, tuberculosis was a disease of young persons - with two peaks of incidence - one in infancy, one in early adult life. Today, tuberculosis is predominantly a disease of the elderly, particularly males. The reason for this age-shift is the steadily diminishing risk of tuberculosis infection. Cohort studies in the early 1900s, which followed persons born during the same time period, convincingly showed that the high rates in old age were the residuals of high rates of infection experienced in earlier life. In 1981, in

Canada, 28% of new active cases occurred in persons aged 65 years or over - a group which constituted only 9.7% of the total population.

Recent studies suggested that a sub-group of this elderly population - those residing in nursing home facilities - were at increased risk of developing active tuberculosis. Tuberculosis disease was thought to be endemic in these facilities with nosocomial transmission and epidemic outbreaks of tuberculosis occurring amongst the residents. The incidence rate for tuberculosis amongst the nursing home elderly was estimated to be four times that for elderly persons residing in the community. The objective of this study was to determine if tuberculosis disease occurrence was similarly increased amongst the nursing home elderly in Alberta.

2.1.2 Specific Aim

The aim of this study was to determine and compare the incidence rate of active tuberculosis amongst the nursing home and non-nursing home elderly in Alberta for the years 1979-1983. (Provincial notification rates for active tuberculosis were used to represent tuberculosis incidence.)

2.1.3 Study Hypothesis

The incidence rate of tuberculosis amongst the nursing home elderly of Alberta was four (or more) times the incidence rate of tuberculosis amongst the non-nursing home elderly.

2.1.4 Determining an Important Difference

For any disease, identifying high risk groups in the general population, that is, persons at increased risk of developing the disease, is of paramount importance from a public health standpoint. Obviously, identification of such groups at risk allows effective health care planning and rational allocation of health care resources and services. Secondly, and more importantly for communicable diseases, preventive measures involving such groups accelerate the process of eradication of the disease.

For this study, an important difference was specified as a four times greater rate for tuberculosis disease amongst nursing home elderly compared to non-nursing home elderly. This factor of magnitude - four times - was chosen for two reasons. First, as outlined in section 1.5 (Tuberculosis and the Institutionalized Elderly), Stead *et al* calculated tuberculosis case-rates amongst elderly nursing home

residents in Arkansas to be four times greater than tuberculosis case-rates amongst elderly persons residing in the community (132). One of the several criteria used in the judgement of a cause-effect relationship is consistency of findings in different studies (134). A similar finding in this study of a four times increased rate amongst the Alberta nursing home elderly would, therefore, have helped satisfy this criterion for causality. Secondly, active case-finding procedures for tuberculosis disease are thought to be justifiable (considering both the low background rate and cost-efficiency) at rates of approximately 100/100,000/year (1/1,000/year). For Alberta in 1981, the incidence rate for tuberculosis in those aged 65 years or over was 23.9/100,000/year. Thus, a four times increased rate amongst the nursing home elderly would have given a case-rate of approximately 96/100,000/year for this group, justifying active case-finding programs.

2.2 Study Design

2.2.1 Type of Study

The research question was addressed using a retrospective cohort study design. The term retrospective, in this context, refers to the temporal relationship between initiation of the study by the investigator, and the

occurrence of disease outcomes being studied. In the retrospective cohort study design, both exposure and outcome have occurred by the time the study is initiated. This design was chosen as being the most efficient method of addressing the research problem, given the constraints of both time and money. Advantages and limitations of such a study design are further discussed in section 2.5.1 (Rationale).

2.2.2 Variables

2.2.2.1 Population Information

Information on the demographics of the general population was obtained from Statistics Canada, 1981 Census of Canada, Population, Catalogue 92-901 (volume 1). For Alberta in 1981, 163,395 persons were 65 years of age or over comprising 7.3% of the total population.

Information on the institutionalized elderly was obtained from Alberta Hospitals and Medical Care, Annual Report 1980/81. Information on the different types of care facilities (nursing homes, auxiliary hospitals, mental health hospitals, lodges) was available. Further breakdown for nursing homes provided information on the total number of facilities, total number of beds, average occupancy and expenditures, distribution of residents by age-group and

sex, admission by previous location and separations by destination. For Alberta, in 1981, there were 80 nursing homes providing a total of 7,286 beds with an average occupancy rate of 98.4%. A total of 6,454 persons aged 65 years or over (3.9% of the total population aged 65 years or over) were resident in nursing home facilities in 1981.

Persons designated as elderly were those persons aged 65 years or over at the time of notification.

2.2.2.2 Independent Variable

The primary (exposure) variable was residence in a nursing home at the time of notification.

Nursing home care referred to facilities providing supervised personal care for persons who required assistance in coping with the activities of daily living, but who were not sufficiently ill to warrant auxiliary or general hospital admission. These facilities were identified by a valid residential address. That is, such facilities were under contract with the Minister of Hospitals and Medical Care to provide care under the terms and provisions of the Nursing Homes Act (1985).

The residential address for each case was identified from five sources namely the notification card, the central

registry file, the case file, the contact follow-up list and the 'home conditions' report. Any discrepancies in the address information were reviewed and corrected. Any case with a hospital address was reviewed to determine both the date of admission to that hospital and the residential address prior to admission. The residential address was available for every notified case and all cases had a contact follow-up list and a 'home conditions' report.

2.2.2.3 Co-variables

Information was obtained from individual case files regarding:

a) date of birth,
b) sex,
c) country of birth/ethnic status,
d) previous disease (and record of treatment),
e) present diagnosis (for example, pulmonary, renal, disseminated, tuberculosis adenitis), and
f) method of diagnosis (culture, pathology, x-ray or clinical).

Information was collected on a) - d) as these variables may have acted as confounders. As described in section 1.2, these variables are known risk factors for tuberculosis

disease. Confounding may have occurred if these variables were also independently associated with exposure (residence in a nursing home). If so, differential distribution of these variables between the two groups (nursing home and non-nursing home elderly) may have resulted in confounding. Unless controlled for, confounding may distort any true estimate of effect. An estimate of the potential magnitude and direction of confounding by these variables in this particular study is described in detail in section 2.5.4 (Validity). Implications for analysis of data are discussed in section 2.4 (Data Analysis).

Information was collected on e) and f) to allow for further analysis by diagnosis and by method of diagnosis. Such analysis first addressed the question of whether primary tuberculosis was common in the nursing home elderly (as suggested by Stead)(128). In addition, analysis by method of diagnosis - bacillary, non-bacillary - helped determine whether surveillance bias (overdiagnosis) may have accounted for differences between the two groups (nursing home and non-nursing home elderly). That is, an excess of tuberculosis cases (more than 20% of all cases in developed countries) not culture-proven, in either study group, would have indicated over-diagnosis of tuberculosis in that group.

2.2.2.4 Dependent (Outcome) Variable

The outcome variable was notification of active tuberculosis to TB services, Division of TB Control, Alberta Community and Occupational Health. Notification was compulsory (by law) as tuberculosis is a communicable disease. All notifications were accepted.

In Alberta, for the years 1979-83, 1074 cases of active tuberculosis were notified to TB Services. Of these, 210 cases (19.6%) occurred in persons aged 65 years or over.

The issues associated with using the tuberculosis case-registry as the data source in this study - with regard to the quality and completeness of the information - are discussed in section 2.5.2 (Rationale).

2.3 Data Collection

2.3.1 Data Abstraction, Editing and Entry

Newly notified cases of tuberculosis in Alberta, for the years 1979-83 were obtained from the Central Registry, Division of TB Services, Alberta Community and Occupational Health.

Information on the previously defined variables was abstracted from the case files onto a standardized data

collection form (see appendix A).

The data set was entered into a microcomputer, using the SPSS/PC statistical package.

2.3.2 Error Checking

Two persons (author and undergraduate student), independently of each other, identified all notified cases of tuberculosis occurring in persons aged 65 years or over in Alberta between 1979 and 1983.

Information from the case files on the relevant variables was abstracted twice by the author. No reference was made to the initial data collected, when collecting the data the second time.

The two independently collected data sets were entered into the computer, each at different times, and compared. Missing or unusual variables were identified, reviewed and corrected, as was information that did not correspond between the two data sets.

2.4 Data Analysis

The incidence rate of tuberculosis disease over five years, 1979-1983, that is, the number of new cases divided

by the total person-time of observation, was calculated for both study groups (nursing home and non-nursing home elderly). The relative risk for crude data was estimated by calculating the rate ratio, that is, the nursing home case rate divided by the non-nursing home case rate. The standard error for the relative risk was calculated using equation one (Appendix B). A 95% confidence interval around the relative risk point estimate was calculated using equation two (Appendix B). To test the difference between the two rates, a test of significance using the following chi-squared statistic

$$\chi^2 = \Sigma \frac{(\text{Observed} - \text{Expected})^2}{\text{Expected}}$$

which has a 1 degree of freedom. All tests of significance were at the 5% level of significance.

