Epidemiology of Tuberculosis in Manitoba

(1992 – 1997)

By

Assaad Al-Mouaiad Al-Azem M.B, Ch.B

A Thesis

Submitted to the Faculty of Graduate Studies

In Partial Fulfillment of the Requirements for

The Degree of

MASTER of SCIENCE

Department of Medical Microbiology

University of Manitoba

Winnipeg, Manitoba

THE UNIVERSITY OF MANITOBA

FACULTY OF GRADUATE STUDIES

*****

COPYRIGHT PERMISSION PAGE

Epidemiology of Tuberculosis in Manitoba (1992-1997)

BY

Assaad Al-Mouaiad Al-Azem

A Practicum submitted to the Faculty of Graduate Studies of The University of Manitoba in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

Acknowledgments

I would like to thank the following people who all contributed to this work in unique and valuable ways

❀ **My advisor,** Dr. Amin Kabani

❀ **My Committee Members,**

Dr. Earl Hershshfield, Dr. Jure Manfreds, and

Dr. Daryl Hoban.

❀ **Tuberculosis Registry Office Staff**

Joann MacMorran, Sonja Olien,

Sharon Flecher, Gabriella Olien.

❀ **Clinical Microbiology Laboratory Staff**

Joyce Wolfe, Lori Takada

❀ **My Friends**

Kim Nichol, Meenu Sharma, Christine Turenne,

Francis Muu.

❀ **My Family**

My Late Father Dr. Mouin Al-Mouaiad Al-Azem

My Mother Izdihar El-Ismail

All My Family Members

Table of Contents

Table of Contents, continued

Table of Contents, continued

Table of Contents, continued

Table of Contents, continued

List of Tables

Page

8 - Molecular Epidemiology of Tuberculosis in Manitoba

List of Figures

Abstract

Tuberculosis in Manitoba is experiencing a declining trend, with a new tuberculosis rate between 1992 and 1997 of 9.2 per 100,000 person–year. Nevertheless, the value still significantly exceeds the 1995 national incidence rate of 6.5 per 100,000.

The use of conventional and molecular epidemiology shows that between 1992 and 1997 there were 610 tuberculosis patients in Manitoba, 178 of which were non-treaty, 261 of which were treaty and 171 of which were foreign-born individuals. In Manitoba, foreign-born tuberculosis patients represented 28% of the total tuberculosis cases. Treaty subgroup patients, with 42.8% of all tuberculosis cases in Manitoba, comprised the largest group of cases despite the fact that they represent only 8.9% of Manitoba's population. Remarkably, the incidence rate of tuberculosis among these individuals was an astonishing 44.3. In comparison, non-treaty patients represented 78.1% of the population but enjoy the low tuberculosis incidence rate of 3.5 per 100,000 person-year. In general, Incidence rates among the three population subgroups increase with age.

Among Manitoba tuberculosis cases with isolates, 194 different fingerprints types were identified. Thirty-six of the fingerprints occurred in cluster form while 158 occurred as unique fingerprints. The dominance of a single fingerprint (FP1) was found in 24.0% (115) of cases with isolates

(Chapter 8, Table 3) and was observed to mainly infect Canadian-born patients (Chapter 8, Table 5). Clustered fingerprints indicate the existence of outbreaks and, in addition, it gives us an idea about the extent of secondary spread. Four different clustered fingerprints infected all three population subgroups, although it remains unknown why these fingerprints infect all population subgroups and others do not. Eight fingerprints in Manitoba infected foreign-born people only, while 5 infected treaty patients. Only one fingerprint was found exclusively in non-treaty individuals.

Tuberculosis in Manitoba can be divide into two facets, domestic and imported. Domestic tuberculosis is so named because the source of both the strain as well as the subjects their place of exposure or infection is Manitoba. Since geography or physical distance cannot provide a barrier to stop the spread of this disease, the type of contact and relationship among individuals appear to be very important factors in the spread of this disease.

In conclusion, this study has described the advantages and disadvantages of a molecular fingerprinting technique, the status of tuberculosis in Manitoba and the contribution of molecular fingerprinting to the knowledge and understanding of this problem. The foundation for further research has also been suggested by this study.

1

Epidemiology of Tuberculosis in Manitoba

(1992 – 1997)

Objectives

1 Epidemiology of Tuberculosis in Manitoba from 1992 to 1997.

2 Molecular Epidemiology of Tuberculosis in Manitoba from 1992 to 1997.

2

Tuberculosis in Manitoba

2.1 Background

2.1.1 Introduction

Tuberculosis (TB) is a disease that has coexisted with humanity since time immemorial. Reports of this disease in Egyptian mummies date as far back as 4000 BC. Infection by *Mycobacterium tuberculosis*, the causative organism of tuberculosis, often occurs at an early age. Although the majority (90%) of these early infections become dormant, 5% of infected people develop the disease immediately. In the remaining 5%, development of the disease occurs much later (Fanning, 1998; Piheu, 1998).

Tuberculosis carries a heavy toll on its victims. In 1650, 20% of all urban deaths in England and Wales were related to tuberculosis (Hart et al, 1996). Canadians similarly suffered tremendously from this disease. One out every five Canadians in the 19th century had tuberculosis and the disease often killed large numbers of its Canadian victims. In 1924, the mortality rate in Canada due to tuberculosis was 84 per 100,000 (CCDR, 1998). The 1964 Royal Commission on Health Services Report (tuberculosis in Canada) established that tuberculosis incidence rates in Manitoba were 90/100,000 in 1937, peaked during the second

world war at 213/100,000, then declined markedly to 31/100,000 by 1962 (Wherrett, 1964).

HIV/AIDS infection has further augmented the spread of tuberculosis and in 1993, the World Health Organization (WHO) for the first time issued a warning proclaiming tuberculosis a global emergency (CCDR, 1998). With the rapid rise of drug resistant *Mycobacterium tuberculosis*, especially in developing countries, tuberculosis will continue to be a serious challenge not only for health care providers and planners, but also for the ordinary person in terms of morbidity and mortality.

2.1.2 Burden of the disease

2.1.2.1 Globally

Approximately 1.7 billion people worldwide (one third of the world population) are infected with *Mycobacterium tuberculosis*. In 1990, the global prevalence of tuberculosis was 20 million cases while the incidence was 8 million cases. Third world countries accounted for 95% or 7.6 million new cases, while developed countries accounted for the remaining 5% or 400,000 new cases. According to a WHO report, out of the 8 million new cases, 2.6 million occurred in the Western Pacific, 2.5 million in South East Asia, and 1.4 million in Africa (Kochi, 1991). WHO predicts that these figures will increase by an astonishing 36% to 10.2 million cases by the year 2000 (which corresponds to 3.9 million new cases in South East Asia, 2.3 million in the Western Pacific and 2.1 million in Africa).

Assuming that tuberculosis control programs remain at their 1990 capacity, the incidence of tuberculosis will increase to 11.9 million by the year 2005 (Dolin et al, 1994; Raviglione et al, 1995).

There is a fundamental difference in age distribution between tuberculosis patients in the third world countries and in industrialized nations. In the former, for example, the majority (75%) of patients tend to fall between the productive ages of 15 and 59. Conversely in the developed countries, tuberculosis affects mainly disadvantaged individuals, most (80%) of whom are at least 50 years of age (Kochi 1991).

Prior to the introduction of anti-tuberculous medication, the mortality rate for individuals with tuberculosis was approximately 50-60% (Raviglione et al, 1995). In 1990, relatively fewer individuals perished from the disease. Nevertheless, 2.9 million deaths were still attributable to tuberculosis, making it the single biggest killer in the world. Of these deaths, 940,000 occurred in South East Asia, 890,000 in the Western pacific and 660,000 in Africa. In comparison, only 40,000 deaths occurred in industrialized countries (Kochi, 1991; Raviglione et al, 1995). Four and half percent of tuberculosis death attributed to HIV/AIDS effect and this percents will increase to 14% of total tuberculosis deaths by the year 1999 (Dolin et al, 1994; Raviglione et al, 1995).

The future incidence and mortality of tuberculosis is expected to worsen. Factors contributing to this deterioration include the rapid increase in population, famine, wars, natural disasters, the HIV/AIDS epidemic and drug resistant *Mycobacterium tuberculosis*. In addition, the combination of HIV/AIDS and drug

resistant *Mycobacterium tuberculosis* will only further complicate an already serious situation (Raviglione et al, 1995). Whereas spontaneous mutations of *Mycobacterium tuberculosis* causing drug resistance are relatively infrequent, the usual causes of resistance include irregular accessibility of drugs, inadequate treatment and patient non-compliance (Pablos-Mendez et al, 1998).

2.1.2.2 Canada

Tuberculosis has been a problem in North America since the pre-Columbian era. The epidemic of tuberculosis in Europe started in the 17th century and reached its climax 100 years later (Grzybowski, 1999). With the arrival of European immigrants in Canada almost 300 years ago, aboriginal people of the Eastern provinces soon became exposed to tuberculosis. In contrast, the aboriginal people of Prairie Provinces were not exposed until the last half of the 19th century when the Canadian-Pacific railway was built and reserves were instituted (Enarson, 1986; Grzybowski, 1999).

In the early part of the 20th century, a study conducted by Ferguson stated that the mortality rate among aboriginal people of Saskatchewan and Alberta reached as high as 9,000 / 100,000 (Ferguson et al, 1949. Grzybowski, 1983). With the improvement of socio-economic conditions, public health services and treatment, however, tuberculosis incidence and mortality rates dropped markedly. The incidence rate in Canada continued its decline to reach 77/100,000 by 1937, only to increase again to 105.7/100,000 during the Second World War. After 1947, the incidence of tuberculosis declined to 33.8/100,000 by 1962, then dropped

further to 6.5 per 100,000 by 1995. The mortality rate similarly declined and plateaued at 0.4 per 100,000 by 1987 (Wherrett, 1964; CCDR, 1998). Non-aboriginal Canadians were the major beneficiaries of this drop. In 1980, 49% of all tuberculosis cases occurred in these individuals. By 1994, only 21% of tuberculosis cases involved non-aboriginal Canadians. Conversely, the percentage of foreign-born people with tuberculosis increased from 35% to 55% during this same period. Meanwhile the percentage, of aboriginal patients diagnosed with the disease increased from 14% in 1980 to 19% in 1994 (Wilkins, 1994).

The common risk factors for infection with tubercle bacilli include country of birth or travel to a country with a high prevalence of tuberculosis, aboriginal origin, disadvantaged status, substance abuse, old age and exposure to tuberculosis patients. In 1995, the risk of tuberculosis infection was 12 times higher for foreign-born people than for non-aboriginal Canadians and 25.8 times higher for aboriginal people. Seventy-five percent of all tuberculosis patients in Canada resided in Ontario, Quebec and British Columbia. Since these three provinces attract the majority of new immigrants to Canada, 90% of foreign-born tuberculosis cases are reported from these provinces. More specifically, foreign-born tuberculosis cases represent 81% of all tuberculosis cases in Ontario, 48% of those in Quebec and 60% of tuberculosis cases in British Columbia. Manitoba, Saskatchewan and the Northwest Territories reported 72% of all treaty tuberculosis cases in Canada. In comparison, tuberculosis in the Atlantic Provinces has very nearly been eradicated (5 per million), indicating that tuberculosis in Canada is becoming concentrated among certain geographic and demographic zones (Long et al, 1999).

2.2 Restriction Fragment Length Polymorphism (RFLP)

RFLP typing, or DNA fingerprinting, is a new and very helpful technique for tuberculosis strain identification and tracing during the investigation of tuberculosis outbreaks (Eisenach, 1994; Cohn et al, 1998). In addition, it can also overcome some of the limitations of traditional typing methods (VAN Embden et al 1993; Cohn et al, 1998). Insertion sequence 6110 is the key to RFLP typing (Drobniewski et al, 1996) and is a 1361 bp fragment that belongs to the IS3 family (Gicquel, 1993). These genomic components of the *Mycobacterium tuberculosis* chromosome exist in different copy numbers (10-15) that vary from strain to strain (Hermans et al, 1990; Drobniewsk et al, 1994; Fomukong et al, 1994), and reports indicate that these insertion sequence elements are stable over time (Gicquel, 1993; Fomukong et al, 1994; Cave et al, 1994). The basic RFLP technique involves DNA extraction from live bacterial cultures followed by Southern blotting and hybridization with specific probes. This, in turn, identifies the strain RFLP type or DNA fingerprint (Hermans et al, 1990; VAN Embden et al 1993; Drobniewsk et al, 1994). In order to facilitate the comparison of results from various laboratories, the procedure itself has been standardized (VAN Embden et al 1993). Furthermore, when compared with classical identification techniques, DNA fingerprinting has been found to be both comparable and reliable (Thierry et al, 1990).

2.2.1 Restriction Fragment Length Polymorphism (RFLP) Application

Each strain of *Mycobacterium tuberculosis* has a unique fingerprint pattern. RFLP has the ability to identify these DNA fingerprints (Eisenach, 1994) and consequently has been used in different epidemiological studies around the world to investigate both the spread of tuberculosis (Friden et al, 1996; Casper et al, 1996) and the prevalence of multidrug-resistant tuberculosis (Shafer et al, 1995) in different communities (Genewein et al, 1993; VAN Deutekom et al, 1997; Kimerling et al 1997; Borgdorff et al, 1998) In addition, this tequniques has also been utilized to assess the effectiveness of tuberculosis infection control (French et al, 1998).

3

Materials and Methods

This study was conducted for the period of January 1, 1992 through December 31, 1997. All tuberculosis patients from Manitoba were included in this study, and the data for all patients underwent analysis. Manitoba tuberculosis cases with isolates culture were subjected to identification, DNA fingerprinting and analysis.

3.1 Data Collection

The Central Tuberculosis Registry in Manitoba is a computerized central system, which collects data on all tuberculosis patients, as well as follow up data on both patients and their contacts. Each patient or contact person processed through the tuberculosis registry office is given unique identifier number. Using the available information, to created three databases. The first database included tuberculosis patients in Manitoba from 01/01/1992 to 31/12/1997. The data contained the patient's unique identifier number, date of birth, place of birth, sex, country of birth, postal code, origin (Canadian-born treaty, Canadian-born non-treaty and foreign-born), date of diagnosis, case finding method, tuberculosis case status (new active and relapse), BCG status, year of landing (foreign-born patients), smear results, culture results, fingerprint type, drug

resistance, chest x-ray and cavity status. The second database included contact tracing data for all tuberculosis patients and their contacts. For each of these individuals, information was collected regarding the type, place and degree of contact, BCG status, date and results of first and second Mantoux and chest x-rays, tuberculosis diagnosis and date of diagnosis. The third database involved only contact people and included their unique identifier number as well as their date of birth.

