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Conventional and molecular epidemiology of Tuberculosis in Manitoba

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Abstract

Background: To describe the demographic and geographic distribution of tuberculosis (TB) in Manitoba, thus determining risk factors associated with clustering and higher incidence rates in distinct subpopulations.

Methods: Data from the Manitoba TB Registry was compiled to generate a database on 855 patients with tuberculosis and their contacts from 1992–1999. Recovered isolates of *M. tuberculosis* were typed by IS6110 restriction fragment length polymorphisms. Bivariate and multivariate logistic regression models were used to identify risk factors involved in clustering.

Results: A trend to clustering was observed among the Canadian-born treaty Aboriginal subgroup in contrast to the foreign-born. The dominant type, designated fingerprint type I, accounts for 25.8% of total cases and 75.3% of treaty Aboriginal cases. Among type I patients residing in urban areas, 98.9% lived in Winnipeg. In rural areas, 92.8% lived on Aboriginal reserves. Statistical models revealed that significant risk factors for acquiring clustered tuberculosis are gender, age, ethnic origin and residence. Those at increased risk are: males ($p < 0.05$); those under age 65 ($p < 0.01$ for each age subgroup); treaty Aboriginals ($p < 0.001$), and those living on reserve land ($p < 0.001$).

Conclusion: Molecular typing of isolates in conjunction with contact tracing data supports the notion of the largest ongoing transmission of a single strain of TB within the treaty-status population of Canada recorded to date. This data demonstrates the necessity of continued surveillance of countries with low prevalence of the disease in order to determine and target high-risk populations for concentrated prevention and control measures.

Background

Tuberculosis (TB) has infected one-third of the world population and kills three million people each year. Glo-

bally, TB is considered the most common cause of death from a single infectious organism, *Mycobacterium tuberculosis* [1–3]. Canadians have a long history of suffering

tremendously from TB. In the 19th century, one fifth of Canadians were infected with this disease and large numbers died. In the beginning of the 20th century, the mortality rate among Aboriginal people of Saskatchewan and Alberta reached as high as 9,000 per 100,000 [4,5].

Improvements in socioeconomic conditions, public health services, drug therapy and medical surveillance in Canada markedly reduced the mortality rate [0.4 per 100,000 by 1987] and overall incidence rates (5.9 per 100,000 by 1998) [6]. However, certain groups in Canada are at higher risk for acquiring TB, such as the Aboriginal population (defined as status and non-status Indian, Metis, Inuit, and Innu), foreign-born individuals from countries with high prevalence rates of TB, the homeless and the HIV-infected population [6]. In 1998, the incidence rate among non-Aboriginal Canadians was 1.5 per 100,000; in contrast, the status Indian, total Aboriginal and foreign-born population had incidence rates of 35.4, 22.5 and 21.4 per 100,000 respectively [7]. Furthermore, the proportion of TB cases reported in Canada from the foreign-born population has increased, from 35% in 1980 to 64% in 1998 [7]. In an attempt to eliminate tuberculosis in Canada, the Tuberculosis Prevention and Control Unit of Health Canada implemented guidelines recommended by the World Health Organization in 1997 [6]. Despite adoption of these guidelines, incidence rates of TB are still high in certain geographic and demographic zones, making elimination of the disease by recommended time periods put forth by Health Canada an increasingly difficult goal [6,8]. Currently, incidence rates in Canada have leveled off and remain fairly constant due to these sustaining population subgroups.

The majority (75%) of TB patients in Canada live in three provinces: Ontario, Quebec and British Columbia. Furthermore, 90% of all TB cases in the country attributed to the foreign-born population reside in these provinces [9]. In Manitoba however, the composition of TB patients is distinctly different: the majority of TB cases are among Canadian-born, with the highest incidence among treaty Aboriginals (48.4 per 100,000 overall, with rates as high as 496.3 per 100,000 in select communities [10,11].

These distinct epidemiological patterns merited a further examination. Consequently, in this study, both conventional in conjunction with molecular methods were used to describe the epidemiology of tuberculosis in Manitoba from 1992 to 1999. The objectives of the study were to describe subgroups within Manitoba at high risk for developing TB, and to define risk factors and possible reasons for the ongoing transmission in order to better target prevention and control programs.

Methods

Setting

Manitoba has a population of 1.14 million (Statistics Canada, 1996). 78.1% are Canadian-born (CB) non-treaty, 8.9% are treaty Aboriginals, and the remainder is foreign-born (FB) [12,13]. It is unknown how many Aboriginal individuals have not claimed treaty status. All diagnosed cases of tuberculosis in Manitoba are registered in the Manitoba Central Tuberculosis Registry (MCTR) at the Health Sciences Center (HSC) in Winnipeg. Case finding in Manitoba is done by clinical diagnosis of symptomatic patients and by contact tracing. Administered treatment is drug therapy of a combination of first line antituberculosis drugs: rifampin, isoniazid, pyrazinamide, ethambutol, and/or streptomycin. Direct observed therapy (DOT) verifies a completed course of treatment. Ninety-five percent of patients under DOT complete treatment in Manitoba [8].