To control for confounding, the data was stratified by age (65-74, 75-84, 85+), by sex and by age and sex. Stratum-specific risk estimates and 95% confidence intervals around the point estimates were calculated. An estimate of confounding by these variables was made by evaluating stratum-specific risk estimates for uniformity (by inspecting the data). If uniform, a summary unconfounded risk estimate was calculated (see equation 3 Appendix B). For the variable 'country of birth/ethnic status', the proportion of cases by ethnic origin - Asian, indigenous Indian, European and Canadian born (non-Indian) - for each

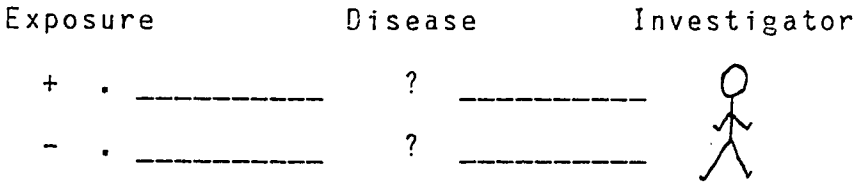
study group, was calculated and compared. For the variable 'previous disease', the proportion of all cases with a history of previous disease in both study groups was calculated and compared.

The power of the study, was calculated (two-sided) at the 5% level of significance using Beaumont and Breslow's formula for cohort studies (135) (see Appendix B, equation 4). All analyses were performed twice - for all notified cases and for all culture-proven cases - in the two study groups.

2.5 Rationale

2.5.1 Study Design

The temporal relationship between the investigator and exposure/outcome variables in a retrospective cohort study is shown in diagramatic form below.



The obvious advantage of such a design is that the study may be completed quickly and inexpensively.

As the outcomes have occurred by the time the study is initiated, there is no induction-period delay, that is, the delay from exposure to outcome of interest. In addition, such a design permits direct calculation of incidence rates. This was important in this study, where tuberculosis case rates in both groups (nursing home and non-nursing home elderly) were to be determined and compared.

The major limitation in such a study design is the necessity and availability of adequate records from which data may be collected. This issue was overcome favourably in this study as tuberculosis is a notifiable infectious disease (notification obligated by law). For each case notified, extensive personal and medical information was routinely collected and recorded. For example, information was collected on all the co-variables (potential confounders) previously identifed (in section 2.2.2.3). Furthermore, all tuberculosis disease notifications in the province of Alberta were centralized to TB Services. Therefore, for this particular study, adequate and accessible information was available for each case.

Alternative study designs considered to address the research question included the counterpart prospective cohort study design and the case-control design.

The major limitation of prospective cohort studies is that they are often extremely expensive and time-consuming. For

this particular study, a prospective cohort design would have been costly, inefficient and susceptible to major losses to follow-up, possibly undermining study validity. Two study groups - nursing home and non-nursing home elderly - would have needed to have been identified, examined and followed for several years. Given the low background rate for tuberculosis in Alberta, the long latency period for tuberculosis (years) and the high population turnover for the elderly, this would have meant large sample sizes and years of follow-up would have been required in order to detect sufficient outcomes and give the study adequate power in the analysis.

The case-control study design has the advantage of being relatively quick and inexpensive. However, for this particular study, the case-control design was the least attractive option for several reasons. First, the case-control design is inefficient for the evaluation of rare exposures. Only approximately 3.7% of Albertans aged 65 years or over were resident in nursing homes. Therefore, sample sizes would have needed to have been extremely large to yield sufficient 'exposed' cases and controls, for adequate statistical power in the analysis. Also, unless the study was population-based, incidence rates of disease in exposed and unexposed populations (crucial to this study) could not have been directly computed. Lastly, case-control studies are considered to be particularly prone to bias -

for example, selection bias, interviewer bias, recall bias, prevalence - incidence bias and others.

In summary, the retrospective cohort study design was chosen as being the most efficient method of addressing the research question for three reasons. First, research could be completed relatively quickly and inexpensively; incidence rates of disease could be directly computed; and lastly, the cohort design was considered to be less prone to bias.

2.5.2 Quality of Information

This study was a registry-based study, with data collected from notification records at the Division of Tuberculosis Services.

The function of the tuberculosis case-registry is to collect relevant information on all new cases occurring in the province. Notification is compulsory as tuberculosis is a communicable disease. Information collected, although useful for historical/research purposes, is primarily collected for the containment of tuberculosis disease. Identification of cases, and contacts of cases, allows primary treatment or preventive therapy to be instituted with the resultant containment of spread of disease.

The issues associated with having used the registry as the

data source pertain to

a) the completeness of the information,
b) the quality of the information (that is, misclassification), and
c) the acceptability of using tuberculosis notification as a measure of tuberculosis incidence.

Incomplete reporting of communicable diseases by physicians is particularly associated with passive surveillance - where the physician voluntarily reports the occurrence of a notifiable disease (136,137).

However, in Alberta, active surveillance is employed for tuberculosis disease to identify all new cases and verify the diagnoses. A multiple and overlapping branching system of notification directs new cases to tuberculosis services. This system involves the physician, the health unit, public health nurses, microbiology laboratories, pharmacies and Vital Statistics, thus increasing the opportunity for identification of new cases.

Inevitably, some cases fail to be reported, whether because of failure in the system of notification or intervention of death before diagnosis. Missing or unreported cases were a potential source of bias if cases were systematically more likely to be missed in either of

the two exposure groups (nursing home or non-nursing home elderly). Conversely, systematic overdiagnosis of tuberculosis cases in either study group - as a result of differential surveillance of the two study groups - was also a potential source of bias. The implications of unreported cases and overdiagnosis of cases as possible sources of systematic error in this study are discussed in section 2.5.4 (Validity).

Misclassification of notified cases, that is, error in the classification of exposure or outcome status, was a potential source of bias. Therefore for every notified case residential address was confirmed from several sources. TB Services obtained the residential address from one or all of the following sources: the microbiology laboratory, the hospital records, the general practitioners office or from the patient. This address was then relayed to the public health nurse associated with the appropriate health unit. The residential address was then confirmed by the public health nurse who visited the stated address for two reasons: primarily to determine the contact follow-up list and also to assess the social circumstances (that is, the 'home conditions' report). The quality of the information with regard to the residential address was thus considered to be high.

The possibility that an institutionalized case would only

be given a street address was also considered to be unlikely. Given that tuberculosis in the institutionalized elderly was considered a priority for TB Services in Alberta, emphasis was placed on identifiying such cases. Therefore, the notification cards were expected to include the full name of the institution along with the street address for any such case. If, for whatever reason, the notification card did not include this information initially, the visiting public health nurse would notify the central registry if the street address in fact represented a residential care facility for the elderly. The notification card would then be corrected. The name of the institution would also be noted clearly by the public health nurse on the contact follow-up list and the 'home conditions' report. The contact follow-up list of such cases obviously included staff employed by the institution.

Therefore, for this study, in order to minimize misclassification, first, all five sources of address for every case were reviewed for concordance. In addition, any contact list with a street address that was extensive or included staff of a care facility was reviewed closely to determine whether the case, in fact, represented an institutionalized case.

Errors in the classification of exposure status (residential address) were thus considered likely to be

negligible and random given the necessity for an accurate and complete contact list for public health measures. Errors in the classification of outcome (notification of tuberculosis disease) were also likely to be negligible and random given that tuberculosis was a notifiable disease. It seemed reasonable to assume that within both study groups (nursing home and non-nursing home elderly) a case of tuberculosis once identified would have been equally likely to have been notified.

The final issue was whether notification of tuberculosis disease was an adequate measure of tuberculosis incidence. Given that notification rates were high (because of active surveillance) and that for each case, diagnosis was verified, it seemed reasonable to calculate incidence rates from notification rates.

2.5.3. Precision

If epidemiologic research is viewed as a measurement exercise, then precision in epidemiologic measurement corresponds to the reduction of random error (138). One major component of random error is sampling error - the attendant random error associated with the selection of study subjects. It could be argued (from a statistical stand-point) that sampling error was negligible in this

particular study, as the entire population eligible for study (those aged 65 years or over in Alberta) were included in the study.

The primary method of reducing random error is to enlarge the size of the study. In this particular study where sample size was fixed, precision was addressed indirectly by calculating the power of the study. Power is defined as the probability of detecting (as statistically significant) a postulated level of effect. Given that we wished to detect a relative risk of four or more, this study had approximately 99% power (two-sided) of detecting a relative risk of four or more at the 5% level of significance.

2.5.4 Validity

Validity in epidemiologic measurement is defined to be the reduction of systematic error (138). Validity in any study may be separated into two components, internal and external validity.

Internal validity corresponds to the validity of inferences drawn as they pertain to the study subjects themselves. External validity or generalizability corresponds to the validity of the inferences drawn as they pertain to subjects outside the study population.

Internal validity implies an accurate measurement other than random error. Systematic error due to bias or confounding may distort any true measurement of effect and thus seriously detract from internal validity. Dozens of potential biases in epidemiologic research have been identified (139). A useful (arbitrary) distinction of biases into two types is often made - selection and information bias.

Selection bias is always potentially a major source of bias as the essential feature of an epidemiologic study is a comparison of two study groups for frequency of outcome or exposure. Selection bias may occur in the cohort design if selection of subjects into either study group is affected by knowledge of outcome status. In this particular study, selection bias was not an issue. Unlike the vast majority of studies where representative samples of individuals in the exposed and unexposed populations are selected, in this study, all eligible persons were included. That is, the entire population of persons aged 65 years or over in Alberta, was included in the study.

Information bias occurs when noncomparable information is obtained from the two study groups. To minimize systematic errors in data collection for this particular study, a standardized data collection form was used (see appendix A). In addition, the data was collected independently at two

different times (see section 2.3 Data Collection).