3.2 Fingerprint Analysis

3.2.1 Sample Collection

A variety of patient samples were collected by a designated nurse or medical staff at the Respiratory Clinic, Health Sciences Centre, and other health care centres in Manitoba. These were sent to the Clinical Microbiology Laboratory for laboratory diagnosis (isolation and identification of *Mycobacterium tuberculosis*).

3.2.2 Specimen Processing:

Samples were processed in the the Mycobacteriology Laboratory (level 2 containment, level 3 operational area) of Standard processing protocol for a specific specimen type was followed as per recommendations of Kent and Kubica, 1985 (Guide for level 3 Mycobacteriology Laboratory Centre of Disease Control (LCDC).

3.2.3 *Mycobacterium Tuberculosis* Identification:

The Accuprobe *Mycobacterium tuberculosis* complex kit (catalogue no 2860) from Gen-Probe Incorporated, San Diego, CA, USA was used to identify *M. tuberculosis* in the clinical samples.

3.2.4 DNA Fingerprinting

3.2.4.1 Genomic DNA Isolation

A loopful of bacterial cells from solid media was inoculated into 500 µl of 1x TE buffer (10mM tris-hydrochloride, pH 8.0 and 1mM ethylene-diamine-tetra acetic acid disodium salt). The suspension was vortexed and heated in a 80°C water bath for 20 minutes before 50 µl of 10 mg/ml lysozyme (Sigma Chem Co. St. Louis, Missori. Catalogue # L-7651) was added. The mixture was (vortexed and then incubated at 37°C for one hour. After incubation, 70 µl of 10% sodium dodecyl sulphate and 6 µl of 10 mg/ml proteinase K (Sigma Aldrich, catalogue # p6556) was added to the suspension. Next, the mixture was vortexed and incubated at 65°C for 10 minutes. 100 µl of 5M sodium chloride was added to the tubes, vortexed and another 80 µl of CTAB/NaCl (4.1% sodium chloride and 10% hexadecyl-trimethyl-ammonium bromide in distilled water) solution was added. The mixture was then once again vortexed and incubated at 65°C for 10 minutes. 800 µl of chloroform:isoamyl alcohol (24:1) was added to tubes, the tubes were vortexed and centrifuged at 12000 g for 5 minutes. The aqueous phase was transferred to a fresh tube in 180 µl aliquots. 108 µl of isopropyl alcohol was added to each tube and all tubes were incubated at -20°C for 30

minutes. The mixture was then centrifuged at 12000 g for 15 minutes, the supernatant discarded and the DNA pellet washed with 1 ml of 70% ethanol. This mixture was then centrifuged for a further 5 minutes, the supernatant discarded and the pellet was left to dry for 30-45 minutes. Once dry, the pellet was redissolved in 20 µl of 0.1x TXE buffer for 45-60 minutes. The extracted DNA was stored at -20°C until used.

3.2.4.2 DNA Digestion

Ten (10x) digestion buffer (100 mM tris-HCl pH 7.5, 100 mM magnesium chloride, 500 mM sodium chloride and 10mM dithioerythritol), 20 µl DNA (RIVM [RIVM # 14323] standard or patient sample), 23 µl distilled water and 2 µl PVUII were mixed together in a tube and centrifuged at 12000 g for 5 seconds. The suspension was then incubated in a 37°C water bath for 6 hours. 20 µl of the product 2.2 µl of Ficoll dye were electrophoresed in a 1% agarose gel. Hind II/PhiX 174 marker was run in a separate well. Electrophoresis was carried out at 100V for 10 minutes and then overnight at 26V, until the 2Kb band of Hind III/PhiX 174 marker was6.6 cm from the well.

3.2.4.3 Southern Transfer

The gel was exposed to UV light for 5 minutes and then washed three times in 0.5 N sodium hydroxide-1.5 M sodium chloride solution (20 minutes each). Next, the gel was rinsed in distilled water and washed 2 times in 0.5 M tris pH 7.5 -1.5M sodium chloride solution for 20 miutes each. The gel was once again rinsed in distilled water. DNA was the transferred onto nylon membrane

overnight in 10x SSC, the membrane was cross linked in UV for 3 minutes, soaked in 2x SSC for 2-3 minutes and baked at 80°C for 2 hours. It was sealed thereafter.

3.2.4.4 Probe Hybridization

The blot was hybridized overnight in prehybridization solution containing DIG-labeled probe in a 65°C water bath. It was subsequently washed and incubated with anti-DIG-AP conjugate. The membrane was incubated with diluted CSPD (Roche Diagnostic, catalogue #1655-88p), sealed and exposed to X-ray film for 15-25 minutes at room temperature.

3.3 Data Entry

All gel pictures were loaded into the computer and analyzed using Molecular Analyst® Software Fingerprinting version 1.1, BioRad, Hercules, CA, USA.

3.4 File Linkage

All database created were stored in MS Access® and then linked together utilizing the Central Tuberculosis Registry Office unique identifier numbers.

3.5 Incidence Rate Calculation

To calculate tuberculosis incidence rates, we used the 1996 Canadian population census from Statistics Canada. Since the study was conducted over six years period (1992-1997), the person-year population of Manitoba throughout this time was determined by multiplying the 1996 population by six. In order to determine the incidence rate for a specific population subgroup, we added all

tuberculosis cases in that subgroup from 1992 to 1997 then divided by the total six-year subgroup person-years. The resulted number of dividing the patients number on the population at risk was subsequently multiplied by 100,000 to obtain the incidence rate per 100,000 person-years.

4

Definitions

4.1 Tuberculosis Registry

The central organization within a province/territory that receives, records and accumulates information on and follows up all reported cases of tuberculosis and maintains a register of persons with tuberculosis (Tuberculosis in Canada 1996, LCDC, Health Canada).

4.2 Tuberculosis Cases

(a) Cases with *Mycobacterium tuberculosis* complex (i.e. *M. tuberculosis, M. bovis* [excluding BCG strain], or *M. africanum*) demonstrated on culture, or

(b) Cases with significant evidence of activity, and preferably a positive (significant) tuberculin reaction even though bacteriological proof has not been demonstrated, such as:

- Chest x-ray change compatible with active tuberculosis, including idiopathic pleurisy with effusion,
- Clinically active nonrespiratory tuberculosis (meningeal, bone, kidney, etc.),
- Pathologic or post-mortem evidence of active tuberculosis (Long et al., 1999).

4.3 New Active and Relapsed tuberculosis

4.3.1 New Active – No documented evidence or history of previously active tuberculosis,

4.3.2 Relapsed – Documented evidence or history of previously active tuberculosis that became inactive.

Note: This applies whether the last episode was in or outside of Canada. (Tuberculosis in Canada 1996, LCDC, Health Canada),(Long et al., 1999).

4.4 Index Case

The initial active tuberculosis case from which the process of contact investigation began (Canadian tuberculosis standards, 1996).

4.5 Infection

This term refers to infection of a host by the *M. tuberculosis* organism, which lies dormant in an asymptomatic state. There is a subsequent approximate 10% risk of future reactivation and the development of active disease in an immune competent host (Canadian tuberculosis standards, 1996).

4.6 Infectious

The condition whereby the subject can transmit infection to others by virtue of production of infectious aerosols. Those with cavitary and laryngeal disease are likely the most infectious. Infectiousness is usually defined on the bases of repeated smear-positive secretions from the airways. The corollary is

that subjects are deemed to be non-infectious usually after three successive sputa are smear negative (Canadian tuberculosis standards, 1996).

4.7 Cavitary disease

This is a radiological diagnostic label referring to signs of lung destruction with the presence of holes on chest x-ray. (Canadian tuberculosis standards, 1996).

4.8 Drug Resistance

This term can be further refined according to acquired or secondary resistance: acquired primary resistance occurs when a patient becomes infected with a resistant organism; secondary resistance occurs when a patient is taking medication usually on the basis of poor adherence (Canadian tuberculosis standards, 1996).

4.9 Multi-Drug-Resistant Tuberculosis (MDRTB)

The presence of resistance to two or more anti-tuberculous drugs, most often considered to be isoniazid and rifampin, the two most important first-line drugs (Canadian tuberculosis standards, 1996).

4.10 Smear

The term used to describe the examination of body secretions under the microscope to determine the presence of acid-fast bacilli. A smear is usually

used to determine infectiousness but initially, before formal culture identification, a positive result may be due to infection with mycobacteria other than *M. tuberculosis*. It therefore requires careful interpretation. The availability of species-specific polymerase chain reaction based probes should overcome this problem (Canadian tuberculosis standards, 1996).

4.11 Culture Positive Disease

The presence of positive *M. tuberculosis* culture of body secretions, most notably sputum (Canadian tuberculosis standards, 1996).

4.12 Mantoux Skin Test

The technical term to describe the injection of 5 tuberculin units into the dermis of forearm. It is the most standardized form of skin testing and the one most often advocated (Canadian tuberculosis standards, 1996).

4.13 Bacillus Calmette Guerin (BCG)

A vaccination against tuberculosis most often used in Canada for Aboriginal Canadians living on reserves, who have the highest rates of disease in Canada (Canadian tuberculosis standards, 1996).

4.14 Contact

A person identified as having come in contact with an active case of disease. The degree of contact is usually further defined on the basis of

closeness e.g., close household, close non-household and casual. (Canadian tuberculosis standards, 1996).

4.15 Aboriginal

This term is usually used to describe the indigenous inhabitants of Canada and their descendants. It embraces those people registered as status Indians living on and off reserves as well as Metis and Inuit (Canadian tuberculosis standards, 1996).

4.16 Treaty people

Under the Indian Act, the federal government has implemented an Indian Registry System to keep records and information about each person with legal (treaty) status (Frideres, 1983; Waldram et al, 1995).

5

Epidemiology of Tuberculosis in Manitoba

5.1 Broad picture of tuberculosis in Manitoba

5.1.1 Population of Manitoba

From the Dimensions series software publication of Statistic Canada (which deals with the 1996 Canadian census), we extracted Canadian and foreign-born population numbers as well as the percentage of treaty people living both on and off reserves. We also extracted treaty population numbers from live databases maintained by the federal government.

The population of Manitoba according to the 1996 Census (Table 1) was 1,100,295. Of these individuals, 859,593 (78.1%) were non-treaty, 98,197 (8.9%) were treaty and 142,505 (13.0%) were foreign-born. In addition, 542,075 (49.3%) individuals were male and 558,220 (50.7%) were female. According to corresponding age distribution, 36.1% of the Manitoba population consisted of individuals who were 24 years of age or younger, while 12.9% were 65 years of age or older. Interestingly, only 3.5% of the treaty population reached an age of 65 suggesting a shorter life expectancy for these individuals.

Postal codes were used to define rural and urban areas as follows: a zero in the second position of the postal code denotes areas rural areas while numbers

one through nine represent urban addresses. Since Statistics Canada maintains a record of the population of each postal code areas, we were able to determine that 769,160 individuals (69.9%) resided in urban areas in 1996 while the remaining 331,135 (30.1%) lived in rural areas.

Table 1 Age distribution of the 1996 Manitoba population

Age	Total		Canadian-Born				Foreign-Born	
			Non-Treaty		Treaty			
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
0-14	244,415	22.2	200,624	23.3	35,856	36.5	7,935	5.6
15-24	153,005	13.9	121982	14.2	17,938	18.3	13,085	9.2
25-44	338,045	30.7	260,371	30.3	29,929	30.5	47,745	33.5
45-64	222,685	20.2	168,186	19.6	11,069	11.3	43,425	30.5
> 65	142,140	12.9	108,420	12.6	3,405	3.5	30,320	21.3
Total	1,100,295	100.0	859,593	100.0	98,197	100.0	142,505	100.0

Source: 1996 Census- Statistics Canada 94F0009XDB96191

Non-treaty people account for 78.1% of the Canadian-born population (i.e.859, 593 individuals) and include all Canadian-born people excluding aboriginal people with a treaty status. In other words, aboriginal people without treaty status as well as first generation foreign-born people are included in this category. Individuals 24 years of age or younger make up 37.5% of this subgroup while individuals 65 years of age or older account for 12.6%. 49.9% of the total non-treaty population was between the ages of 25 and 64.

Foreign-born people 24 years of age or younger account for 14.8% of this population subgroup. Interestingly, this value is approximately 2.5 times less than that of non-treaty people and 3.7 times less than that of treaty people, implying

that either relatively few immigrants arrive in Canada at a young age or that the majority of these children are actually born in Canada and therefor are classified as non-treaty. Also, 21.3% of these (foreign-born) individuals were 65 years of age or older, a value nearly 6 fold higher than that of treaty group counterparts and 40% higher than that of the same age group of non-treaty individuals. The remaining 64% of the total foreign-born population fell between 25 and 64 years of age.

Tables 2 and 3 demonstrate the demographic composition and percentage representation of Manitoba's male and female populations (respectively) by population subgroup. The tables show no serious differences in the distribution trend between males and females and will be useful in the comparison of the demographic distribution of the Manitoba population and tuberculosis cases in Manitoba.