Sample Data

Data on all TB patients and identified contacts from January 1, 1992 to December 31, 1999 was obtained from the MCTR. Data fields such as the patient's unique identifier number, date of birth, birthplace, sex, country of birth, postal code, origin (CB treaty / non-treaty or FB), date of diagnosis, case finding method, TB status (new, active or relapse), BCG status, year of landing (foreign patients), smear results, culture results, TB DNA fingerprint type, drug resistance, chest X-rays and cavity status were extracted from the patient records and the information was entered into a database. This data set did not include patient name, allowing data analysis while maintaining the patient confidentiality. Specimens were collected by designated medical staff at the Respiratory Clinic, HSC, and other health care centers in Manitoba. The collected samples were sent to the Clinical Microbiology Laboratory at HSC for isolation and identification of *M. tuberculosis*. The Accuprobe *M. tuberculosis* complex kit (GenProbe Incorporated, San Diego, CA, USA) was used to identify *M. tuberculosis* in the clinical samples. Samples were subsequently processed for DNA sub-typing according to the internationally standardized methodology of IS6110 restriction fragment length polymorphisms (RFLP) [14]. Procedures outlined by Small *et. al.* to minimize the possibility of cross-contamination [15] was strictly adhered to by staff at the HSC and no evidence of cross-contamination was observed.

RFLP Analysis

All gel pictures containing the IS6110 RFLP patterns were analyzed to determine clustering using Molecular Analyst[®] Software Fingerprinting version 1.12, BioRad, Hercules, CA, USA. Clustering establishes groups of patients from which isolates with identical or near identical fingerprints are found and are likely to be linked epidemiologically

Table 1: Bivariate logistic regression analysis of risk factors associated with clustering.

Characteristic	Incidence (person-year/100 000)	Clustered n = 426 (%)	Non-Clustered n = 203 (%)	Odds Ratio (95%) CI	p value
<u>Sex</u>					
Female	8.4	167 (39.2)	102 (50.2)	1 (reference)	
Male	10.1	259 (60.8)	101 (49.8)	1.57 (1.12–2.19)	0.011
<u>Age*</u>					
0 to 14	3.1	18 (4.2)	4 (2.0)	4.61 (1.39–16.84)	0.004
15 to 24	5.8	51 (12.0)	17 (8.4)	3.07 (1.58–6.03)	0.000
25 to 44	10.4	170 (39.9)	47 (23.1)	3.70 (2.33–5.89)	0.000
45 to 64	10.7	102 (23.9)	48 (23.6)	2.17 (1.35–3.52)	0.000
65 +	18.4	85 (20.0)	87 (42.9)	1	
<u>Origin</u>					
Canadian-Born (non-treaty)	3.3	97 (22.8)	60 (29.6)	1	
Canadian-Born (treaty)	48.4	254 (59.6)	27 (13.3)	5.82 (3.46–9.54)	0.000
Foreign-Born	20	75 (17.6)	116 (57.1)	0.340 (0.261–0.620)	0.000
<u>Residence</u>					
Winnipeg	9.7	235 (55.1)	153 (75.4)	1	
other urban	4.1	14 (3.3)	11 (5.4)	0.829 (0.369–1.829)	0.809
reserves	33.7	148 (34.7)	15 (7.4)	6.424 (3.563–10.947)	0.000
other rural	9.2	29 (6.9)	24 (11.8)	0.787 (0.443–1.392)	0.051
<u>Site of Infection</u>					
Extrapulmonary		111 (26.1)	66 (32.5)	1	
Pulmonary		315 (73.9)	137 (67.5)	1.367 (0.951–1.969)	0.112

* χ^2 test for overall linear trend in age = 32.6, $p < 0.001$

[16]. Clustered cases were identified by searching each fingerprint against the created database containing all other patterns over the eight-year period using the Dice coefficient with 1.5% position tolerance and verified visually. Isolates with identical patterns or differing by a single band were considered the same [17]. All created databases were stored in Microsoft Access® and linked together utilizing the MCTR unique identifier numbers.

Statistical Analysis

Population figures from the 1996 Statistics Canada Census were used to calculate tuberculosis incidence rates. Since the study was conducted over an eight-year period, the person-year population of Manitoba throughout this time was determined by multiplying the 1996 population by eight. To determine the incidence rate for a specific population subgroup, we added all TB cases in that subgroup from 1992 to 1999 then divided by the total eight-year subgroup person-years. The resulting number was multiplied by 100,000 to obtain the incidence rate per 100,000 person-years. To compare risk factors for recent TB acquisition of the subpopulation of interest, we used clustering versus non-clustering (unique) as the outcome variable. Bivariate and multivariate logistic regression analyses were carried out using NCSS 2000 software (NCSS, Kaysville, UT, USA). Variables used in the bivariate

model (table 1) were gender, age (five subgroups), ethnic origin (three subgroups), residence (four subgroups) and site of infection. A chi-squared test for linear trend was performed on the subgroups. Multivariate models using gender, age, ethnic origin, residence, site of infection, status (new or relapse), drug resistance, BCG status, chest x-ray and cavity were analyzed and potential interactions were assessed for significance. Variables significant at the $p < 0.05$ level were kept in the final multivariate model, summarized in Table 2.