Misclassification - errors in the classification of exposure or outcome status - was another potential source of information bias. As outlined earlier (in section 2.5.2), errors in the classification of exposure status (residential address) were considered likely to be negligible and random, given the necessity for an accurate and complete contact list for public health measures. Errors in the classification of outcome (notification of tuberculosis disease) were also likely to be negligible and random, given that tuberculosis was a notifiable disease.

Systematic error associated with differential surveillance of the two study groups may have distorted any true estimate of effect. Given the nursing home concept, it could be argued that because of differential surveillance of the two study groups (nursing home and non-nursing home elderly), underreporting of tuberculosis cases was more likely to occur in the non-nursing home elderly population. That is, cases may have been more likely to be missed in the community than in the nursing home. The basis for this argument is that the nursing home system is based on the medical/hospital system. Nursing home facilities are required under provincial regulations to employ qualified nursing staff (in a certain nurse to resident ratio) and to arrange accessible general practitioner care for each

resident. In addition, all nursing home residents are medically screened (most for tuberculosis) on entry into the nursing home, and undergo regular health assessments forthwith. In addition, tuberculosis in the nursing home elderly was a priority of TB Services. By this reasoning, most 'true' cases of tuberculosis in nursing homes should have been identified. By extension, cases may have been missed amongst the elderly in the community because of much less medical surveillance. Potentially, this systematic error could have led to bias in the direction of overestimating case rates in the nursing home elderly. However, from indirect evidence, it seems that the magnitude of this potiential bias was likely to be negligible. The size of the problem of missed cases was estimated from a study that showed only 1.7% of tuberculosis cases were diagnosed after death (102). The actual proportion of undiagnosed/missed cases was estimated to be slightly greater as not all undiagnosed tuberculosis cases died and not all persons who died were autopsied. However for the purposes of this study the magnitude of this potential bias was thought to be neglible.

The converse side of this bias (surveillance bias) is over diagnosis of tuberculosis. Overdiagnosis refers to finding 'cases' which are not true cases, that is, suspect active cases, not culture-proven. In tuberculosis epidemiology, overdiagnosis is often a function of active screening. As

indicated, most nursing home residents are screened for tuberculosis on entry into the facility. Therefore, it may have been expected that the direction of this systematic error would again have been to overestimate case rates in the nursing home population. The magnitude and direction of this potential bias was addressed in analysis by comparing the two study groups (nursing home and non-nursing home elderly) by method of diagnosis. In Canada, approximately 80% of tuberculosis cases should be culture-proven (given the technology available). Obviously, if cases were overdiagnosed in either study group, the proportion of culture-proven (bacillary) cases would fall. Therefore, by comparing the proportion of bacillary cases in each study group, bias due to over diagnosis in either group was able to be estimated.

Confounding by particular variables may also have distorted the true estimate of effect and thus detracted from the internal validity of the study. By definition, a confounding variable must be associated with exposure, and independent of exposure must be a risk factor for the disease of interest (140). For this study, potential confounding variables (as outlined in section 2.2.2.3) included age, sex, country of birth/ethnic status and previous disease.

Two studies suggest that the risk of institution-

alization in a nursing home, increases with increasing age (117,118). If so, the age-distribution in the two study groups (nursing home and non-nursing home elderly) may have differed, with a greater proportion of older persons in the nursing home population. Tuberculosis case rates also increase with increasing age. Therefore the variable age may have acted as a confounder in this study. It is to be expected that confounding by this variable, would lead to an overestimation of the relative risk in the nursing home population. Potential confounding by this variable was controlled for in the analysis by means of stratification. That is, the data were stratified by levels of age (65-74, 75-84, 85+). The rationale of stratification for the control of confounding is that, within each stratum, the range of the stratification variable is restricted. Thus within strata, study subjects (exposed and unexposed) cannot differ much on the stratification variable, thus stratum-specific risk estimates are relatively free from potential bias due to this variable.

As demonstrated in figure 2, tuberculosis incidence in Canada rises progressively with age in men. For women the rates are similar to men up to age 30 years, then rise more slowly. Therefore, if sex-distribution in the two study groups (nursing home and non-nursing home elderly) differs, the variable sex could have acted as a confounder. The potential confounding effects of this variable was again

controlled for in analysis by means of stratification.

Tuberculosis case rates are approximately 26 times higher amongst indigenous Indians and Asian immigrants in Canada, than amongst the Canadian-born (non-Indian) population (126,127). Therefore, if the variable 'country of birth/ethnic status' is distributed unequally amongst the two study groups, there is potential for confounding by this variable. It is possible that residency in a nursing home was less likely for indigenous Indians and Asian immigrants - because of cultural differences - than for Canadian-born (non-Indian) persons. If so, unequal distribution of this variable amongst the study groups may potentially have led to lower case rates in the nursing home population because of the relative absence of high risk groups in the nursing home population. Thus any real difference in tuberculosis case rates between the two study groups as a result of exposure (residence in a nursing home) may have been obscured. To address confounding by this variable for each study group (nursing home and non-nursing home elderly) the proportion of cases by four ethnic groups - Asian immigrant, indigenous Indians (registered and unregistered), Canadian born (non Indian) and European immigrants were calculated and compared.

Previous disease is a recognized risk factor for tuberculosis. This variable may act as a confounder if

previous disease is also associated with exposure (residence in a nursing home). It is possible that elderly persons with compromised lung function (as a result of previous tuberculosis) were more likely to be admitted to nursing home facilities. If so, unequal distribution of the variable would have led to confounding in the direction of overestimating the tuberculosis case rate in the nursing home elderly population in this study. However, this may not be a reasonable assumption. Community surveys in British Columbia indicate that approximately 4% of persons aged 65 years or over show evidence of previous disease (24). A survey of nursing home residents also indicates that approximately 4% have evidence of previous tuberculosis disease (106). It seemed reasonable to assume that population figures for previous tuberculosis in the community and in nursing homes were similar in Alberta. If so, with equal distribution of this variable in the two study groups (nursing home and non-nursing home elderly), by definition, this variable could not act as a confounder. To address this issue, the proportions of cases with a history of previous disease in the two study groups were estimated.

External validity pertains to whether inferences drawn from the study are applicable to persons outside the study population. Clearly, internal validity of the study is a prerequisite for external validity. This particular study was population-based and the results reflect the

exposure-disease association in the province of Alberta. The question is whether the results are applicable to other nursing home populations outside the province. The answer to this question is a matter of informed judgement. Other populations would need to be compared to Alberta with respect to factors that may influence exposure and outcome. For example, nursing home facilities would need to be compared with respect to admission requirements and health regulations. Also, population differences, such as differences in the age, sex and ethnic composition of the general and nursing home populations, the background rate of tuberculosis disease and the accessibility and availability of health care in other study populations would all need to be considered.

For this particular study, the main concern was to achieve internal validity, as valid studies may be generalizable to a lesser or greater degree. Invalid studies are obviously not generalizable.

CHAPTER THREE

RESULTS

3.1 All Notifications

For the years 1979-83 in Alberta, 1074 cases of tuberculosis were notified to TB Services.

The 1981 mid-year census population of Alberta was 2,237,725 persons. Assuming this population estimate to be uniform for each year of study (1979-83), the number of person-years contributed to the study were (2,237,725 x 5) 11,188,625.

The overall rate for the general population was

$$= \frac{1074}{11,188,625} = \underline{9.6/10^5} \text{ person years (py)}$$

Of these 1074 cases, 210 (19.6%) occurred in persons aged 65 years or over.

The 1981 census population of over 65s in Alberta was 163,395. Therefore, the number of person-years contributed to the study by the over 65s were 816,975.

The overall rate for persons aged 65 years or over was equal to $\underline{25.7}/10^5$py.

Table 6. Tuberculosis case rate by place of residence in persons aged 65 years or over in Alberta, 1979-83.

Place of Residence	Cases	Population	Person-Years	Rate/10^5py
nursing home	12	6,454	32,270	37.2
non-nursing home	198	156,941	784,705	25.2
Total	210	163,395	816,975	25.7

The relative risk (that is, risk of tuberculosis associated with residence in a nursing home) was computed by calculating the quotient of the case rates for the nursing home and non-nursing home populations.

$$\text{Relative Risk (R.R.)} = \frac{37.2}{25.2} = \underline{1.47}$$

To test the difference between the nursing home and non-nursing home case rates, a test of significance using the following χ^2 statistic was used.

$$\chi^2 = \Sigma \frac{(\text{Observed-Expected})^2}{\text{Expected}}$$, which has 1 degree of freedom.

Expected values were based on the overall population rate

for the over 65s (see Appendix B). That is, with an overall rate of $25.7/10^5$py and 32,270py contributed by the nursing home population, we would have expected 8.29 cases in the nursing home population. For the non-nursing home population with 784,705py contributed we would have expected 201.67 cases. Using the above χ^2 formula, χ^2 was equal to 1.73 with a p value > 0.1. Therefore, we did not reject the null hypothesis (Ho) (that R.R. was equal to 1). The standard error (SE) for the relative risk was calculated using equation 1 (Appendix B).

$$SE(R.R.) = \frac{\sqrt{12}}{8.29} = 0.4174$$

A 95% confidence interval (C.I.) around the R.R. was calculated using equation 2 (Appendix B) and was equal to (0.65, 2.29).