Table 2 Age distribution of the male Manitoba population (1996)

Age	Total		Canadian-Born				Foreign-Born	
			Non-Treaty		Treaty			
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
0-14	125,320	23.1	102,875	24.2	18,315	37.5	4,130	6.0
15-24	77,750	14.3	62,128	14.6	9,167	18.8	6,455	9.4
25-44	168,480	31.1	130,135	30.7	14,595	28.9	23,750	34.5
45-64	110,355	20.4	83,707	19.7	5,183	10.6	21,465	31.2
> 65	60,160	11.1	45,613	10.8	1,587	3.3	12,965	18.9
Total	542,075	100.0	424,458	100.0	48,847	100.0	68,765	100.0

Source: 1996 Census- Statistics Canada 94F0009XDB96191

Table 3 Age distribution of the female Manitoba population (1996)

Age	Total		Canadian-Born				Foreign-Born	
			Non-Treaty		Treaty			
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
0-14	119,095	21.3	97,744	22.5	17,541	35.5	3,850	5.2
15-24	75,255	13.5	59,854	13.8	8,771	17.8	6,630	9.0
25-44	169,565	30.4	130,241	29.9	15,334	31.1	23,995	32.5
45-64	112,325	20.1	84,484	19.4	5,886	11.9	21,960	29.8
> 65	81,975	14.7	62,807	14.4	1,818	3.7	17,355	23.5
Total	558,220	100.0	435,130	100.0	49,350	100.0	73,740	100.0

Source: 1996 Census- Statistics Canada 94F0009XDB96191

5.1.2 Tuberculosis in Manitoba

Table 4, categorizes tuberculosis cases in Manitoba by age and origin (Canadian-born and foreign-born). Between January 1,1992 and December 31,1997 there were 610 reported cases of tuberculosis in the province. While the majority of individuals with tuberculosis (72% or 439 patients) were born in Canada (including both treaty and non-treaty individuals), the remaining 28% (171 patients) consisted of foreign-born individuals. Among non-treaty individuals, the majority of patients (39.9% or 71 people) were 65 years of age or older. On the other hand, only 15.7% of treaty patients (41 individuals) belong to this age group. In the 25-44 age group, the opposite situation was observed. Whereas the majority of treaty patients (112 cases or 42.9%) were between the ages of 25 and 44, only 16.9% of non-treaty cases (30 patients) belonged to this category.

Table 4 Age distribution of tuberculosis cases in Manitoba from 1992-1997

Age	Total		Canadian-Born				Foreign-Born	
			Non-Treaty		Treaty			
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
0-14	46	7.5	12	6.7	25	9.6	9	5.3
15-24	53	8.7	8	4.5	27	10.3	18	10.5
25-44	211	34.6	30	16.9	112	42.9	69	40.4
45-64	143	23.4	57	32.0	56	21.5	30	17.5
> 65	157	25.7	71	39.9	41	15.7	45	26.3
Total	610	100.0	178	100.0	261	100.0	171	100.0

Of the total 610 tuberculosis patients in Manitoba between 1992 and 1997, males accounted for 327 (53.6%). Two hundred and forty-one of these patients (73.7%) were Canadian-born while 86 (26.3%) were foreign-born (Table 5). In comparing the differences between the age group distribution of male tuberculosis cases (Table 4) and the natural demographic distribution of the same population subgroups (Table 2), we see that occurrence of tuberculosis increased with the age.

Table 5 Age distribution of male tuberculosis cases in Manitoba from 1992-1997

Age	Total		Canadian-Born				Foreign-Born	
			Non-Treaty		Treaty			
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
0-14	22	6.7	6	5.8	10	7.3	6	7.0
15-24	33	10.1	5	4.8	17	12.4	11	12.8
25-44	108	33.0	18	17.3	64	46.7	26	30.2
45-64	75	22.9	36	34.6	23	16.8	16	18.6
> 65	89	27.2	39	37.5	23	16.8	27	31.4
Total	327	100.0	104	100.0	137	100.0	86	100.0

In Table 6 we compare the age group and population subgroup distribution of females tuberculosis cases. Here we see that 283 patients (46.4%) were female, of which 198 (70%) were Canadian-born and 85 (30%) were foreign-born.

Table 6 Age distribution of female tuberculosis cases in Manitoba from 1992-1997

Age	Total		Canadian-Born				Foreign-Born	
			Non-Treaty		Treaty			
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
0-14	24	8.5	6	8.1	15	12.1	3	3.5
15-24	20	7.1	3	4.1	10	8.1	7	8.2
25-44	103	36.4	12	16.2	48	38.7	43	50.6
45-64	68	24.0	21	28.4	33	26.6	14	16.5
> 65	68	24.0	32	43.2	18	14.5	18	21.2
Total	283	100.0	74	100.0	124	100.0	85	100.0

5.1.2.1 Distribution of Cases by Population Subgroups, Age and Gender

The three main population subgroups in Manitoba include **Non-Treaty**, **Treaty** and **Foreign Born** individuals.

5.1.2.1.1 Non-Treaty Canadian-Born Subgroup

This subgroup constitutes 29.2% of all reported Manitoba tuberculosis cases and 40.6% of cases among Canadian-born patients. Approximately 39.9% of non-treaty patients were 65 years of age or older, while demographically this age group represents 12.6% of the population. Among the remaining age groups, the percentage of tuberculosis cases was lower than the corresponding natural population distribution. Upon comparison of non-treaty, treaty and foreign-born population subgroups we found that non-treaty individuals had the highest

percentage of patients in the 65 years of age or higher age category (Tables 4, 5 and 6).

5.1.2.1.2 Treaty Subgroup

Tuberculosis patients with treaty status represent 261 (42.8%) of the 610 total cases and 59.4% of Canadian-born cases. One hundred and sixty-four tuberculosis patients with treaty status were between the ages of zero and 44, representing 62.8% of the total treaty cases and over 50% of all tuberculosis patients of this age. Demographically, the same age group (0-44) represents 85.5% of the total treaty population. In comparison, the percentage of treaty patients at 45 years of age or older was 32.7% while demographically this group represents 14.8% of the total treaty population. (Table 1 & 4). Importantly, the trend of tuberculosis spread among male and female patients was not significantly different (Tables 4 and 5).

5.1.2.1.3 Foreign-Born Subgroup

One hundred and seventy-one tuberculosis patients (28.0%) were foreign-born. The distribution of these tuberculosis patients within the aforementioned age groups is similar to their population distribution, although two exceptions exist (Table 4). These include male patients 65 years of age or older with 39.8% higher representation (Table 5) and 25-44 year old females with 35.8% higher representation (Tables 6).

5.1.21.2 Incidence Rates

Table 7 shows the overall incidence rates of tuberculosis in Manitoba as well as the incidence rates among Manitoba population subgroups according to age. While the general tuberculosis incidence rate in was 9.2 per 100,000 person-year, the highest incidence rate (by age group) occurred in patients 65 years of age or older 18.4 per 100,000 person-year. Incidence rates for the three main population subgroups were as follows: 3.5 for non-treaty people, 44.3 for treaty people and 20.0 for foreign-born people.

Among non-treaty people, the tuberculosis incidence rate was 3.5, a value one third that of the Manitoba rate, 12.7 fold lower than the treaty rate and 5.7 time lower than the foreign-born rate. The highest incidence rate among non-treaty individuals occurred among people 65 years of age or older.

The foreign-born tuberculosis incidence rate was two to three times higher than the incidence rate of tuberculosis among the total population of Manitoba. Furthermore, the incidence rate of tuberculosis among foreign-born children was higher than that for any other group of children.

In treaty people, the incidence rate of tuberculosis was four to ten times higher than that among the total population of Manitoba.

Table 7 Incidence rate of tuberculosis in Manitoba (1992-1997) per 100,000 person-years by age and population subgroups.

Age	Total	Canadian-Born		Foreign-Born
		Non-Treaty	Treaty	
0-14	3.1	1.0	11.6	18.9
15-24	5.8	1.1	25.1	22.9
25-44	10.4	1.9	62.4	24.1
45-64	10.7	5.7	84.3	11.5
> 65	18.4	10.9	200.7	24.7
Total	9.2	3.5	44.3	20.0

5.1.2.2.1 Male and Female Incidence Rates

With an incidence rate of 24.7 per 100,000, males 65 years of age or older have the highest risk of developing tuberculosis among all subgroups. The rate was highest among treaty males (241.5), followed by foreign-born males at 34.7 and non-treaty males at 14.3 (Table 8).

The highest incidence rate of tuberculosis in females was 165.0 and occurred among treaty females aged 65 years or more. Among non-treaty individuals, the highest incidence rates (8.5) once again occurred in females 65 years of age or older. In contrast, the rate among foreign-born females was highest in those 25-44 years of age, at 29.9 (Table 8).

Table 8 Incidence rate of tuberculosis in Manitoba (1992-1997) per 100,000 person-years by age and population subgroups (Males and females population)

Age	Total		Canadian-Born				Foreign-Born	
			Non-Treaty		Treaty			
	Male	Female	Male	Female	Male	Female	Male	Female
0-14	2.9	3.4	1.0	1.0	9.1	14.3	24.2	13.0
15-24	7.1	4.4	1.3	0.8	30.9	19.0	28.4	17.6
25-44	10.7	10.1	2.3	1.5	73.1	52.2	18.2	29.9
45-64	11.3	10.1	7.2	4.1	74.0	93.4	12.4	10.6
> 65	24.7	13.8	14.3	8.5	241.5	165.0	34.7	17.3
Total	10.1	8.4	4.1	2.8	46.7	41.9	20.8	19.2

6

Residence of Tuberculosis Cases in Manitoba

Treaty people account for 8.9% of Manitoba's population (that is, 98,197 individuals). While 62,249 treaty people (63.4%) live on reserves, 35,948 (36.6%) live off reserves.

6.1 Winnipeg

Sixty percent of Manitoba's population, or 660,055 individuals, live in Winnipeg. Of these Winnipeg residents, 116,665 (17.5%) are foreign-born and 543,390 (81.4%) are Canadian-born. Among Canadian-born individuals, 28,840 (4.4%) are treaty people and 514,632 (77.9%) are non-treaty (Table1).

Table 1 Population subgroups and their distribution in Manitoba (1996 Census)

Population subgroup	Residence			
	Winnipeg	Reserve	Other*	Manitoba
Non-Treaty	514,632	0	344,961	859,593
Treaty	28,758	62,249	7,190	98,197
Foreign-Born	116,665	0	25,840	142,505
Total	660,055	62,249	377,991	1,100,295

* Urban areas other than Winnipeg and rural areas other than reserves.

6.2 Reserves

Eighty percent of those individuals living off reserves reside in Winnipeg. The remaining 7,190 (20%) treaty persons live in areas other than Winnipeg or reserves (Table 1).

6.3 Tuberculosis Cases in Manitoba

We used the previous residence definition (Winnipeg, reserves and other) to understand the distribution of tuberculosis in different areas of Manitoba. Since Winnipeg is the largest city in Manitoba, it is not unexpected to find the largest number of Manitoba tuberculosis cases (383 or 62,8%) living in this city. Of the 383 Manitoba tuberculosis patients living in Winnipeg, 121(31.6%) are non-treaty while 97 (25.3%) are people with treaty status. Interestingly, the majority of tuberculosis patients (165 or 43.1%) residing in Winnipeg are foreign-born individuals (Table 2)

One hundred and thirty-five tuberculosis patients reside on reserves. Of these patients, 126 (93.3%) are individuals with treaty status and 9 (6.7%) are non-treaty patients (Table 2).

In comparison, 92 patients (15.1%) live either in urban areas other than Winnipeg or in rural areas other than reserves while most of these (48 individuals or 52.2%) were non-treaty people, thirty-eight patients (41.3%) were treaty individuals and 6 (6.5%) were foreign-born (Table 2).

6.4 Residence of Patients by Population Subgroup

6.4.1 Non-Treaty Subgroup

Of the total 178 non-treaty patients, 121(68%) live in Winnipeg and 48 (52%) live in areas other than Winnipeg or the reserves. Nine patients (5.1%) reside on reserves (Table 2).

6.4.2 Treaty Subgroup

The majority of tuberculosis patients with treaty status (126 individuals or 48.3%) reside on reserves. Ninety-seven patients (37.2%) live in Winnipeg. The remaining 38 patients live either in non-reserve rural areas or in urban areas other than Winnipeg (Table 2).

Table 2 Residence of tuberculosis patients in Manitoba from1992-1997

Population Subgroup	Residence						
	Winnipeg		Reserve		Other		Total
	(n)	(%)	(n)	(%)	(n)	(%)	(n)
Non-Treaty	121	31.6	9	6.7	48	52.2	178
Treaty	97	25.3	126	93.3	38	41.3	261
Foreign-Born	165	43.1	0	0	6	6.5	171
Total	383	100.0	135	100.0	92	100.0	610

6.4.3 Foreign Born Subgroup

The majority of foreign-born patients (165 individuals or 96.5%) lives in Winnipeg, with only 6 individuals (3.5%) living elsewhere (Table 2).

6.5 Tuberculosis Incidence Rates

Table 3 shows that tuberculosis incidence rates vary tremendously from one resident area to another. For example, the highest incidence rate (33.7)

occurred in reserves, while individuals living in places other than Winnipeg or the reserves experienced a rate of only 4.1. The Winnipeg incidence rate (9.7) was comparable to the overall Manitoba incidence rate of 9.2.

6.5.1 Winnipeg

Within any given resident area, tuberculosis incidence rates also fluctuate between population subgroups. In Winnipeg patients, the incidence rate among non-treaty people was only 3.9, 2.3 times lower than the Manitoba rate. On the other hand, the rate among treaty people was an astonishing 56.2, 6 fold higher than that of Manitoba. Foreign-born people experienced a rate of 23.6, 2.6 times higher than Manitoba's rate (Table 3).

6.5.2 Reserves

The incidence rate of tuberculosis among individuals living on reserves was 33.7. Although this value is 3.7 times higher than the overall provincial rate, it is actually lower than both the treaty provincial and Winnipeg treaty rates (Table 3).

6.5.3 Other

Incidence rates among individuals living in areas other than Winnipeg or reserves vary considerably. As seen in Table 3, these values range from 2.3 and 3.9 for non-treaty and foreign-born people, respectively, to an incredible 88.1 for treaty individuals.

Table 3 Incidence rate of tuberculosis per 100,000 person-year among Manitoba resident areas and population subgroups from1992-1997

Population subgroup		Residence			
		Winnipeg	Reserves	Other*	Manitoba
Canadian-Born	Non-Treaty	3.9	0	2.3	3.5
	Treaty	56.2	33.7	88.1	44.3
Foreign-Born		23.6	0	3.9	20.0
Total		9.7	33.7	4.1	9.2

* Urban areas other than Winnipeg and rural areas other than reserves.

7

Description of Tuberculosis Cases

Of the 610 reported tuberculosis cases in Manitoba between 1992 and 1997, 554 were new active cases and the remaining 56 (9.2%) were relapse cases (Table 1).