In summary, the crude data provided a R.R. of 1.47 (95% C.I. 0.65, 2.29) with a non-significant χ^2 value of 1.73. On this basis, we did not reject Ho (R.R. = 1). That is, there was no reason to believe that nursing home and non-nursing home tuberculosis case rates were different.

As outlined in section 2.1.4, an important difference for the purposes of this study was a R.R. of four or more for the nursing home population. Using Beaumont and Breslow's formula for power in cohort studies (135) (see equation 4 Appendix B) this study had greater than 99.9% power to

detect a R.R. of four or more. Given the available sample size, the smallest R.R. that could have been detected with 80% power was 2.04.

3.1.1 Confounding

As outlined in section 2.5.4, possible confounding by certain variables - age, sex, ethnic status, previous disease - may have distorted the true estimate of effect. In this regard, the distribution of these variables in the two study populations was considered and any potential confounding was controlled for in analysis as follows.

3.1.1.1 Age

First, to determine whether the age-distribution was unequal amongst the study groups, age-distribution by 10-year strata were compared as follows.

Table 7. Age-distribution (as percentage of study population) by 10-year age-group in nursing home and non-nursing home elderly.

Age-Group	Nursing Home	Non-nursing Home	Ratio
65-74	15.9	61.5	0.26
75-84	38.5	29.8	1.29
85+	45.6	8.7	5.24
Total	100.0	100.0	

Age-distribution differed between the two study groups, therefore there was potential for confounding by this variable even if age-specific incidence rates were the same in nursing and non-nursing home residents. Potential confounding was addressed by stratification.

Table 8a. Comparison of age-specific case rates for nursing home and non-nursing home elderly in Alberta 1979-83.

	Nursing Home Elderly				Non-Nursing Home Elderly			
Age-Group	Population	Person-Years	Cases	Rate/10^5py	Population	Person-Years	Cases	Rate/10^5py
65-74	1,026	5,130	2	39.0	99,524	497,620	90	18.1
75-84	2,486	12,430	6	48.3	46,179	230,895	83	35.9
85+	2,942	14,710	4	27.2	11,238	56,190	25	44.5
Total	6,454	32,270	12		156,941	784,705	198	

Table 8b. Stratum-specific relative risk.

Age-Group	R.R.	95% C.I.	χ^2	P
65-74	2.15	(-0.83,5.13)	1.23	> 0.1
75-84	1.35	(0.27,2.43)	0.53	> 0.1
85+	0.61	(0.01,1.21)	0.99	> 0.1

There was an apparent trend in the risk estimates (that is, decreasing risk with increasing age). None of the stratum-specific (unconfounded) risk estimates was significant and 95% C.I.s were wide due to small sample sizes. A summary relative risk (adjusted for age) was equal to 1.01. (See Equation 3, Appendix B.)

3.1.1.2 Sex

To determine whether the sex-distribution was unequal amongst the two study groups, the proportion of females per 10-year stratum in each study group was determined and shown in Table 9.

Table 9. Per cent of females in the study groups.

Age Group	Nursing Home	Non-Nursing Home
65-74	55.8	53.2
75-84	65.6	54.9
85+	69.3	59.0
Overall	65.8	54.1

Sex distribution was unequal both overall and per 10-year stratum, between the two study groups. Therefore, the variable, sex, may have acted as a confounder. Potential confounding by the variable sex was first addressed by stratification. (See Table 10a.)

Table 10a. Comarison of sex-specific case rates for nursing home and non-nursing home elderly in Alberta 1979-83.

Sex	Nursing Home Elderly				Non-Nursing Home Elderly			
	Population	Person-Years	Cases	Rate/10^5py	Population	Person-Years	Cases	Rate/10^5py
male	2,209	11,045	4	36.2	72,036	360,180	113	31.4
female	4,245	21,225	8	37.7	84,895	424,475	85	20.0
Total	6,454	32,270	12		156,931	784,655	198	

Table 10b. Stratum-specific relative risks

Stratum	R.R.	95% C.I.	χ^2	p value
male	1.15	(0.01,2.29)	0.08	> 0.1
female	1.89	(0.58,3.20)	3.31	> 0.05

Neither stratum-specific risk estimate was significant. The 95% confidence intervals were wide and each contained the other stratum specific relative risk. Thus, on empirical grounds, the stratum specific relative risks appeared to be homogenous. The summary relative risk was equal to 1.55.

As both age-and sex-distributions were unequal amongst the study groups and both variables were potential confounders, the data was further stratified by age and sex. (See Table 11a)

Table 11a. Comparison of age-and sex-specific rates for nursing home and non-nursing home elderly in Alberta 1979-83.

	Nursing Home Elderly				Non-Nursing Home Elderly			
Male Stratum	Population	Person-Years	Cases	Rates/ 10^5py	Population	Person-Years	Cases	Rates/ 10^5py
65-74	453	2,265	1	44.2	46,602	233,010	54	23.2
75-84	854	4,270	1	23.4	20,821	104,105	46	44.2
85+	902	4,510	2	44.3	4,613	23,065	13	56.4
Total	2,209	11,045	4		72,036	360,180	113	
Female Stratum	Population	Person-Years	Cases	Rate/ 10^5py	Population	Person-Years	Cases	Rates/ 10^5py
65-74	573	2,865	1	34.9	52,917	264,585	36	13.6
75-84	1,632	8,160	5	61.3	25,348	126,740	37	29.2
85+	2,040	10,200	2	19.6	6,630	33,150	12	36.2
Total	4,245	21,225	8		84,895	424,475	85	

Table 11b. Stratum-specific relative risk.

Stratum	R.R.	95% C.I.	χ^2	p value
Male:				
65-74	1.91	(-1.79,5.61)	0.42	> 0.1
75-84	0.53	(-0.51,1.57)	0.42	> 0.1
85+	0.79	(-0.31,1.89)	0.11	> 0.1
Female:				
65-74	2.57	(-2.45,7.59)	0.95	> 0.1
75-84	2.10	(0.26,3.94)	2.88	> 0.05
85+	0.54	(-0.20,1.28)	0.77	> 0.1

None of the stratum-specific risk estimates were significant and confidence intervals were wide. Although there was an apparent increased risk in the 65 to 74 year age group (both male and female), it was not possible to conclude that the observed association was not due to chance. That is, the wide confidence intervals reflected the small numbers in some strata. Of the six nursing home strata, five contained two or less cases. Both male and female 65 to 74 age-strata in the nursing home population contained only one case, making interpretation difficult. A summary relative risk (adjusted for age and sex) was equal to 1.05 (non-significant), compared with the unadjusted

relative risk of 1.47. Thus, the data suggest that confounding by these variables in this study was present and was in the direction of overestimating the true relative risk.

3.1.1.3 Ethnic Origin

The variable 'ethnic origin' may have acted as a confounder if distribution of known high risk groups (Asians, indigenous Indians) was unequal amongst the two study groups. Reliable data on the nursing home population by ethnic group was not available. Therefore, tuberculosis cases by ethnic origin were compared between the study groups. (See Table 12).

Table 12. Comparison of tuberculosis cases in nursing home and non-nursing home elderly in Alberta 1979-83 by ethnic origin.

Ethnic Origin*	Nursing Home Cases (%)	Non-Nursing Home Cases (%)
Asian/other high risk countries	0(0)	37(18.7)
Indigenous Indian	3(25.0)	48(24.2)
Europeans and Canadian born non-Indian)	9(75.0)	107(54.0)
Total	12(100.0)	192(96.9)

*Ethnic status was unknown for 6 cases in the non-nursing home population.

If Asian or indigenous Indian persons had been under-represented in nursing home facilities, the true R.R. would have been under-estimated, as these ethnic groups are known high-risk groups for tuberculosis. Approximately 7,370 Asian persons and 2,512 indigenous Indians (registered and unregistered) were living in Alberta in 1981. (Sources: Statistics Canada, 1986 Census, Catalogue 93-154 and Research Branch, Corporate Policy, Department of Indian and Northern Affairs, Ottawa.) Potential confounding by this variable was addressed by recalculating tuberculosis case rates for White persons in both study groups, by removing Asian and Indian numerator and denominator data from both study groups. As regards denominator data, it was assumed

that 4% of Asian and Indian persons aged 65 years or over were resident in nursing home facilities. The percentage 4% was chosen, as overall, nursing home residents represented approximately 4% of the total population aged 65 years or over in Alberta. This was thought to represent a conservative estimate as it was believed that Asians and indigenous Indians were underrepresented in nursing homes because of cultural differences. Therefore, if ethnic groups had been equally distributed amongst the two study groups, 4% of persons aged 65 years or over in each ethnic group would have been resident in a nursing home facility. For this study this would have meant 295 Asian and 100 Indian elderly persons would have been resident in a nursing home.

The tuberculosis case rates for 'Whites' (that is, minus Asian and Indian numerator and denominator data) were equal to $29.7/10^5$py for the nursing home population and $14.5/10^5$py for the non-nursing home population. This gave a relative risk (unconfounded by Asian/Indian data) of 2.05 (0.71, 3.39). The risk estimate was nonsignificant and the upper limit of the 95% C.I. was less than four. In addition, the relative risk did not take into account confounding by the variables age and sex (that is, the relative risk was likely over estimated).

3.1.1.4 Previous Disease

The variable 'previous disease' is a known risk factor for tuberculosis disease, and thus may have acted as a confounder in this study if unequally distributed amongst the two study groups. Comparison of nursing home and non-nursing home cases by previous disease is shown in Table 13.

Table 13. Comparison of nursing home and non-nursing home tuberculosis cases in Alberta in 1979-83 by previous disease.

Previous disease	Nursing Home Cases(%)	Non-Nursing Home Cases(%)
yes	3(25.0)	62(31.3)
no	9(75.0)	136(68.7)
Total	12(100.0)	198(100.0)

Both study groups showed a similar distribution of cases by previous disease. Surveys of the community and nursing home elderly in British Columbia have shown that approximately 4% of both populations have evidence of previous disease. It seemed reasonable to assume that the situation in Alberta was comparable. Therefore, with equal distribution of this variable amongst the two study groups,

by definition, this variable could not have acted as a confounder. The similar distribution of cases by previous disease in this study appeared to confirm this.

3.1.1.5 Other Institutionalized Elderly

Of the 210 cases occurring in the elderly, 12 occurred in nursing home elderly, 8 occurred in elderly residents of lodges, 4 occurred in auxiliary hospital elderly and 1 occurred in an elderly resident of a mental institution. That is, 25 cases in total occurred amongst the 'institutionalized elderly'. Information on the elderly populations resident in these facilities was available (141). Case rates were then calculated by place of residence (see table 14).

Table 14. Tuberculosis case rates by place of residence.

Residence	Population	Person-Years	Cases	Rate/10^5py
nursing home	6,454	32,270	12	37.2
lodge	7,037	35,185	8	22.7
auxiliary hospital	2,800	14,000	4	28.6
mental hospital	929	4,645	1	21.5
total	17,220	86,1000	25	29.0

The overall 'institutionalized' rate for the over-65s was equal to 29.0/10^5py. The overall 'non-institutionalized' rate for the over-65s was equal to 25.3/10^5py. The crude relative risk associated with 'institutionalization' was equal to 1.15 (0.70, 1.60), moderately decreased from the crude R.R. calculated for the nursing home elderly only.

3.2 Bacillary (culture-proven) Notifications

Separate analyses were performed for bacillary (culture-proven) notifications to address the issue of surveillance bias. Of the 210 cases notified in persons aged 65 years or over, 162 (77%) were bacillary

(culture-proven). For nursing home elderly, 9 of 12 cases (75%) were culture-proven, while for non-nursing home elderly 153 of 198 (77%) were culture-proven.

Approximately 80% of all tuberculosis cases in Canada should be culture-proven (given the technology available) (142). Both study groups approached this figure (75% and 77% for nursing home and non-nursing home elderly respectively). If there had been surveillance bias or overdiagnosis in either study group, we would have expected the proportion of bacillary cases to fall in that study group. However, the proportion of bacillary cases for both study groups was similar and close to that expected in a developed country. Therefore, from these data it seems reasonable to conclude that surveillance bias is not likely in this study.

Table 15. Bacillary case rates for nursing home and non-nursing home elderly in Alberta 1979-83.

Residence	Population	Person-Years	Cases	Rate/10^5py
nursing home	6,454	32,270	9	27.9
non-nursing home	156,941	784,705	153	19.5
Total	163,395	816,975	162	19.3

The crude data for the bacillary notifications provided a R.R. of 1.47 with a 95% C.I. (0.49,2.37), essentially unchanged from the crude R.R. for all notifications, suggesting that surveillance bias was not a major issue in this study. The test of significance gave a χ^2 value of 1.17 ($p > 0.1$): therefore, we did not reject Ho. That is, there was no reason to believe that the nursing home and non-nursing home bacillary case rates were different.

Further analyses, to control for the same confounding variables outlined in the previous section, were performed for bacillary cases and follows below.

Table 16a. Comparison of age-specific bacillary case rates for nursing home and non-nursing home elderly in Alberta 1979-83.

Stratum	Nursing Home Elderly				Non-Nursing Home Elderly			
	Population	Person-Years	Cases	Rate/10^5py	Population	Person-Years	Cases	Rate/10^5py
65-74	1,026	5,130	1	19.5	99,524	497,620	64	12.9
75-84	2,486	12,430	4	32.2	46,179	230,895	68	29.5
85+	2,942	14,710	4	27.2	11,238	56,190	21	37.4
Total	6,454	32,270	9		156,941	784,705	153	

Table 16b. Stratum-specific relative risk.

Age-Group	R.R.	95% C.I.
65-74	1.51	(-1.47,4.49)
75-84	1.09	(0.03,2.15)
85+	0.73	(0.02,1.44)

The age-specific trend was less apparent than for all notifications. None of the stratum-specific relative risks were significant and the confidence intervals were wide reflecting the small numbers in some strata. A summary relative risk (adjusted for age) was equal to 0.92.

Table 17a. Comparison of sex-specific bacillary rates for nursing home and non-nursing home elderly in Alberta 1979-83.

	Nursing Home Elderly				Non-Nursing Home Elderly			
Stratum	Population	Person-Years	Cases	Rate/10^5py	Population	Person-Years	Cases	Rate/10^5py
male	2,209	11,045	2	18.1	72,036	360,180	92	25.5
female	4,245	21,225	7	33.0	84,895	424,475	61	14.4
Total	6,454	32,270	9		156,931	784,655	153	

Table 17b. Stratum-specific relative risks.

Stratum	R.R.	95% C.I.
male	0.71	(-0.27,1.69)
female	2.29	(0.58,3.99)

Neither stratum-specific risk estimate was significant and confidence intervals were wide. A summary relative risk (adjusted for sex) was equal to 1.53. Insufficient data were available to stratify bacillary cases by age and sex.

Table 18. Comparison of nursing home and non-nursing home bacillary cases by ethnic origin.

Ethnic origin*	Nursing Home Cases(%)	Non-Nursing Home Cases(%)
Asian/other high risk countries	0(0)	27(17.6)
Indigenous Indian	3(33.3)	42(27.5)
Europeans	2(22.2)	51(33.3)
Canadian born (non Indian)	4(44.4)	28(18.3)
Total	9(100)	148(96.7)

*Country of birth/ethnic origin was unknown for 5 cases (3.3%) in the non-nursing home elderly.

Distribution of bacillary cases by ethnic origin in the two study groups was essentially the same as the distribution of all cases by ethnic origin. An estimate of potential confounding by this variable was detailed in section 3.1.1.3.

Table 19. Comparison of nursing home and non-nursing home bacillary cases by previous disease.

Previous disease	Nursing Home Cases(%)	Non-Nursing Home Cases(%)
yes	2(22.2)	47(30.7)
no	7(77.7)	106(69.3)
Total	9(100)	153(100)

Both groups showed a similar distribution of bacillary cases by previous disease, essentially unchanged from the distribution of all cases by previous disease.

3.3 Distribution of Cases by Clinical Diagnosis

Pulmonary tuberculosis was the predominant diagnosis for all study groups, both for all notifications and for

bacillary cases only. No primary cases of tuberculosis were identified in either of the study groups. (See Tables 20 and 21.)

Table 20. All notified cases by diagnosis and by place of residence.

Diagnosis	Nursing Home	Other institutionalized Elderly	Non-institutionalized Elderly
	Cases(%)	Cases(%)	Cases(%)
pulmonary	10(83.3)	10(76.9)	140(75.7)
other respiratory	1(8.3)	1(7.7)	15(8.1)
miliary	1(8.3)	0	8(4.3)
adenitis	0	1(7.7)	9(4.9)
genito-urinary	0	0	6(3.2)
skeleton	0	0	1(0.5)
abdominal	0	0	3(1.6)
other	0	1(7.7)	3(1.6)
Total	12(100)	13(100)	185(100)

Table 21. Bacillary cases by diagnosis and by place of residence.

Diagnosis	Nursing Home	Other Institutionalized Elderly	Non-Institutionalized Elderly
	Cases(%)	Cases(%)	Cases(%)
pulmonary	8(88.9)	10(90.9)	116(81.7)
other respiratory	1(11.1)	0	5(3.5)
miliary	0	0	8(5.6)
adenitis	0	0	4(2.8)
genito-urinary	0	0	6(4.2)
skeleton	0	0	0
abdominal	0	0	2(1.4)
other	0	1(9.1)	1(0.7)
Total	9(100)	11(100)	142(100)

CHAPTER FOUR

DISCUSSION AND CONCLUSIONS

4.1 Discussion

The years 1979 to 1983 inclusive, were chosen for study, as reasonably complete and accurate population information was available for both study groups. The 1981 Census of Canada provided personal and demographic information on the general population. Information on elderly persons in Alberta was obtained from both a Senior Citizens Secretariat survey in 1981 (141) and the following government publication - Alberta Hospitals and Medical Care, Annual report, 1980/81. For Alberta in 1981, 7.3% of the general population were 65 years of age or over. Of these, 6,454 persons (3.9% of the over-65 population) were resident in nursing home facilities. This figure was similar to other studies which estimated that approximately 4-5% of persons aged 65 years or over were resident in long-term care facilites at any one time (119).

It seemed reasonable to assume that the population figures in 1981 represented a 'mean' population for each study group for the five years 1979-83. Person-years contributed to the study were, therefore, calculated by multiplying these population figures by five. A total of 816,975 person-years were contributed to the study - 784,705 person-years by the

non-nursing home elderly, 32,270 person-years contributed by the nursing home elderly.