Table 1 Status of tuberculosis cases in Manitoba from 1992-1997

Case Status	Tuberculosis Cases	
	(n)	(%)
New Active	554	90.8
Relapse	56	9.2
Total	610	100.0

7.1 Site of Infection

For the purpose of this analysis, respiratory tuberculosis includes both respiratory cases as well as cases diagnosed as respiratory and non-respiratory tuberculosis at the same time. This combination is the dominant category in "site of infection", accounting for 464 (76.1%) of the 610 cases from 1992-1997 in Manitoba (Table 2).

Table 2 Site of infection among population subgroups of tuberculosis patients in Manitoba from 1992-1997

Population subgroup	Site of Infection							
	Respiratory		Non-Respiratory		Unknown		Total	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Non-Treaty	134	28.9	43	29.9	1	50.0	178	29.2
Treaty	226	48.7	35	24.3	0	0	261	42.8
Foreign-Born	104	22.4	66	45.8	1	50.0	171	28.0
Total	464	100.0	144	100.0	2	100.0	610	100.0

Non-Respiratory tuberculosis was responsible for only144 cases (23.6%). The site of infection in the remaining 2 cases (0.3%) could not be identified (Table 2).

7.1.1 Respiratory Tuberculosis

Of those patients with respiratory disease, 134 (28.9%) were non-treaty individuals, 226 (48.7%) were treaty individuals and 104 (22.4%) were foreign-born individuals (Table 2). As seen in Table 3, respiratory tuberculosis can be further divided into a variety of different types. With 348 patients (75%), pulmonary tuberculosis represents the main type of respiratory tuberculosis.

Table 3 Types of respiratory and mixed (respiratory and non-respiratory) tuberculosis cases in Manitoba from 1992-1997

Diagnosis	Tuberculosis cases	
	(n)	(%)
Pulmonary	348	75.0
Pleurisy	49	10.6
Primary	38	8.2
Miliary	27	5.8
Other Respiratory	2	0.4
Total	464	100.0

7.1.2 Non-Respiratory Tuberculosis

Forty-three patients (29.9%) with non-respiratory tuberculosis were non-treaty individuals, 35 patients (24.3%) were individuals of treaty status and 66 patients (45.8%) were foreign-born individuals (Table 2). Among the common types of non-respiratory tuberculosis diagnosed in Manitoba from 1992-1997, lymph node tuberculosis occurred most often (Table 4).

Table 4 Types of non-respiratory tuberculosis cases in Manitoba from 1992-1997

Diagnosis	Tuberculosis cases	
	(n)	(%)
Lymph Node	79	54.9
Genitourinary Tract	27	18.7
Bone/ Joint	15	10.4
Abdomen	13	9.0
Central Nervous System	5	3.5
Cutaneous	1	0.7
Skin	1	0.7
Breast Abscess	1	0.7
Ear	1	0.7
Other	1	0.7
Total	144	100.0

7.2 Frequency of Respiratory and Non-Respiratory Tuberculosis Among the Population Subgroups

Among the various subgroups, respiratory tuberculosis occurred in 75.3% of non-treaty patient, 86.6% of treaty patients and 60.8% of foreign-born patients. Respiratory cases were greatest among treaty patients and least among foreign-born patients. In comparison, non-respiratory tuberculosis was responsible for disease in 24.2% and non-treaty patients, 13.4% of treaty patients and 38.6% of foreign-born patients. Non-respiratory cases were highest among foreign-born patients and lowest in treaty patients.

7.3 Chest X-Rays

The chest x-rays of 451 (73.9%) tuberculosis patients in Manitoba from 1992-1997 were abnormal (Table 5), while 113 (18.5%) were normal. The x-ray status of 15 patients could not be identified. X-rays were not performed for 31 individuals (5.1%).

Table 5 Status of chest x-rays from tuberculosis patients in Manitoba from 1992-1997

Chest x-ray	Tuberculosis Cases	
	(n)	(%)
Abnormal	451	73.9
Normal	113	18.5
Not-Done	31	5.1
Unknown	15	2.5
Total	610	100.0

7.4 Cavity

Tables 6 shows the number of respiratory tuberculosis cases with x-ray cavities as well as the percentage of the three main population subgroups in Manitoba with cavities. Out of the 564 total tuberculosis cases with abnormal chest x-rays, 89 X-rays (15.8%) revealed cavities and 475 (84.2%) did not. The majority of patients with x-ray cavities (52 cases or 58.4%) were treaty individuals. On the other hand, only 20 non-treaty patients (22.5%) and17 foreign-born patients (19.1%) had x-ray cavities.

Table 6 Distribution of tuberculosis cases with x-ray cavities among population subgroups in Manitoba from 1992-1997

Population	Respiratory cases	Tuberculosis Cases with Cavity	
	(n)	(n)	(%)
Non-Treaty	134	20	22.5
Treaty	226	52	58.4
Foreign-Born	104	17	19.1
Total	464	89	100.0

7.5 Smear and Culture Results

7.5.1 Smear Results

The smear results from tuberculosis patients in Manitoba from 1992-1997 are shown in Table 7. The types of samples taken from tuberculosis patients include sputum, bronchial wash, gastric wash, urine or any other site of infection. Two hundred and seventy two (44.6%) smears were positive and 235 (38.5%) were negative. A smear was not performed in 103 (16.9%) instances.

Approximately half of all treaty patients (130 individuals or 49.8%) were smear positive. In comparison, 79 non-treaty patients (44.4%) and 63 foreign-born patients (36.8%) were positive. Smear results were negative for 76 foreign-born patients (44.4%), 95 treaty patients (36.4%) and 64 non-treaty patients (35.9%).

Out of the 464 respiratory cases, 236 (50.8%) were smear positive and 191 (41.2%) were smear negative. Smears were not performed in 37 cases (8.0%). Of the 144 non-respiratory cases, 35 (24.3%) were positive while 43 (29.9%) were smear negative. Smears were not performed in the remaining 66 cases (45.8%). In

two cases, the type of infection could not be identified. One of these cases produced smear positive results, the other was smear negative (Table 7).

Table 7 Smear results and infection site of tuberculosis cases in Manitoba from 1992- 1997

Site of Infection	Smear Result							
	Positive		Negative		Not-Done		Total	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Respiratory	236	86.8	191	81.3	37	35.9	464	76.1
Non-Respiratory	35	12.9	43	18.3	66	64.1	144	23.6
Unknown	1	0.3	1	0.4	0	0	2	0.3
Total	272	100.0	235	100.0	103	100.0	610	100.0

7.5.2 Culture Results

Culture results of the 610 tuberculosis cases in Manitoba between 1992 and 1997 are shown in Table 8. Positive cultures were seen in 479 cases (78.5%) whereas 74 cases (12.1%) were negative. Cultures were not performed in 57 cases (9.3%).

As seen in Table 8, the majority of respiratory cases (377 cases or 81.3%) yield positive culture results. Only 11.9% of such cases (55 patients) gave negative results. Cultures were not performed in 32 cases (6.9%). In comparison, significantly fewer non-respiratory tuberculosis cases (100 cases or 69.4%) gave positive culture results. While 19 patients (13.2%) had negative results and cultures were not done in 25 cases.

Positive culture results were seen in 128 non-treaty individuals (71.9%), 216 treaty patients (82.8%) and 135 foreign-born patients (78.9%). On the other hand, negative culture results were seen in 22 non-treaty individuals (12.4%), 30 treaty cases (11.5%) and 22 foreign-born patients (12.9%).

Table 8 Culture results and infection site of tuberculosis cases in Manitoba from 1992- 1997

Site of Infection	Smear Result							
	Positive		Negative		Not-Done		Total	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Respirator	377	78.7	55	74.3	32	56.1	464	76.1
Non-Respiratory	100	20.9	19	25.7	25	43.9	144	23.6
Unknown	2	0.4	0	0	0	0	2	0.3
Total	479	100.0	74	100.0	57	100.0	610	100.0

8

Molecular Epidemiology of Tuberculosis in Manitoba

8.1 Tuberculosis Cases With and Without Isolates

Of the 610 Manitoba tuberculosis patients between 1992 and 1997, 479 (78.5%) cases had isolates while 131 (21.5%) did not. Table 1 categorizes these tuberculosis cases according to population subgroups of Manitoba, residence of patients, site of infection, disease status of the cases and age group. By so doing, we are able to not only examine the percentage of cases with isolates among different groups but to also determine the extent to which we can generalize the results obtained from fingerprint analysis. As indicated by the data presented in Table 1, the availability of isolates amongst the various groups ranged from 69.4% to 87.5%. One clear exception was that of the 0-14 age group with only 39.1% of the 18 cases having isolates.

Table 1 Manitoba tuberculosis cases with and without isolates (1992-1997)

Groups	Total	With Isolates		No Isolates	
		(n)	(%)	(n)	(%)
Total	610	479	78.5	131	21.5
Non-Treaty	178	128	71.9	50	28.1
Treaty	216	216	82.8	45	17.2
Foreign-Born	171	135	78.9	36	21.1
Rural Reserves	135	116	85.9	19	14.1
Rural Non-Reserves	67	51	76.1	16	23.9
Urban Winnipeg	383	292	76.2	91	23.8
Urban Non-Winnipeg	25	20	80.0	5	20.0
Respiratory	464	377	81.3	87	18.8
Non-Respiratory	144	100	69.4	44	30.6
New Active cases	554	430	77.6	124	22.4
Relapse cases	56	49	87.5	7	12.5
Age (0 – 14)	46	18	39.1	28	60.9
(15 – 24)	53	44	83.0	9	17.0
(25 – 44)	211	172	81.5	39	18.5
(45 – 64)	143	113	79.0	30	21.0
(> 65)	157	132	84.1	25	15.9

8.2 Fingerprints of Tuberculosis Cases in Cluster and Unique Forms

Fingerprints of tuberculosis cases occur in either cluster (where each fingerprint infects at least two patients) or unique form (where each fingerprint infects only one patient). In Manitoba, 479 cases out of 610 (between 1992 and 1997) had isolates and, of this number, 321 (67.0%) belonged to the cluster group. The remaining 158 (32.9%) cases were infected with unique fingerprints. Table 2 displays the data regarding the distribution of cluster and unique fingerprints among different groups of tuberculosis cases with isolates. Group classification of tuberculosis cases in Table 2 is identical to that of Table1. In most groups, over 50% of all cases occur in cluster form. Two apparent

exceptions include the group of foreign-born individuals in which only 37.8% of fingerprints are in cluster form and people 65 years of age or older with 49.2% of cases in the same cluster form. For unique form fingerprints, less than 50% of all cases in most groups fall within this category. Once again, foreign-born cases and patients 65 years of age or older constitute the two exceptions, with 62.2% and 50.8% of cases, respectively, involving unique fingerprints.

Table 2 also shows the number of different fingerprints in each group of cluster and unique form fingerprints. From this data it is very interesting to notice and compare two important groups, the first being the group of foreign-born individuals and the second being the group of treaty patients. While foreign-born patients have a higher number and therefore a higher percentage of cases with unique fingerprints than any other group, the number and percentage of cases sharing cluster fingerprints is consequently low among these patients in comparison with the remaining groups. Conversely, the opposite can be said of treaty patients. In this instance, the number and percentage of cases infected with unique fingerprints is considerably low while the number and percentage of treaty patients infected with cluster fingerprints is higher than any other group. Thus the picture we derive about foreign-born patient fingerprint types indicates that this group of patients likely contracted tuberculosis prior to immigration to Canada or landing in Manitoba and these fingerprints were introduced upon their arrival to Manitoba. Among treaty patients, on the other hand, the pattern of fingerprint spread favors the notion of a tuberculosis outbreak among these individuals.

Table 2 Cluster (more than two patients per FP) and unique (one patient per FP) fingerprint distribution among different group types (1992-1997).

Groups	Total (n)		Cluster			Unique	
	FP*	patients	FP*	(n)	(%)	(n)**	(%)
Total	194	479	36	321	67.0	158	32.9
Non-Treaty	72	128	22	78	60.9	50	39.1
Treaty	47	216	23	192	88.9	24	11.1
Foreign-Born	101	135	17	51	37.8	84	62.2
Rural Reserves	27	116	15	104	89.7	12	10.3
Rural Non-Reserves	33	51	9	27	52.9	24	47.1
Urban Winnipeg	144	292	30	177	60.6	114	39.0
Urban Non-Winnipeg	17	20	9	12	60.0	8	40.0
Respiratory †	147	374	35	262	70.1	112	29.9
Non-Respiratory †	67	103	21	57	55.3	46	44.7
New Active cases	183	430	36	283	65.8	147	34.2
Relapse cases	21	49	10	38	77.6	11	22.4
Age (0 – 14)	14	18	10	14	77.8	4	22.2
(15 – 24)	21	44	11	34	77.3	10	22.7
(25 – 44)	70	172	30	132	76.7	40	23.3
(45 – 64)	55	113	18	76	67.3	37	32.7
(> 65)	91	132	24	65	49.2	67	50.8

FP* = Number of fingerprints in total and cluster form. (n)** = Number of patients and fingerprints in unique form. †In two cases the site of infection was not identified.

8.3 Frequency of IS6110-RFLP Fingerprints

One hundred and ninety-four different fingerprint types were identified from these 479 cases, 36 of which occurred in cluster form and 158 of which were unique. Clustered fingerprints were shared by as few as two patients or as many as 115 patients per fingerprint. Among these clustered fingerprints, 17 different fingerprint types were shared by two patients. Another three different clustered fingerprints were each shared by three patients, three fingerprints were each shared by four patients, two fingerprints were each shared by eight patients

and three fingerprints were each shared by ten patients. The remaining eight different fingerprints infected 115, 24, 22, 20, 14, 11, 9 or 5 patients. The dominant fingerprint was clearly fingerprint type 1, affecting 115 (24.0%) of all cases with isolates.

Table 3 shows the frequency of different fingerprints among tuberculosis cases in Manitoba between 1992 and 1997. Of the 479 tuberculosis cases with isolates, 321 (67%) cases occurred in cluster form while the remaining 158 (32.9%) cases involved unique fingerprints.