Consistent with national figures for both Canada and the United States (26,36), in Alberta, over the five years of study, a disproportionate number of tuberculosis cases occurred in persons aged 65 years or over. Although constituting only 7.3% of the population, this age group gave rise to 210 cases, approximately 20% of all tuberculosis cases. The case rate for the general population was $9.6/10^5$py, whereas for those aged 65 years or over the rate was $25.7/10^5$py.

Twelve of the 210 cases occurred in the nursing home elderly (giving a case rate of $37.2/10^5$py) and 198 cases occurred amongst the non-nursing home elderly (giving a case rate of $25.2/10^5$py). This gave rise to a crude relative risk 1.47. That is the crude data suggested that residence in a nursing home was associated with a 1.47 times increased risk of developing tuberculosis disease compared to non-nursing home elderly. The χ^2 test of association ($\chi^2 = 1.73$) was not significant ($p > 0.1$). Therefore we did not reject (that is, we accepted) the null hypothesis (that R.R. = 1). That is, for this study, the nursing home elderly tuberculosis case rate was not shown to be different from the non-nursing home elderly tuberculosis case rate.

However, the objective of this study was not to determine

the exposure - disease association *per se*, but to determine whether the relative risk for tuberculosis for the nursing home elderly was four or more compared to the non-nursing home elderly. This factor of magnitude - four times - was chosen for both academic and practical reasons (see section 2.1.4 Determining an Important Difference). Therefore, the width of the 95% confidence interval (C.I.) was important, as the C.I. represented the range within which the true magnitude of effect lay with a 95% degree of assurance. The 95% C.I. for the R.R. of 1.47 was equal to 0.65-2.29. Therefore for the crude data, 95% of the time the true magnitude of effect was no greater than 2.29. In addition, this study had greater than 99.9% power to detect a relative risk of four or more.

An issue for this study was whether confounding by certain variables (age, sex, ethnic status, previous disease) may have distorted the true estimate of effect to the extent that the null hypothesis could have been rejected.

The age distribution in the two study groups was reversed, with approximately five times as many elderly aged 85 years or over in the nursing home population compared to the non-nursing home population. That is, the age-distribution differed between the two study groups. As increasing age is also associated with increasing rates of tuberculosis, there was potential for confounding by this variable. This was

addressed by stratifying the data on the variable age (by 10-year age groups). Stratum-specific relative risks (unconfounded by age) differed from the crude relative risk (1.43) and from each other. As seen in Table 8b, the stratum specific relative risks were as follows: 65-74 = 2.15, 75-84 = 1.35, 85+ = 0.61. The question was whether the stratum-specific risk estimates were homogeneous and not different from the crude relative risk or whether the risk estimates represented confounding and interaction by the variable age (as indicated by the apparent trend in risk estimates). No formal tests for homogeneity of relative risks are readily available from the published literature. However, the following suggested that the stratum-specific risk estimates were likely homogeneous. First, none of the stratum-specific relative risks were significant (at the 5% level). Secondly the 95% confidence intervals were wide, particularly for the 65-74 age group, reflecting small sample sizes and thus greater variance in the estimation of effect. In the 65-74 stratum, only two cases were present in the (exposed) nursing home elderly population. If, however, only one case had occurred in this stratum, the stratum-specific risk estimate would have decreased to 1.08 and the apparent trend would have disappeared from the data. From the point of view of biologic plausibility it is also difficult to argue why there should have been any trend with increasing age. Both age groups (65-74 and 85+) had

lived during an endemic, untreated era of tuberculosis. That is, both age groups were likely to have been exposed to and infected by Mycobacterium tuberculosis. Thus both age groups were likely to have had similar susceptibility (all things being equal) to tuberculosis disease. Empirical evidence suggests, therefore, that the apparent trend in relative risks with age was not likely to be statistically significant. A summary relative risk (adjusted for age) was equal to 1.01 and non significant.

However, it was unreasonable to consider confounding by the variable, age, in isolation, as another potential confounding variable, sex, is obviously interrelated with age. The sex-distribution of the two study groups differed with a greater percentage of females (overall and for each 10-year age group) in the nursing home elderly population. This variable may, therefore, have acted as a confounder; thus the data were stratified by sex. Stratum-specific risk estimates were shown in Table 10b (male = 1.15, female = 1.89). The data suggested that the two risk estimates were not significantly different from each other or from the crude relative risk. Each 95% confidence interval contained the other stratum-specific relative risk. Neither stratum-specific risk estimate was significant and although confidence intervals were wide, neither upper limit approached 4.0. The two relative risks were thus considered homogenous, and a summary relative risk (adjusted for sex)

was equal to 1.55.

However, as the variables, age and sex, were interrelated, potential confounders and unequally distributed amongst the study groups, the data was stratified by both age and sex. Stratum-specific relative risks adjusted for age and sex are shown in Table 11b. Interpretation of these data was difficult because of the small sample sizes. Of the six nursing home strata, five contained two or less cases. As a result 95% confidence intervals were wide. None of the stratum-specific risk estimates was significant. The only confidence intervals with upper limits greater than 4.0 occurred in both male and female 65-74 strata. However both these nursing home strata contained only one case and this was reflected in the wide confidence intervals. In addition, neither risk estimate was significant at the 5% level. The summary relative risk (adjusted for both age and sex) was equal to 1.05.

Therefore, after stratifying on both age and sex, the data suggested that confounding by these variables in this study was in the direction of overestimating the true relative risk. That is, the crude relative risk which suggested a 1.47 times increased risk of tuberculosis amongst the nursing home elderly may have been an overestimation. When controlling for age and sex the unconfounded relative risk was equal to 1.05 suggesting that there was essentially no

difference in the risk of tuberculosis for the two groups of elderly (nursing home and non-nursing home).

The variable, ethnic status, may have acted as a potential confounder if Asian/Indian persons (known high risk groups) were underrepresented in the nursing home population. By removing Asian/Indian numerator and denominator data (assuming 4% of all ethnic groups were resident in nursing homes) and calculating 'White' tuberculosis case rates for the two study groups, an estimate of confounding by this variable was made. The recalculated R.R. was equal to 2.05 (95% C.I. 0.71, 3.39), a moderate increase from the crude R.R. of 1.47. The R.R. was not significant and the upper limit of the 95% C.I. was less than four. In addition, this risk estimate did not take into account the effect of confounding by the variables age and sex and thus was likely overestimated.

Confounding by the variable, previous disease, was considered to be unlikely. Both study groups showed a similar distribution of tuberculosis cases by previous disease. In addition, previous surveys in British Columbia of the general population and the nursing home population (24,106) had indicated that approximately 4% of persons aged 65 years or over in both populations had chest x-ray evidence of previous tuberculosis disease. It seemed reasonable to assume that population surveys in Alberta

would have been comparable. Thus with equal distribution of this variable amongst the two study groups, by definition, this variable could not have acted as a confounder. The similar distribution of cases by previous disease in both study groups appeared to confirm this.

The final potential source of bias related to tuberculosis cases amongst those elderly institutionalized in a facility other than a nursing home. If institutionalization *per se* was the risk factor for tuberculosis, inclusion of numerator and denominator data from other institutionalized elderly in the non-nursing home population may have led to an underestimation of the true exposure - outcome association.

The overall case rate for the 'institutionalized' elderly was equal to $29.0/10^5$py, whilst the overall case rate for the 'non-institutionalized' elderly was equal to $25.3/10^5$py. Therefore, the relative risk associated with 'institutionalization' was equal to 1.15 (95% C.I. 0.70, 1.60), moderately decreased from the relative risk associated with nursing home residence only (R.R. = 1.47). Therefore, inclusion of 'institutionalized' cases with the non-nursing home data obviously did not lead to an underestimation of the true relative risk, far less to the extent that the null hypothesis may have been rejected. For this study, the crude data suggested that institutionalization *per se* was not a risk factor for tuberculosis in the elderly. Also

relevant was the fact that it was studies on the nursing home elderly - not the institutionalized elderly - which stimulated this research to determine whether tuberculosis case rates were significantly increased amongst the nursing home elderly population in Alberta.

For developed countries such as Canada, given the technology available, approximately 80% of tuberculosis cases should culture-proven (bacillary). For this particular study, overall, 162 of 210 cases (77%) were bacillary. More importantly, for both study groups (nursing home and non-nursing home elderly) the proportions of tuberculosis cases culture-proven were 75% and 77%, respectively, both close to the 'gold standard' of 80%. The interpretation of such data is that surveillance bias in either study group was unlikely.

The relative risk for bacillary cases was 1.43 (95% C.I. 0.49,2.37). Therefore, for definitive cases of tuberculosis, the risk estimate was essentially unchanged from the previous (crude) overall relative risk. Again the relative risk was not significant and 95% of the time the true magnitude of effect was no greater than 2.37. Therefore based on the overall bacillary data we did not reject the null hypothesis (R.R. = 1).

Potential confounding by the variables previously outlined was addressed as before. Stratum-specific risk estimates

for the 10-year age groups for bacillary cases were essentially unchanged from those for the overall data. The trend in relative risks was less apparent. The increased risk estimate in the 65-74 group was based on only one case in the nursing home population, and was reflected in the wide 95% C.I. The summary relative risk (adjusted for age) was equal to 0.92.

Sex-specific risk estimates for bacillary cases (see Table 17b) differed from those for overall data. For males, the risk estimate decreased (from 1.15 to 0.71), whilst for females the risk estimate increased (from 1.89 to 2.29). These changes in the risk estimates and any difference between them was likely due to chance given the small sample sizes. For nursing home males two of four cases (50%) were culture-proven, whilst for nursing home females, seven of eight cases (87.5%) were culture-proven. In comparison, for the non-nursing home population, for males, 81% of cases were culture-proven, whilst for females 72% of cases were culture-proven. It seemed reasonable to assume that once a suspect active case was identified, efforts for definitive diagnosis would have been similar for both study groups and within study groups, similar for both males and females.

Therefore, hypothetically, if the proportion of culture proven cases in the non-nursing home population had been similar for the nursing home population, we would have

expected 3.25 bacillary cases for males and 5.75 bacillary cases for females in the nursing home population. If case rates were then calculated using these hypothetical data, stratum-specific bacillary risk estimates for males and females would have been almost identical to those for the overall data. That is, the stratum-specific (bacillary) relative risk for males would have been 1.15 and for females would have been 1.88. Therefore, the differences between the sex-specific risk estimates for the bacillary data and the overall data probably reflected the small numbers in the nursing home strata. Neither stratum-specific risk estimate was significant and a summary relative risk (adjusted for sex) was equal to 1.53.

The possibility that the bacillary stratum-specific risk estimates by sex may have been confounded by the variable age, could not be addressed as there were insufficient data to stratify by both age and sex.

The proportions of bacillary cases by ethnic origin for the two study groups (see Table 18) were essentially the same as for all notified cases. The potential confounding associated with the variable, ethnic origin, was adequately addressed when considering all cases.

Lastly, both study groups showed a similar distribution of bacillary cases by previous disease. As outlined earlier, it was unlikely that this variable acted as a confounder in

this study.

From section 3.3 it was shown that pulmonary tuberculosis was the predominant diagnosis for both study groups. This was so, both for all notifications and for bacillary cases only. No cases of primary tuberculosis were identified in either study group. Therefore, this study did not confirm the findings of previous studies which suggested that primary tuberculosis was common amongst the nursing home elderly (128).

In conclusion, this study was unable to demonstrate that residence in a nursing home was associated with an elevated risk of tuberculosis in elderly Albertans. That is, this study was unable to determine a difference in the tuberculosis case rates between the nursing home and non-nursing home elderly. The crude relative risk of 1.47 (nonsignificant) was marginally confounded by the variables age and sex (in the direction of overestimation) and the variable ethnic status (in the direction of underestimation). For the crude data, 95% of the time the true magnitude of effect was no greater than 2.29. The data were sufficient to have had 99.9% power to detect a relative risk of four or more.

Both study groups had equal proportions of culture-proven notified cases (close to the 'gold standard'). This suggested that surveillance bias was unlikely in this

study.

4.2 Conclusions

4.2.1 Comparison of Studies of Institutionalized Elderly

As outlined in section 1.5 (Tuberculosis and the Institutionalized Elderly) several studies had suggested that tuberculosis was endemic in nursing home facilities with both nosocomial spread and epidemic outbreaks of tuberculosis disease having occurred amongst the residents (128-133). This study did not confirm such findings. The relative risk for this study was equal to 1.47 (95% C.I. 0.65-2.29) and was not significant at the 5% level. That is, this study was unable to determine a difference in the tuberculosis case rates between the nursing home and non-nursing home elderly. Also, 95% of the time the true magnitude of effect would be found to be no greater than 2.29 that is, less than 4. The factor of magnitude of interest - four times - was chosen both in reference to the previous studies (132,133), and also with respect to the cost-efficiency of tuberculosis screening (see section 2.1.4 Determining an Important Difference).

For this study, the relative risk for tuberculosis amongst the nursing home elderly was lower (by a factor of two to four times) than the relative risks estimated in previous

studies. This obvious discrepancy in risk estimates needs to be considered, and may essentially be related to study validity. For this particular study, the efforts to minimize bias and control for confounding, thereby increasing the internal validity of the study, have been detailed in section 2.5.4 (Validity).

For previous studies, it is possible that bias may have distorted the true estimate of effect resulting in an overestimation of the relative risk for nursing home elderly. For example, in the seminal paper by Stead *et al*, on a tuberculosis epidemic in a nursing home facility (128), the study results suggest surveillance bias. Only three of eight cases (37.5%) in the nursing home were culture-proven. As outlined earlier, given the technology available, in developed countries, at least 80% of tuberculosis cases should be culture-proven. The low percentage of bacillary cases suggest surveillance bias or overdiagnosis. Also in this regard, chest x-ray diagnoses (presumptive of tuberculosis) were made 'unblinded' by the sole author.

Potential biases were also evident in the subsequent prospective cohort study which determined tuberculosis cases in the nursing home elderly in Arkansas (132). First, follow-up investigation (tuberculin skin testing) of residents was neither random nor complete. Rather,

investigation of residents was based on whether a case or suspect active case of tuberculosis was discovered in particular facilities. Surveillance bias, therefore, was an obvious possibility. Therefore, it may not have been valid to conclude that there was a greater proportion of skin test 'convertors' in nursing homes in which a previously documented case of tuberculosis had occurred. The proportion of culture-proven cases was also not reported. However, the fundamental methodologic flaw in the study (132) was the lack of an equivalent, unexposed (that is, non-nursing home elderly) cohort. Tuberculosis case rates for the non-nursing home elderly were estimated from public health notifications which were voluntarily reported. Also, the community elderly were not initially investigated (with skin test and chest x-ray) nor followed prospectively over three years for the development of active disease. Obviously, the two cohorts were incomparable. Therefore, any risk estimate comparing the risk of tuberculosis amongst nursing home and non-nursing home elderly was likely to be inaccurate. Even if the cohorts had been comparable, risk estimates did not take into account the effect(s) of potential confounding variables.

The higher tuberculosis case rates amongst the Tennessee nursing home elderly (133) were likely overestimated as a result of differential misclassification. Exposure status (nursing home, non-nursing home) for annual notified cases,

was not defined as residence at the the time of diagnosis, but rather a persons complete residential history. Therefore, tuberculosis disease in a person diagnosed at home with a history of several weeks in a nursing home facility 20 years previous, was categorized as a nursing home case. Approximately 20% of persons aged 65 years or over are resident at some time in a nursing home (119). Therefore this differential misclassification of cases was likely to have resulted in an overestimation of the case rate amongst the nursing home elderly.

In summary, the discrepancy in risk estimates (for nursing home elderly) between this study and previous studies, may be due to methodologic differences among the studies. It may be argued that previous studies overestimated the relative risk for nursing home elderly as a result of systematic error in the study design or analysis. For this study, potential systematic errors in design and analysis were addressed thoroughly, possibly giving this study greater internal validity. However, this study does not represent the definitive study of tuberculosis amongst the nursing home elderly. The most obvious study deficiency is the small number of tuberculosis cases amongst the nursing home elderly population. This made detailed analysis (that is, controlling for confounding) more difficult. However, the objective of this study was not to determine the precise relative risk for tuberculosis amongst the nursing home

elderly, but rather whether the relative risk was four (or more) times amongst the nursing home elderly. This study was unable to determine a difference in the tuberculosis case rates between the nursing home and non-nursing home elderly in Alberta (under Ho that R.R. = 1). Also 95% of the time, the true magnitude of effect (that is, R.R. for nursing home elderly) would be found to be no greater than 2.29.

Further studies are required to confirm these findings. Consistency of findings in different studies, by different investigators at different times, is one of the criteria used in the judgement of the validity of an hypothesis (134). Therefore, studies of tuberculosis amongst the nursing home and non-nursing home elderly in other provinces are required to determine whether the risk estimate for tuberculosis amongst the nursing home elderly in Alberta is comparable to the risk estimates for nursing home elderly in other provinces.

4.2.2 Etiology of a Tuberculosis Epidemic

Another criterion in the judgement of the validity of an hypothesis is biologic plausibility (134). From this perspective it may be argued that epidemic outbreaks of tuberculosis are unlikely to occur amongst the nursing home elderly. The dynamics of a tuberculosis epidemic requires

in the first place, that a large proportion of the group of individuals exposed to tuberculosis must not be previously infected (143).

However, the majority of todays elderly are likely to have been infected, given the 1930s tuberculin surveys in North America which showed that approximately 80% of persons had been infected with tuberculosis by the age of 30 years (132). A definitive review of tuberculosis epidemics (143), studied reports of 109 epidemic outbreaks. Approximately 75% occurred in previously uninfected school children ('school epidemics'). The remaining 25% of epidemic outbreaks involved young, tuberculin-negative adults (several in closed environments e.g., naval ships). No epidemic outbreak involving elderly persons was reported.

Epidemic outbreaks in nursing homes would therefore have to represent first, preferential survival of uninfected persons and secondly, preferential distribution of these susceptible persons into nursing homes. There is no good evidence in the literature to substantiate either of these concepts.

4.2.3 Significance of this Study

As outlined in section 2.1.4 (Determining an Important Difference), a relative risk of four or more for

tuberculosis amongst the nursing home elderly of Alberta would result in a case rate of greater than 1/1000/year for this elderly sub-group. If this were so, screening of the nursing home elderly for tuberculosis might be justified. Two criteria for determining whether a disease is appropriate for screening are that the disease should be serious, and the disease should be prevalent amongst the population being screened (144).