8.4 Frequency of Fingerprints and Yearly Distribution

Table 4 shows the frequency of fingerprints together with the time of spread between 1992 and 1997. In this table, cluster fingerprints with 9 patients or more can be seen in at least four years out of six, meaning that there was new ongoing spread of these fingerprints between 1992 and 1997. For the 17 cluster fingerprints each infecting two patients, eight of these were diagnosed in the same year. Eight tuberculosis cases with fingerprint type 15 were diagnosed in 1997. Unique fingerprints composed 25% to 42.5% of all tuberculosis cases throughout the years of 1992 to 1997, peaking at 42.5% in 1997.

Table 3 Frequency of IS6110-RFLP fingerprints in Manitoba tuberculosis cases with isolates (1992-1997)

Fingerprint Type	Total	
	(n)	(%)
Cluster		
1	115	24.0
5	24	5.0
2	22	4.6
72	20	4.2
71	14	2.9
73	11	2.3
112	10	2.1
77	10	2.1
3	10	2.1
14	9	1.9
15	8	1.7
179	8	1.7
37	5	1.0
59	4	0.8
171	4	0.8
132	4	0.8
127	3	0.6
109	3	0.6
142	3	0.6
8	2	0.4
12	2	0.4
43	2	0.4
44	2	0.4
56	2	0.4
75	2	0.4
87	2	0.4
97	2	0.4
98	2	0.4
105	2	0.4
107	2	0.4
117	2	0.4
120	2	0.4
125	2	0.4
152	2	0.4
153	2	0.4
192	2	0.4
Subtotal Cases in Clusters	321	67.0
Unique Cases	158	32.9
Total Cases	479	100.0

Table 4 Frequency of IS6110-RFLP fingerprints and yearly distribution in Manitoba tuberculosis cases with isolates (1992-1997)

Fingerprint Type	1992	1993	1994	1995	1996	1997	1992-97
1	8	28	31	19	18	11	115
5	0	5	5	5	6	3	24
2	2	5	2	1	7	5	22
72	3	4	6	1	2	4	20
71	1	4	2	4	0	3	14
73	3	2	0	2	4	0	11
112	2	1	3	2	2	0	10
77	2	0	2	2	0	4	10
3	1	1	2	0	3	3	10
14	3	0	0	2	3	1	9
15	0	0	0	0	0	8	8
179	0	0	3	2	2	1	8
37	2	2	0	1	0	0	5
59	0	3	0	0	1	0	4
171	0	0	0	1	2	1	4
132	1	0	0	1	1	1	4
127	1	1	0	0	1	0	3
109	1	0	0	2	0	0	3
142	0	0	1	1	0	1	3
8	1	0	0	0	1	0	2
12	2	0	0	0	0	0	2
43	0	0	2	0	0	0	2
44	1	1	0	0	0	0	2
56	0	0	0	2	0	0	2
75	1	0	1	0	0	0	2
87	0	0	0	2	0	0	2
97	0	1	0	0	1	0	2
98	0	0	0	1	1	0	2
105	0	1	0	0	1	0	2
107	0	0	1	1	0	0	2
117	2	0	0	0	0	0	2
120	2	0	0	0	0	0	2
125	2	0	0	0	0	0	2
152	1	1	0	0	0	0	2
153	0	0	0	2	0	0	2
192	0	2	0	0	0	0	2
Subtotal Cases in Clusters	42	62	61	53	56	46	321
Unique Cases	21	21	28	30	25	34	158
Total Cases	63	83	89	83	81	80	479

4.5 Population Subgroups and Tuberculosis Fingerprints

Table 5 addresses the distribution of tuberculosis fingerprints in Manitoba among different population subgroups. Clustered fingerprints have been arranged individually in addition to unique fingerprints. Non-treaty patients were infected by 47 different fingerprints while treaty and foreign-born patients were infected by 72 and 101 different fingerprints, respectively. Although four fingerprints (FP1, FP2, FP15 and FP59) infected all three population subgroups, large number of fingerprints appear to exclusively infect only one subgroup.

Treaty patients represent the largest group of tuberculosis patients, with 216 individuals or 45.1% of all treaty patients in Manitoba having isolates. In total, this population subgroup was infected with 47 different kinds of fingerprints. Twenty-three clustered fingerprints infected 192 (88.9%) of the treaty patients while the remaining 24 (11.1%) treaty patients were infected with unique fingerprints. Out of the 23 clustered fingerprints, 5 fingerprints exclusively infected treaty patients. Another 13 clustered fingerprints had at least 50% or more of their patients treaty people. Interestingly, though treaty people formed the largest group of tuberculosis patients, this group was also infected with the fewest number of fingerprints. This observation supports the notion of an active, viable tuberculosis outbreak among this population subgroup.

Seventy-two fingerprints affected non-treaty patients. Twenty-two of these fingerprints were clustered and infected 78 (60.9%) individuals. Unique fingerprints, (50) claimed 39.1% of non-treaty patients. One clustered fingerprint

was exclusively non-treaty. For ten other clustered fingerprints, 50% or more of their patients were non-treaty.

Foreign-born patients had the largest number of fingerprints (101) and 51 (37.8%) individuals of foreign-born origin shared 17 clustered fingerprints. Eight different clustered fingerprints were exclusively foreign-born while another 6 clustered fingerprints had 50% or more of their subjects as foreign-born individuals. The dominant fingerprint was FP112 with 9 foreign-born subjects and one non-treaty patient. Unique fingerprints, in total, were responsible for infection in 84 (62.2%) foreign-born individuals.

Table 5 Fingerprint types identified in population subgroups in Manitoba (1992-1997)

Fingerprint Type	Canadian-Born				Foreign-Born	
	Non-Treaty		Treaty			
	(n)	(%)	(n)	(%)	(n)	(%)
1	26	22.6	87	75.7	2	1.7
2	5	22.7	14	63.6	3	13.6
15	5	62.5	1	12.5	2	25.0
59	1	25.0	1	25.0	2	50.0
125	1	50.0	1	50.0	0	0
5	2	8.3	22	91.7	0	0
72	6	30.0	14	70.0	0	0
71	3	21.4	11	78.6	0	0
73	5	45.5	6	54.5	0	0
14	8	88.9	1	11.1	0	0
179	1	12.5	7	87.5	0	0
37	4	80.0	1	20.0	0	0
171	1	25.0	3	75.0	0	0
12	1	50.0	1	50.0	0	0
43	1	50.0	1	50.0	0	0
44	1	50.0	1	50.0	0	0
192	1	50.0	1	50.0	0	0
112	1	10.0	0	0	9	90.0
109	1	33.3	0	0	2	66.7
107	1	50.0	0	0	1	50.0
153	1	50.0	0	0	1	50.0
8	0	0	1	50.0	1	50.0
56	2	100.0	0	0	0	0
77	0	0	10	100.0	0	0
75	0	0	2	100.0	0	0
87	0	0	2	100.0	0	0
97	0	0	2	100.0	0	0
98	0	0	2	100.0	0	0
3	0	0	0	0	10	100.0
132	0	0	0	0	4	100.0
127	0	0	0	0	3	100.0
142	0	0	0	0	3	100.0
105	0	0	0	0	2	100.0
117	0	0	0	0	2	100.0
120	0	0	0	0	2	100.0
152	0	0	0	0	2	100.0
Subtotal Cases in Cluster	78	24.3	192	59.8	51	15.9
Unique	50	31.6	24	15.2	84	53.2
Total Cases	128	26.7	216	45.1	135	28.2

8.6 Tuberculosis Fingerprints and Age Distribution

Table 6 analyzes Manitoba tuberculosis fingerprints and the age distribution of their corresponding patients. Clustered fingerprints are tabled individually in addition to unique fingerprints. These fingerprints are subsequently divided into five age group categories.

The first age group (0-14) had 14 fingerprints of which 10 occurred in cluster form to create 14 (77.8%) cases and 4 (22.2%) of which were unique.

Twenty-one different fingerprints infected the second age group (15-24). Clustered fingerprints accounted for 11 different types and were responsible for 34 (77.3%) cases. On the other hand, 10 unique fingerprints were responsible for 22.2% of the cases.

The third group (25-44) represents the largest age group with 172 patients. Of the 70 total fingerprints, 40 were unique and 30 were clustered, with the latter infecting 132 (76.7%) individuals. Fifty-nine (34.2%) of the cases in this group involved fingerprint 1.

One hundred and thirteen cases occurred in individuals between the ages of 45 and 64. Among these patients, 55 different fingerprints could be identified. Thirty-seven unique fingerprints were found in 32.7% of the cases, while 18 clustered fingerprints infected 76 (67.3%) of the cases. Patients infected with fingerprint type 1 represented 25.7% or 29 cases.

The fifth and final group (≥ 65) represents the second largest group of patients, with 132 cases infected by 91 fingerprints. The fact that this group has the largest number of unique fingerprints (67 types or 50.8% of all cases),

indicates that many infections in the elderly are the result of reactivation of previous infection. In contrast, less than 50% of all cases in this age category involved clustered fingerprints with only 24 types being of this form. Patients infected with fingerprint type 1 represent 7.6% of all cases, a number much lower than that of other groups.

Table 6 Age distribution of different fingerprint patterns in Manitoba (1992-1997)

Fingerprint Type	Age					Total
	0 – 14	15 – 24	25 – 44	45 – 64	> 65	
1	4	13	59	29	10	115
5	0	3	10	7	4	24
2	0	1	5	8	8	22
72	0	1	2	8	9	20
71	1	3	9	2	1	14
73	0	1	4	2	4	11
112	1	3	2	1	3	10
77	1	1	3	2	3	10
3	1	0	4	3	2	10
14	2	1	4	2	0	9
15	0	6	2	0	0	8
179	1	0	2	2	3	8
37	0	0	2	2	1	5
59	0	0	3	0	1	4
171	0	1	2	1	0	4
132	0	1	2	1	0	4
127	0	0	0	2	1	3
109	1	0	1	0	1	3
142	0	0	2	0	1	3
8	0	0	1	0	1	2
12	0	0	1	0	1	2
43	0	0	1	1	0	2
44	0	0	0	0	2	2
56	0	0	0	0	2	2
75	0	0	0	0	2	2
87	1	0	1	0	0	2
97	0	0	1	0	1	2
98	0	0	2	0	0	2
105	0	0	2	0	0	2
107	0	0	0	0	2	2
117	0	0	0	1	1	2
120	0	0	2	0	0	2
125	0	0	2	0	0	2
152	0	0	1	0	1	2
153	1	0	1	0	0	2
192	0	0	1	1	0	2
Number of Clusters	10	12	30	18	24	36
Unique	4	10	40	37	67	158
Total Cases	18	44	172	113	132	479

8.7 Tuberculosis Fingerprints and Site of Infection

Table 7 deals with tuberculosis fingerprints in Manitoba and the site of infection. While respiratory tuberculosis affected 374 (78.1%) patients, non-

respiratory tuberculosis affected 103 (21.5%) cases. In two cases the site infection could not be identified. Among all respiratory tuberculosis cases, 147 different fingerprints were identified. One hundred and twelve unique fingerprints infected 29.9% of respiratory patients while 35 different clustered fingerprints were responsible for 262 (70.1%) respiratory cases. Among the 35 clustered fingerprints, 14 were 100% respiratory in nature, another 8 fingerprints had at least 70% respiratory patients and 12 had 50% to 70% respiratory patients. The remaining one fingerprint had 33.3% respiratory patients.

Among the 103 non-respiratory cases, 67 total fingerprints were identified, 46 of which were unique and 21 of which were clustered. Only one fingerprint with two patients was exclusively non-respiratory. The remaining fingerprints had a wide range (7% - 66.7%) of non-respiratory patients.

Table 7 Tuberculosis fingerprint types and site of infection in Manitoba from 1992-1997

Fingerprint Type	Total	Respiratory		Non-Respiratory	
	(n)	(n)	(%)	(n)	(%)
1	115	107	93.0	8	7.0
5	24	22	91.7	2	8.3
2	22	13	59.1	9	40.1
72	20	15	75.0	5	25.0
71	14	12	85.7	2	14.3
73	11	6	54.5	5	45.5
112	10	6	60.0	4	40.0
77	10	6	60.0	4	40.0
3	10	7	70.0	3	30.0
14	9	9	100.0	0	0
15	8	8	100.0	0	0
179	8	7	87.5	1	12.5
37	5*	4	80.0	0	0
59	4	3	75.0	1	25.0
171	4	4	100.0	0	0
132	4*	2	50.0	1	25.0
127	3	1	33.3	2	66.7
109	3	3	100.0	0	0
142	3	1	66.7	2	33.3
8	2	2	100.0	0	0
12	2	2	100.0	0	0
43	2	1	50.0	1	50.0
44	2	2	100.0	0	0
56	2	2	100.0	0	0
75	2	1	50.0	1	50.0
87	2	2	100.0	0	0
97	2	2	100.0	0	0
98	2	2	100.0	0	0
105	2	1	50.0	1	50.0
107	2	1	50.0	1	50.0
117	2	2	100.0	0	0
120	2	1	50.0	1	50.0
125	2	0	0	2	100.0
152	2	2	100.0	0	0
153	2	2	100.0	0	0
192	2	1	50.0	1	50.0
Unique	158	112	70.9	46	29.1
Total Cases	479	374	78.1	103	21.5

* Site of infection was not identified for two cases (0.4% of the total)

8.8 Fingerprints Types and Residence of Tuberculosis Patients

As seen in Table 8, the majority of tuberculosis cases with isolates live in Winnipeg. Consequently, a majority of fingerprint types are also found in the same area. In Winnipeg alone there were 292 tuberculosis cases with 144 different fingerprint types. Of these cases, 39% were infected with (114) unique fingerprints while the remaining 178 (61%) individuals were infected by one of 30 clustered fingerprints. The dominant single fingerprint was fingerprint type 1, being responsible for 70 (24%) Winnipeg cases. Twenty cases occurred in urban areas other than Winnipeg. Eight of these involved unique fingerprints while 12 fingerprints occurred in cluster form.

In rural areas, reserves were the main reservoir of tuberculosis cases. Of the 116 reserve cases, 12 (10.3%) involved unique fingerprints and 104 (89.7%) involved one of 15 clustered fingerprints for a total of 27 different fingerprint types. Fingerprint type 1 was identified in 39 (33.6%) cases, thereby becoming the dominant fingerprint. In rural areas other than the reserves, 51 cases were found. Unique fingerprints were identified in 24 (47.1%) cases while 27 (52.9%) cases involved one of 9 clustered fingerprints.

Table 8 Number of tuberculosis cases by fingerprint type and residence in Manitoba from 1992-1997

Fingerprint type	Residence (Rural)		Residence (Urban)	
	Reserve	Non-Reserve	Winnipeg	Non-Winnipeg
1	39	5	70	1
5	15	4	4	1
2	10	1	11	0
72	4	5	9	2
71	7	6	0	1
73	0	3	5	3
112	1	0	9	0
77	9	0	1	0
3	0	1	9	0
14	3	0	6	0
15	0	0	7	1
179	7	0	0	1
37	1	0	4	0
59	0	0	4	0
171	0	0	4	0
132	0	0	4	0
127	0	0	3	0
109	0	0	3	0
142	0	0	3	0
8	0	1	1	0
12	1	0	1	0
43	0	0	2	0
44	0	1	0	1
56	0	0	1	1
75	2	0	0	0
87	2	0	0	0
97	2	0	0	0
98	1	0	1	0
105	0	0	2	0
107	0	0	2	0
117	0	0	2	0
120	0	0	2	0
125	0	0	2	0
152	0	0	2	0
153	0	0	2	0
192	0	0	2	0
Unique	12	24	114	8
Total	116	51	292*	20

*Three patients gave both Winnipeg and non-Winnipeg addresses. Consequently, this value may be either 292 or 295.

Figure 1 Manitoba Map and the reserves with treaty patients infected by cluster fingerprints

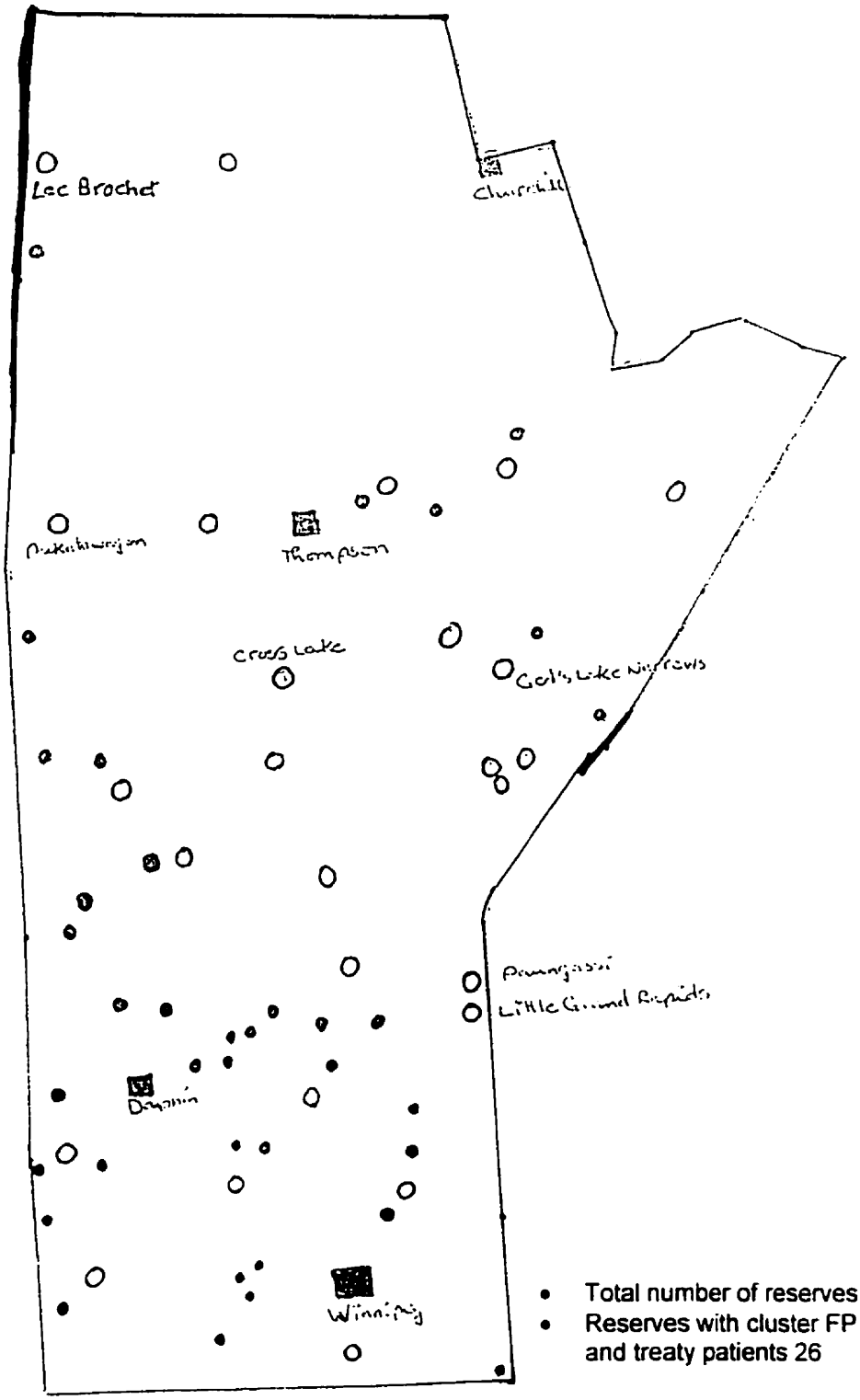


Figure 2 Manitoba Map and the reserves with treaty patients infected by cluster fingerprint type 1

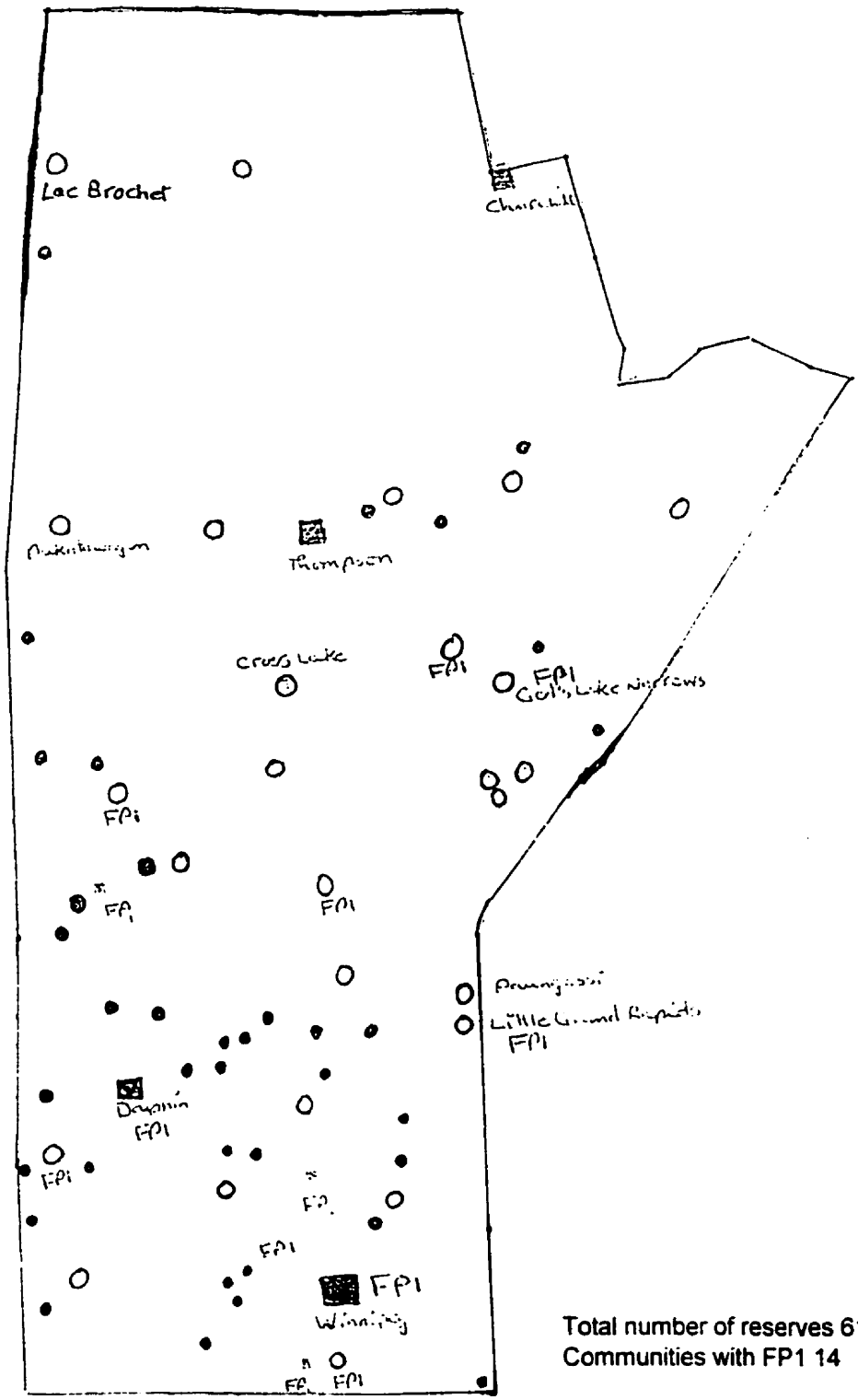


Figure 3 Manitoba Map and the reserves with treaty patients infected by cluster fingerprint type 5

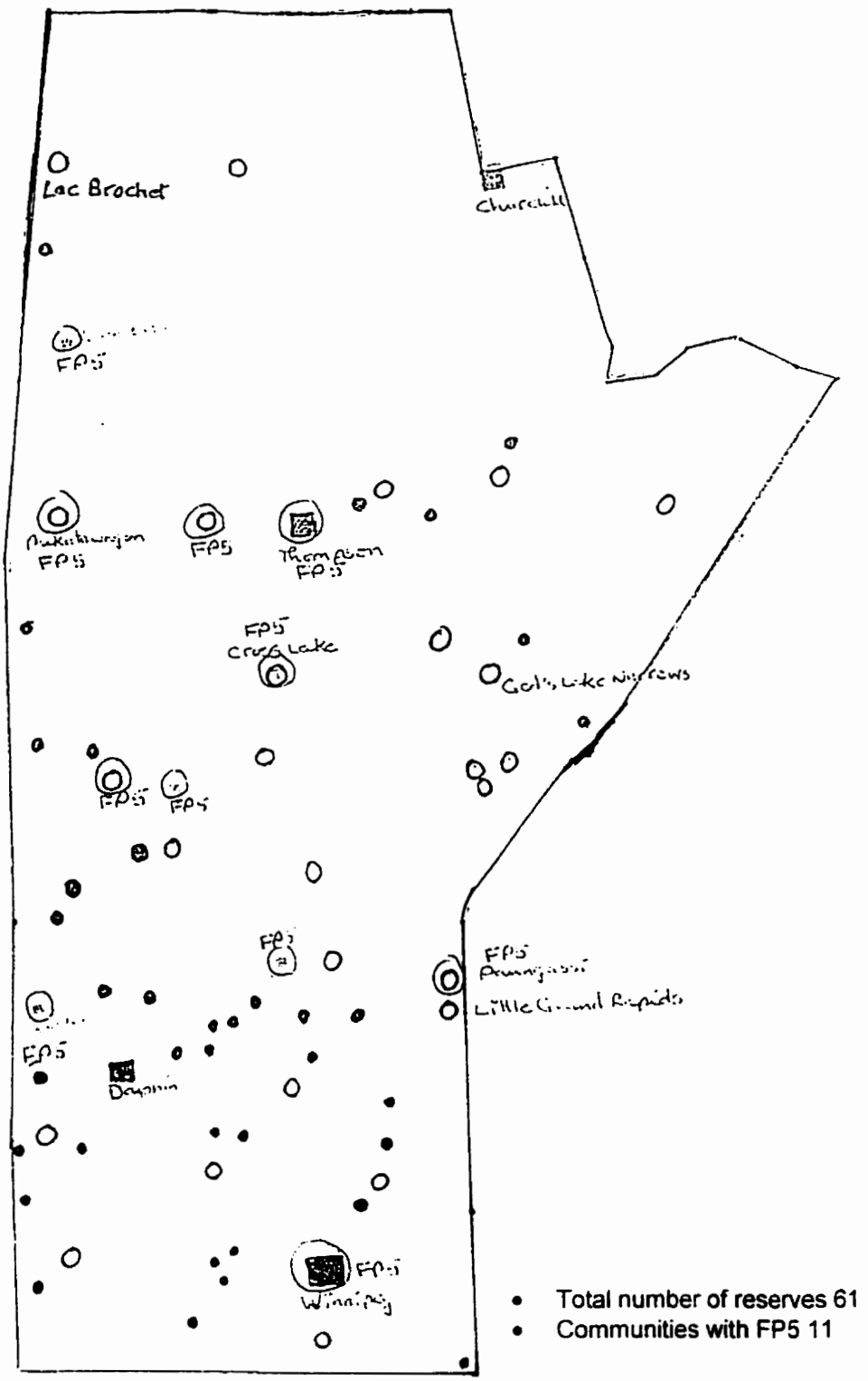


Figure 4 Manitoba Map and the reserves with treaty patients infected by cluster fingerprint type 2