With regard to the former criterion, tuberculosis is a serious disease both for the individual and the community. If untreated, 25% of persons with tuberculosis die within two years, and 25% go on to become chronic excretors of tubercle bacilli (102). Therefore, if the individual is untreated, spread of infection (and subsequent risk of disease) continues throughout the community. As a rule of thumb, screening for tuberculosis is thought to be cost-efficient at case rates of greater than 1/1000/year ($100/10^5$py) - four times the overall tuberculosis case rate for the over 65s in Alberta. Therefore, if the relative risk for tuberculosis amongst the nursing home elderly in Alberta was equal to four or more (compared to the non-nursing home elderly), tuberculosis could be considered sufficiently prevalent in the nursing home elderly population to satisfy the second criterion.

Guidelines for surveillance of persons in residential care

facilities are in place both on a national and provincial level (142,145). The issue is whether screening of these elderly residents at the time of admission, plus on-going surveillance for tuberculosis, is justified.

This study was unable to determine a difference in the tuberculosis case rates between the nursing home and non-nursing home elderly in Alberta. The range of estimate in the case rate for nursing home elderly was from $16.4/10^5$py to $57.7/10^5$py. Even if we were to accept the upper limit of the range, $57.7/10^5$py, this case rate is still well below $100/10^5$py - the minimum case rate at which tuberculosis screening is thought to be justified. Therefore, on the basis of this study, it may be argued that tuberculosis is not sufficiently prevalent amongst the nursing home elderly of Alberta to justify active surveillance programs for tuberculosis. In addition, only one of the tuberculosis cases amongst the nursing home elderly was identified by screening at the time of admission of the resident into the nursing home. Surveillance for tuberculosis requires several diagnostic tools - tuberculin skin tests, chest x-ray and sputum examination. It seems cost inefficient to screen 6,454 persons each year in order to identify one new active case of tuberculosis every 5 years.

The findings of this study, however, must be considered in

the context of the low prevalence of tuberculosis (over all ages) in the province of Alberta. It is possible that a similar study in an area with high prevalence of tuberculosis, may not give rise to similar findings, and draw the same conclusions as this study.

From the other perspective there is also evidence that care facilities in Alberta are not fully compliant with the guidelines for tuberculosis surveillance as recommended by Tuberculosis Services. A survey of 37 care facilities in Alberta indicated that only 22% of those facilities had written policies and procedures for tuberculosis surveillance. As a result, only approximately 50% of newly admitted residents were actively screened for tuberculosis (19% by tuberculin test, 31% by chest x-ray). Over one-fifth of all facilities reported no ongoing surveillance for tuberculosis (146).

Therefore, in conclusion, given both the low prevalence of tuberculosis and the apparent lack of systematic surveillance for tuberculosis in the nursing home facilities in Alberta it may be argued that a surveillance program for tuberculosis in this elderly sub-group is unwarranted. This would allow more rational allocation of these health care resources - to higher risk groups - in the effort to prevent and control the spread of tuberculosis disease.

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APPENDIX A

INTAKE/UPDATE QUESTIONNAIRE

TUBERCULOSIS SERVICE

Alberta

INTAKE / UPDATE

☐ X-RAY REQUEST

DATE OF INTAKE YY MM DD | AHCIC | HEALTH UNIT | SUB OFFICE | DATE OF BIRTH YY MM DD | OTHER FILE NO | NAME CHECK | TB FILE NO

NAME SURNAME | FIRST | INITIAL | OTHER (MAIDEN, ALIAS) | SEX ☐M ☐F

ADDRESS | POSTAL CODE | PHONE NO

MARITAL ☐M ☐S ☐D ☐W ☐C/L ☐SEP | ETHNIC ORIGIN ☐METIS ☐INUIT ☐TR. ☐OTHER (SPECIFY) | BAND AND NO.

COUNTRY OF BIRTH | ARR. IN CAN YEAR | OCCUPATION | NEXT OF KIN | PHONE NO

CORRESPONDANCE TO REFERRING DOCTOR: | ADDRESS | POSTAL CODE

COPY TO PATIENT ☐YES ☐NO | COPY TO OTHER: | ADDRESS | POSTAL CODE

REASON FOR REFERRAL ☐IMMIG. ☐EMPLOY. ☐SCHOOL ☐POST SECD. ☐DOCTOR ☐SELF ☐HEALTH UNIT ☐LAB ☐POSTMORTUM ☐OTHER (SPECIFY)

SOURCE CASE YEAR ☐CONTACT ASSOCIATION ☐CLOSE ☐CASUAL

TUBERCULIN LAST NEG YY MM DD | FIRST POS YY MM | CURRENT YY MM DD | BCG ☐U/K ☐NO ☐YES YEAR ☐SCAR

CLINICAL ☐IMMUNOSUPPRESSED ☐OTHER SPECIFY: | PREVIOUS T.B. ☐YES ☐NO YEAR | PROV/COUNTRY | PREVIOUS MEDICATION ☐YES ☐NO ☐ACTIVE ☐PREVENT

ADDITIONAL INFORMATION | HEALTH UNIT STAMP

SIGNATURE OF HEALTH NURSE

DO NOT WRITE BELOW THIS LINE

CONSULTATION

T B S DOCTOR: _____

T.B. DIAGNOSIS (✓)

☐ACTIVE ☐SUSPECT ACTIVE

☐INACTIVE ☐PRESUMED INACTIVE

SITE _____

TYPE _____ YR. ACT. _____

TREATMENT ADEQUATE?

☐YES SPECIFY _____

☐NO SPECIFY _____

NON-CASE (✓)

☐CONTACT ☐NON CONTACT

☐BCG REACTOR ☐REACTOR ☐NON-REACTOR

PROPHYLAXIS: ☐YES ☐NO

TREATMENT ADEQUATE ☐YES ☐NO

ACTION (✓) SPECIFY/DATE YY MM DD

☐X-RAY _____

☐SPUTUM _____

☐CBC/PLATELETS _____

☐AST _____

☐TUBERCULIN _____

☐INIT/CONT TREATMENT _____

☐SYMPTOM INQUIRY _____

☐VISUAL TESTS _____

☐REPORT COMLIANCE _____

☐OTHER (_____) _____

☐NO FURTHER INVESTIGATION REQUIRED UNLESS EXPOSED TO T B OR SYMPTOMS OF ILL HEALTH APPEAR OR AS REQUIRED BY A SPECIFIC PROGRAM

INTERIM TREATMENT SUMMARY

DIAGNOSIS: DATE:

METHOD OF DIAGNOSIS:
SPECIMEN SMEAR CULTURE DATE

SENSITIVITIES:

OTHER:

IN HOSPITAL TREATMENT: DURATION:

OUT PATIENT TREATMENT: DURATION:

COMPLIANCE/COMMENTS: TOTAL TREATMENT:

☐ DECEASED DATE: ☐ TUB. DEATH ☐ NON TUB. DEATH

CDH 1936 (88/1/2M)

APPENDIX B

EQUATIONS

Appendix B

Expected Values

	Cases	Persons-Year
Nursing Home	D_1	N_1
Non-Nursing Home	D_0	N_0
	D	N

Expected values are calculated as follows:

$$E_1 = (D/N)N_1$$

$$E_0 = (D/N)N_0$$

Chi-square Statistic

Let $R_1 = D_1/N_1$ and $R_0 = D_0/N_0$. Then the rate ratio (or relative risk) is $RR = R_1/R_0$. A test of $H_0 : RR = 1$ is given by

$$\chi^2 = \frac{(D_1 - E_1)^2}{E_1} + \frac{(D_0 - E_0)^2}{E_0} \quad \text{d.f.} = 1$$

Equation 1

$$RR = \frac{R_1}{R_0} = \frac{D_1/N_1}{D_0/N_0} = \frac{D_1}{R_0 N_1}$$

If we assume that D_1 is a Poisson random variable then $Var(D_1) = E(D_1)$. If we assume that R_0 and N_1 are relatively error-free compared to D_1 then $R_0 N_1$ can be treated as a constant. This implies that

$$Var(RR) = Var\left(\frac{D_1}{R_0 N_1}\right) = \left(\frac{1}{R_0 N_1}\right)^2 Var(D_1)$$

$$= \left(\frac{1}{R_0 N_1}\right)^2 E(D_1)$$

$$\widehat{Var}(RR) = \left(\frac{1}{R_0 N_1}\right)^2 D_1$$

$$\widehat{SE}(RR) = \frac{\sqrt{D_1}}{R_0 N_1}$$

Equation 2

A 95% confidence interval for RR is

$$RR \pm 1.96SE(RR).$$

Equation 3

A summary RR is $\sum w_i RR_i$, where the summation is across all strata, and where the weights are given by

$$w_i = \frac{E_{1i}}{\sum E_{1i}}.$$

The E_{1i} are the expected number of nursing home cases, computed as above.

Equation 4

Beaumont and Bleslow's formula for power in cohort studies is

$$z_\beta = 2(RR^{1/2} - 1)E^{1/2} - z_\alpha$$

where

$RR = RR$ of interest

$E =$ Expected number of cases (computed as above)

$\alpha = 0.05$,

$z_\alpha = 1.96$ two-sided.)