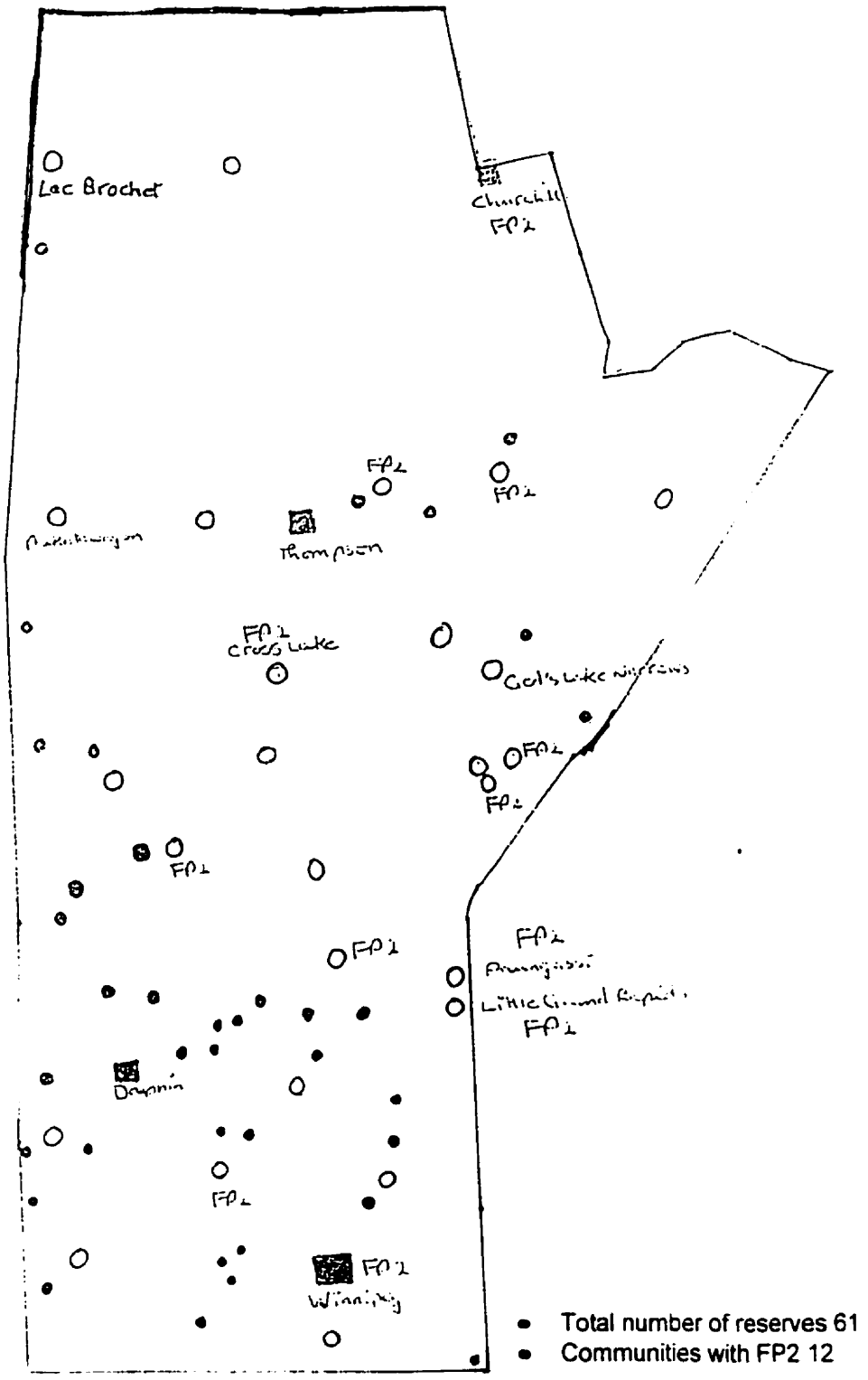
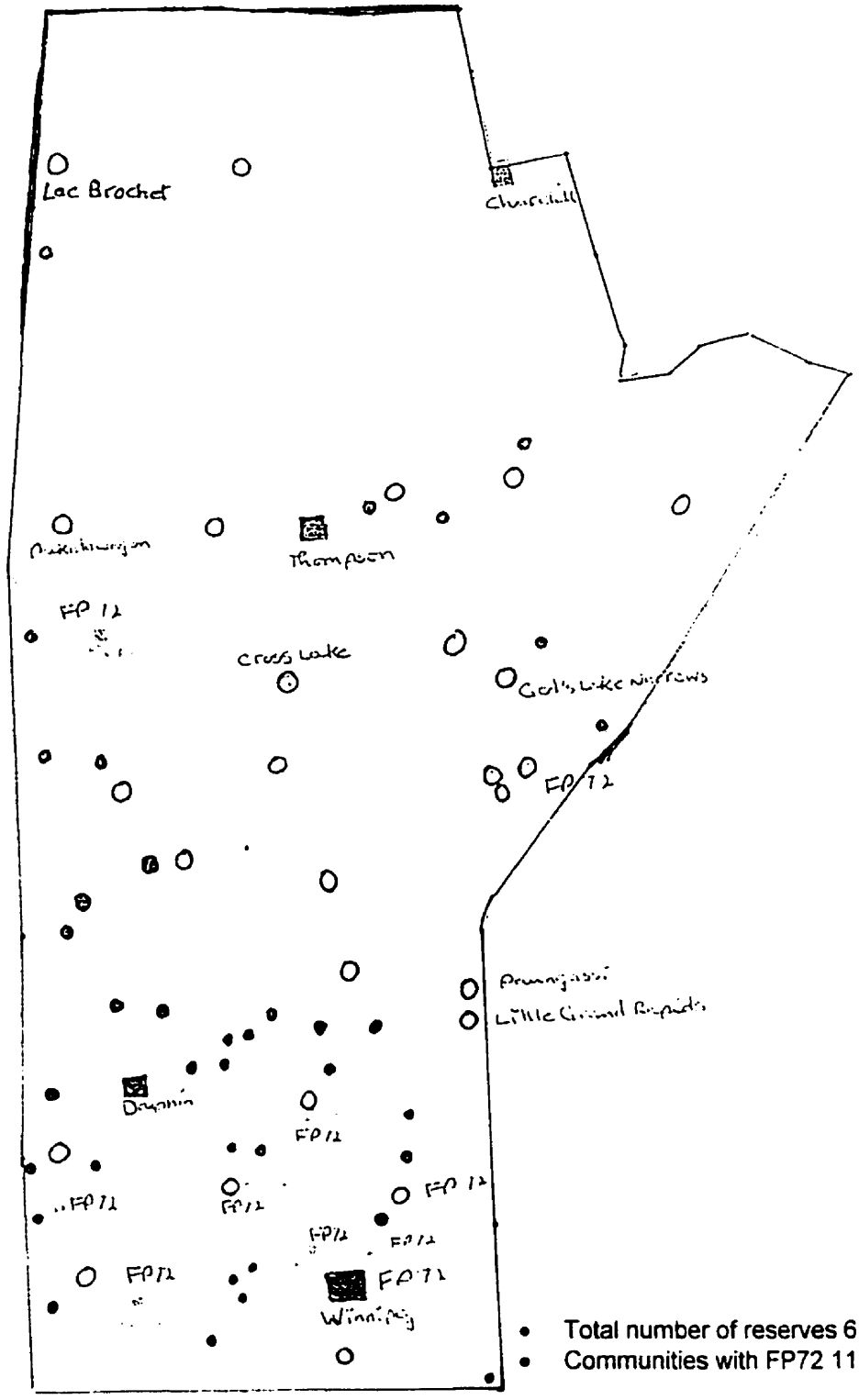


Figure 5 Manitoba Map and the reserves with treaty patients infected by cluster fingerprint 72



8.9 Fingerprint Distribution Among Treaty Patients Living on Reserves

Out of 116 tuberculosis patients with isolates living on reserves, 102 were treaty patients. Unique fingerprints infected 11 (10.8%) cases. Cluster fingerprints infected 91 (89.2%) individuals with 12 different fingerprints. God's Lake Narrows was clearly the hottest outbreak spot with 26 cases with isolates, 23 of which were infected by fingerprint type 1. Pukatawagan was the second hot spot with 10 cases with isolates. On this reserve the two dominant fingerprints were FP5 (5) and FP71 (4).

Figure 1 provides us with a diagrammatic representation of the Manitoba reserves with treaty patients infected by clustered fingerprints. Out of the 61 total reserves in Manitoba, 26 reserves (open circle) harbored clustered fingerprints. Figure 2 shows us the distribution of fingerprint type 1. Between reserve and non-reserve areas, fingerprint type 1 spread among 14 different communities. Winnipeg had the largest number of patients with 72 cases; while God's Lake Narrows was the second hottest spot with 23 patients followed by Little Grand Rapids with 6 patients. Moose Lake had 3 patients and Waywayseecappo had 2 cases. The remaining 9 communities each had one tuberculosis case infected by fingerprint type 1. Figure 3 displays the distribution of tuberculosis fingerprint type 5 in 11 communities of Manitoba, including Winnipeg. Fingerprint type 2 was found in 12 communities of Manitoba while fingerprint type 72 was found in 11 communities. Excluding fingerprint types 71 and 179, the common feature among clustered fingerprints with 3 patients or more was their existence in Winnipeg in addition to many other communities.

8.10 Countries of Origin of Foreign-Born TB cases with Cluster Fingerprint

The purpose of Table 9 is to investigate the possibility of foreign-born tuberculosis patients with clustered fingerprints contracting their fingerprints in Manitoba versus somewhere outside the province. Among foreign-born tuberculosis cases in Manitoba between 1992 and 1997 there were 17 fingerprints in clustered form. Table 9 contains these clustered fingerprints as well as the countries of origin for the patients infected by them. Fingerprint 112 is the largest single fingerprint in terms of the number of patients it infects. Fingerprint type 3 spread among patients from five different countries, all of which had immigrated from South East Asia. In comparison, fingerprint type 2 spread among patients from Africa, South East Asia and Canada, indicating that the disease was likely contracted somewhere in Manitoba. Similarly, since the two patients infected with fingerprint1 were originally from India and Malta, these foreign-born patients probably contracted tuberculosis while in Manitoba. A similar conclusion can also be drawn for fingerprint 59 since the foreign-born patients affected with this fingerprint originated from Jamaica and the Philippines.

Table 9 Countries of origin of patients with clustered fingerprint tuberculosis cases in Manitoba (1992-1997)

Countries	(n)		Countries	(n)
Fingerprint 3			**Fingerprint 109**	
Vietnam	4		Vietnam	1
Laos	3		Laos	1
Cambodia	1		**Fingerprint 8**	
China	1		Italy	1
Hong Kong	1		**Fingerprint 107**	
Fingerprint 2			India	1
Africa	1		**Fingerprint 112**	
Ethiopia	1		Philippine	9
Vietnam	1		**Fingerprint 117**	
Fingerprint 1			Philippine	2
India	1		**Fingerprint 120**	
Malta	1		Philippine	2
Fingerprint 15			**Fingerprint 127**	
Kenya	1		Philippine	3
Saudi Arabia	1		**Fingerprint 132**	
Fingerprint 59			Philippine	4
Philippine	1		**Fingerprint 142**	
Jamaica	1		Philippine	3
Fingerprint 105			**Fingerprint 152**	
Philippine	1		Philippine	2
Hong Kong	1		**Fingerprint 153**	
			Philippine	1

9

Discussion

Tuberculosis in Manitoba is experiencing a declining trend, especially when we compare the tuberculosis incidence rate between 1992 and 1997 (9.2 per 100,000 person –year) with the rates of tuberculosis in Manitoba from the dawn of this century until the 1960's. Nevertheless, this value still significantly exceeds the 1995 national incidence rate of 6.5 per 100,000 (Njoo et al., 1998). Furthermore tuberculosis in Manitoba is unlike tuberculosis in other Canadian provinces in its composition of patients. Foreign-born tuberculosis patients represent 81% of Ontario tuberculosis patients, 48% of Quebec tuberculosis patients and 60% of tuberculosis patients in British Colombia (Long et al., 1999). In Manitoba, foreign-born tuberculosis patients represented 28% of the total tuberculosis cases between 1992 and 1997. Treaty subgroup patients, with 42.8% of all tuberculosis cases in Manitoba, comprised the largest group of cases despite the fact that they represent only 8.9% of Manitoba's population. Furthermore, the incidence rate of tuberculosis among treaty patients (44.3) was higher than both the provincial rate of 9.2 and the national rate of 6.5 by 4.8 and 6.8 times respectively. In comparison, the non-treaty population of Manitoba (excluding foreign-born and treaty individuals) represents 78.1% of the total provincial population but they enjoy the low tuberculosis incidence rate of 3.5 per

100,000 person-year. The tuberculosis incidence rate among treaty people was 12.7 times higher than the non-treaty incidence rate while the foreign-born incidence rate was 5.7 times greater than this same rate. Incidence rates among the three population subgroups increased with age. This increase was more pronounced among individuals 65 years of age or older (Chapter 5, Table 7).

Treaty people remain at high risk of developing tuberculosis even when they no longer reside on reserves. For example, incidence rates among treaty people living in Winnipeg or in other locations (urban area other than Winnipeg and rural area other than the reserve) were 56.2 and 88.1 per 100,000 person-year respectively. Both values are noticeably higher than the reserves of 33.7 per 100,000 person-year (Chapter 6, Table 3). The reason for this high tuberculosis incidence rate among displaced treaty persons is thought to be explained by the tremendous amount of stress experienced by these people when moved from their reserve sanctuary, thereby making them more vulnerable to tuberculosis infection. This increase could alternately be explained by the fact that when treaty individuals move to a place such as Winnipeg, their subsequent exposure to individuals with tuberculosis will increase their chance of developing tuberculosis; consequently the incidence rate will also increase.

Among treaty tuberculosis patients 86.6% of the cases were respiratory in nature. Foreign-born tuberculosis patients had 60.8% respiratory cases. Since respiratory cases are more infectious than non-respiratory, treaty patients are subsequently more infectious. This finding clarifies why tuberculosis in treaty patients appears to occurs as point source outbreaks.

More than three-quarters (78.5%) of all cases of tuberculosis had isolates. With the exception of children aged 0-14 years, a high percentage of isolates (between 69% and 85%) were found among all groups of Manitobans. This high percentage of cases with isolates among different population groups indicates that the results are generalizable to the entire population. The low percentage (39.1%) of isolates in children aged 0 – 14 years is probably due to the fact that most of these cases are primary tuberculosis cases (which are seldom diagnosed with isolates).

The first question someone may ask about tuberculosis fingerprints in Manitoba is why do we observe such a large number (194) of fingerprints among the cases with isolates, especially unique (only one patient infected by each unique fingerprint) fingerprints (158)? It would subsequently follow that the second logical question would address the source of those strains responsible for unique fingerprints since such fingerprint types are unique to the province of Manitoba? We can understand that foreign-born patients might bring their unique fingerprints from their home countries, but it is considerably more difficult to comprehend how Canadian-born patients, in general, and treaty people, in particular, contracted such unique fingerprints. In view of the fact that treaty patient economic status is low and because some of the patients are children less than 14 years of age (Chapter 8, Table 2), travel outside the province or country is limited. The only reasonable explanation, therefore, would suggest that stringent techniques may produce a large pool of unique fingerprints that are not really unique. A second explanation, related to the bacteria, the host, or a

combination of both, may be that after infection, bacteria become dormant and that this dormancy might lead to substantial genetic changes in the bacteria and, consequently, lead to the development of a new strain.

One of the benefits of the molecular fingerprinting technique is that is gives us the opportunity to study the composition and type of fingerprints among tuberculosis cases with isolates in Manitoba. The dominance of single fingerprint (FP1) was found in 24.0% (115) of cases with isolates (Chapter 8, Table 3) and in 35.8% (321) of clustered fingerprints (Chapter 8, Table 2). Furthermore, It was found to infect mainly Canadian-born patients (113 person 98.3%)(Chapter 8, Table 5).

Clustered fingerprints indicate the existence of outbreaks and, In addition, give us an idea about the extent of secondary spread. Figures show that 192 (88.9%) of all treaty patients were infected by clustered fingerprints. While 51(37.8%) foreign-born patients were infected by this type of fingerprints. Four different clustered fingerprints infected all the three population subgroups, although it remains unknown why these fingerprints infected all population subgroups and the remaining fingerprints did not. The common feature among clustered fingerprints with large numbers of patients was that each had patients both in Winnipeg and scattered throughout selective reserves. Seventeen clustered fingerprints had two patients each and nine of these (fingerprints) had their patients diagnosed with tuberculosis in the same year. Although 4 fingerprints with two patients in each cluster had their patients diagnosed in consecutive years, the significance of this difference may not be important if one

patients was diagnosed in December and the other was diagnosed in January of the following year. Four more clustered fingerprints with two patients in each cluster had at least one full year between the diagnosis of the first and the second case. Although the last group might be classified as clustered, in reality this group of patients more closely resembles one infected by unique fingerprint.

The majority of clustered fingerprints in foreign-born patients infected people from the region where they originally immigrated from. Except for eight clustered fingerprints in which the patients were foreign-born as well as Canadian-born, five fingerprints had only two patients (most of whom were family members and one of which was born in Canada). This implies that foreign-born patients pose less of a danger in passing their infection to the main stream population than we might expect. On the contrary, it seems that Canadian-born patients may be responsible for transmission of this disease to the foreign-born patient group.

The high percentage of unique fingerprints among different age groups appeared to increase with age. Unique fingerprints were identified in up to one forth of all tuberculosis cases with isolates involving individuals 44 years of age or younger and this proportion increased to one-third among patients between 45 and 64 years of age. Almost half of all cases in patients 65 years of age or older involved unique fingerprints. These findings suggest that the older the patients, the greater his/her chance of developing a unique fingerprint. Another important finding is the distribution of different fingerprints among various places of residence. Some Manitoba reserves had as many as 12 unique fingerprints, an

unexpected observation due to the remote nature of these locales. In Winnipeg, unique fingerprints represented 40% of tuberculosis cases.

Eight fingerprints in Manitoba infected only foreign-born people while five infected only treaty individuals. Only one fingerprint infected exclusively non-treaty individuals. Looking at foreign-born tuberculosis patients in Manitoba, we find 17 clustered fingerprints infecting 51 (37.8%) patients. Only 23 of these patients were infected with fingerprints shared by patients in other population subgroups. A number of patients infected with those fingerprints shared between foreign-born people and non-treaty people were found to be related. For example, children of immigrants are considered to be non-treaty if they are born in Canada and this classification would consequently result in patients from different population subgroups being infected by the same fingerprints. The data shows, that only 23 patients (17.0%) out of 135 cases with isolates shared their clustered fingerprints with other population subgroups. This finding indicate that the transmission of tuberculosis between foreign-born patients and other population subgroups is minimal. We can only speculate on the reasons for this pattern. Language, cultural and social barriers present an obvious obstacle however other factors related to the bacteria or the host may also cause a delay in bacterial transmission.

Tuberculosis in Manitoba is a multifaceted problem. We can divide tuberculosis in Manitoba into two main categories, domestic and imported. Domestic tuberculosis is so named because the source of both the strain and the subject as well as their place of exposure or infection is Manitoba. Treaty people

are the subjects of such disease and, although various tuberculosis strains common to multiple patients are frequently identified, FP1 is the predominant strain responsible for the domestic tuberculosis. Despite the fact that the reason for the dominance of FP1 remains unknown, it has been speculated that perhaps this strain was the first strain introduced to Manitoba. Host and/or strain virulence factors may also play a role. Routine BCG usage among treaty people could further foster the natural selection of FP1 by increasing body protection against other susceptible strains through selective immunity. Winnipeg and the reserves of northern Manitoba are the two reservoirs which maintain the bulk of tuberculosis cases with clustered fingerprints. Sixty percent of Manitoba's entire population lives in Winnipeg (Chapter 6, Table 1) and traffic between Winnipeg and the reserves is continuous. Since neither geography nor physical distance can provide a barrier to stop the spread of this disease perhaps the types of contact relationships are important factors in the spread of the tuberculosis. The presence of a high percentage of respiratory tuberculosis cases and the large number of positive smear results among FP1 patients suggests that this population subgroup may be more infectious than other groups. Delay in or lack of health service provision may, to some extent, also explain the spread of disease and the frequent occurrence of cavitary disease in treaty people.

Imported tuberculosis is the other facet of the tuberculosis problem in Manitoba. The dominance of unique fingerprints among foreign-born individuals suggests that these patients have contracted the disease outside the province and have subsequently imported tuberculosis into Manitoba during the

immigration procedure. Foreign-born tuberculosis patients reside largely in the Winnipeg area and spread of the disease from foreign-born patients to the main stream society is limited.

Molecular fingerprinting is a very useful tool, allowing us to understand the tuberculosis problem in Manitoba. Without the help of fingerprinting, we would not be able to distinguish between the domestic and imported problem in terms of the subjects and type of tuberculosis fingerprint spread among them. Molecular fingerprinting also identifies the fingerprints that infect each population subgroup, emphasizes characteristics such as dominance of fingerprint type 1, reveals the presence of clustered and unique fingerprints and disclose the distribution of different fingerprints both geographically and demographically. It can also help in confirming the accuracy of contact tracing results.

The disadvantage of this technique however, is that it inadvertently creates a large number of fingerprints to the extent of causing confusion when we attempt to understand unique fingerprints. Nevertheless, we cannot be certain that these fingerprints are a result of this technique or a consequence of unknown phenomenon. In addition, fingerprinting can only be done retrospectively.

In conclusion, this study has described the advantages and disadvantages of the molecular fingerprinting technique, the status of tuberculosis in Manitoba and the contribution of molecular fingerprinting to the knowledge and understanding of this problem.

Further research suggested by this study includes the study of the dominant fingerprint type 1, unique fingerprints, transmission of different fingerprints and secondary transmission between different population subgroups.

10

References

Borgdorff MW. Nagelkerk NJD. VAN Soolingen D. Broekmans JF. 1999. Transmission of tuberculosis between people of different ages in the Netherland: An analysis using DNA fingerprinting. *Int J Tuberc Lung Dis.* 3 (3): 202-206.

Canada Communicable Disease Report. 1998. Proceedings of the national consensus conference on tuberculosis. Dec 3-5, 1997.

The Canadian lung association. 1996. Canadian tuberculosis standard. Fourth edition. The Lowe-Martin Group Inc.

Casper C. Singh SP. Rane S. Daley CL. Schecter GS. Riley LW. Kreiswirth BN. 1996. The transcontinental transmission of tuberculosis: A molecular epidemiological assessment. *American Journal of Public Health.* 86 (4): 551-553

Cave MD. Eisenach KD. Templeton G. Salfinger M.Mazurek G. Bates JH. and Crawford JT. 1994. Stability of DNA fingerprint patern produced with IS6110 in strains of *Mycobacterium tuberculosis. Journal of Clinical Microbiology. 32*(1): 262-266

Cohan DL, O'Brien RJ. 1998. The use of restriction fragment length polymorphism (RFLP) analysis for epidemiological studies of tuberculosis in developing countries. *Int J Tuberc Lung Dis.* 2(1):16-26.

Dimensions Series: Ethnocultural and Social Characteristics of the Canadian Population [94F004XCB], Ottawa: Statistics Canada, 1999.

Dimensions Series: Portrait of Aboriginal Population in Canada [94F0011XCB], Ottawa: Statistics Canada, 1999.

Dolin PJ. Raviglione MC. Kochi A. 1994. Global tuberculosis incidence and mortality during 1990-2000. *Bulletin of the World Health Organization.* 72 (2): 213-220.

Drobniewski FA. Kent RJ, Stoker NG and Uttley. 1994. Molecular biology in the diagnosis and epidemiology of tuberculosis. *Journal of Hospital Infection.* 28: 249 – 263.

Drobniewski FA. Pozniak AL. 1996. Molecular diagnosis, detection of drug resistance and epidemiology of tuberculosis. *British Journal of Hospital Medicine.* 56 (5): 204-208

Enarson DA, Grzybowski. 1986. Incidence of active tuberculosis in the native population of Canada. *CMAJ.* 134:1149-1152

Fanning AE. 1998. Globalization of tuberculosis. *CMAJ.* 158:611-2.

Ferguson RG, Simes AB. 1949. BCG vaccination of Indian infant in Saskatchewan. *Tubercle.* 30:5-11.

Frieden TR. Woodley CL. Crawford JT. Lew D. Dooley SM. 1996. The molecular epidemiology of tuberculosis in New York city: The importance of nasocomial transmission and laboratory error. *Tubercle and Lung Disease.* 77: 407-413.

Fomukong NG. Tang TH. Al-Maamary. Ibrahim WA. Ramayah S. Yates M. Zainuddin ZF. 1994. Insertion sequence typing of *Mycobacterium tuberculosis:* characterization of widspread subtype with single copy of IS 6110. *Tubercle and Lung Disease.* 75: 435-440.

French AL. Welbel SF. Dietrich SE. Mosher LB. Breal PS. Paul WS. Kocka FE. Weinstein RA. 1998. Use of DNA fingerprinting to assess tuberculosis infection control. *Annals of Internal Medicine.* 129 (11): 856-862.

Frideres JS. 1983. Native people in Canada contemporary conflects. Second edition. Prentice-Hall Canada Inc., Scarborough, Ontario.

Genewein A. Telenti A. Bernasconi C. Mordasini C. Weiss S. Maurer AM. Rieder HL. Schopfer K. Bodmer T. 1993. Molecular approach to identifying route of transmission of tuberculosis in the community. *Lancet.* 342: 841-44.

Gicquel B. 1993. RFLP typing of *Mycobacterium tuberculosis* bacilli. *Tubercle and Lung Disease.* 74: 223-224.

Grzybowski S. Allen EA. 1999. Tuberculosis: 2. History of the disease in Canada. *CMAJ.* 160(7): 1025-1028.

Grzybowski S. 1983. Tuberculosis: A look at the world situation. *Chest.* 84:756-761

Hart CA, Beeching NJ, Duerden BI. 1996. Tuberculosis into the next century. *J. Med Microbiol.* 44:1-34.

Hermans PWM. VAN Soolingen D. Dale JW. Schutema ARJ. McAdam RA, Catty D. VAN Embden JDA. 1990. Insertion element IS986 from *Mycobacterium tuberculosis:* a useful tool for diagnosis and epidemiology of tuberculosis. *Journal of Clinical Microbiology.* 28 (9): 2051-2058.

Kimerling ME. Benjamin WH. Lok KH. Curtis G. Dunlap NE. 1998. Restriction fragment length polymorphism screening of *Mycobacterium tuberculosis* isolates: Population surveillance for targeting disease transmition in a community. *Int J Tuberc Lung Dis.* 2(8):655-662.

Kochi A. (1991) The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercle* 72:1-6.

Live Database 1992-1997, Indian Registry System, Indian and Northern Affairs Canada. Manitoba Region.

Long R, Njoo H, Hershfield E. 1999. Tuberculosis: 3. Epidemiology of the disease in Canada. *CMAJ.* 160(11): 1185-1190.

MacMorran J. 1997. Tuberculosis. A handbook for public health nurses and other health care worker. 3rd edition, Manitoba Lung Association.

Njoo H, Nault P, Farzad E. 1998. Tuberculosis in Canada 1996. LCDC, Health Protection Branch, Health Canada.

Pablos-Mendez A, Raviglione MC, Laszlo A, et al. (1998) Global surveillance for antituberculosis-drug resistance, 1994-1997. *N Engl J Med,* 338(23): 1641-1649.

Piheu JA. 1998. Tuberculosis 2000: problem and solutions. *Int J Tuberc Lung Dis.* 2(9):696-703.

Raviglione MC. Snider DE. Kochi A. 1995. Global epidemiology of tuberculosis: Morbidity and mortality of a worldwide epidemic. *JAMA*, 273(3):220-226.

Shafer RW. Small PM. Larkin C. Singh SP> Kelly P. Sierra F. Schoolnik G and Chirgwin KD. 1995. Temporal trend and transmission patterns during the emergence of multidrug-resistant tuberculosis in New York city: A molecular epidemiology assessment. *The Journal of Infectious Diseases.* 171(January): 170-176.

Thierry D. Brisson-Noil A. Vincent-Levy-Frebault V. Nguyen S. Guesdon JL. And Gicquel B. 1990. Caracterization of a *Mycobacterium tuberculosis* insertion sequence, IS6110 and its application in diagnosis. *Journal of Clinical Microbiology.* 28 (12): 2668-2673.

VAN Deutekom H. Gerritsen JJJ. VAN Soolingen D. VAN Ameijden EJC. VAN Embden JDA and Coutinho RA. 1997. A molecular epidemiological approach to studing the transmission of tuberculosis in Amsterdam. *Clinical Infectious Diseases.* 25:1071-7

VAN Embden JDA. Cave MD. Crawford JT. Dale JW. Eisnach KD. Gicquel B, Hermans P. Martin C. McAdam R. Shinnick TM. And Small P. Strain identification of *Mycobacterium tuberculosis* by DNA fingerprinting: Recommendation for a standarized methodology. 1993. *Journal of Clinical Microbiology*. 31(2): 406-409.

Waldram JB. Herring DA. Young TK. 1995. Aboriginal health in Canada. University of Toronto press.

Wherret GJ. 1964. Royal commission on health services, tuberculosis in Canada.

Wilkins K. 1996. Tuberculosis, 1994. *Health reports*. 8(1):33-39