Results

Tuberculosis Trends

Between January 1st 1992 and December 31st 1999, there were 855 reported cases of tuberculosis in Manitoba. The majority of individuals with tuberculosis were born in Canada (70.6%) and almost half of the total patients were CB with treaty status (44.4%). Non-treaty CB individuals contributed 26.2% of total cases and FB population contributed 29.4% (figure 3).

The age distribution of TB cases varies between the three population subgroups. For the treaty status subgroup, the incidence in the oldest (65+) age group was 17.3 times that in the youngest (0–14) age group, whereas this ratio

Table 2: Multivariate logistic regression analysis of risk factors associated with clustering

Characteristic	Incidence (person-year/100 000)	Clustered n = 426 (%)	Non-Clustered (unique) n = 203 (%)	Odds Ratio (95%) CI	p value
Sex					
Female	8.4	167 (39.2)	102 (50.2)	1 (reference)	
Male	10.1	259 (60.8)	101 (49.8)	1.959 (1.306–2.938)	0.0011
Age*					
0 to 14	3.1	18 (4.2)	4 (2.0)	2.55 (0.74–8.88)	0.1401
15 to 24	5.8	51 (12.0)	17 (8.4)	2.53 (1.20–5.34)	0.0151
25 to 44	10.4	170 (39.9)	47 (23.1)	3.26 (1.92–5.54)	0.0000
45 to 64	10.7	102 (23.9)	48 (23.6)	1.47 (0.87–2.50)	0.1523
65 +	18.4	85 (20.0)	87 (42.9)	1	
Origin†					
Canadian-Born (non-treaty)	3.3	97 (22.8)	60 (29.6)	1	
Canadian-Born (treaty)	48.4	254 (59.6)	27 (13.3)	4.108 (2.163–7.803)	0.0000
Foreign-Born	20.0	75 (17.6)	116 (57.1)	0.248 (0.149–0.412)	0.0000
Residence‡					
Winnipeg	9.7	235 (55.1)	153 (75.4)	1	
other urban	4.1	14 (3.3)	11 (5.4)	0.490 (0.195–1.230)	0.1289
reserves	33.7	148 (34.7)	15 (7.4)	1.206 (0.546–2.665)	0.6433
other rural	9.2	29 (6.9)	24 (11.8)	0.410 (0.203–0.830)	0.0132

* age overall effect, χ^2 test = 21.83 with 4 different factors, $p < 0.001$ † origin overall effect, χ^2 test = 81.54 with 2 different factors, $p < 0.001$ ‡ residence overall effect, χ^2 test = 9.26 with 3 different factors, $p < 0.05$

was 10.9 for the non-treaty population, and only 1.3 for the foreign-born population (Figure 3).

Dividing Manitoba into rural and urban categories indicates that the majority of FB individuals and non-treaty Canadians with TB reside within the city of Winnipeg, while the majority of treaty-status individuals with TB reside in rural areas (figure 1). Winnipeg, as the major urban center of Manitoba, hosts 98.4% of all FB TB patients, and 62.8% of total patients. Aboriginal reserve land includes 22.1% (189) of total patients, with nine reserves in northern Manitoba harboring 159 (84%) of these cases. The TB incidence rate per 100,000 person-years for these nine isolated communities ranged from 19.9 to 496.3 per community. Almost all of these cases were in registered treaty individuals. The remaining 15.1% of total patients live in urban areas other than Winnipeg and rural areas other than reserves. Individuals living in urban places other than Winnipeg or rural areas other than reserves experienced a rate of only 4.1 per 100,000 person-year. The overall Winnipeg incidence rate (9.7 per 100,000 person-years) was comparable to the overall Manitoba's rate (9.2 per 100,000 person-years).

Molecular typing and clustering of cases

Isolates of *M. tuberculosis* were obtained from a total of 629 patients (73.6%) for molecular typing to establish clustering. The remaining balance of cases were diagnosed

by means other than microbiological and thus no culture was available for sub-typing. The patient characteristics of these unavailable isolates were compared to those available to observe any significant differences that may affect estimation of clustering. The distribution of patients was roughly the same for both and was deemed not significant. Fingerprint patterns of less than six RFLP bands were observed in 15 isolates. These fingerprints did not cluster, and therefore secondary sub-typing of these isolates, i.e. spoligotyping, was not performed [16].

In total, 249 different fingerprints were obtained, and 203 of them were unique. The 46 that were not unique formed clusters that linked patients into groups containing as little as two and as many as 162 individuals per cluster. The dominant fingerprint type over the study period was fingerprint type 1 (FP1), a strain containing a 12-band IS6110 pattern that was tested sensitive to primary drugs. This strain afflicted 162 (25.8%) individuals of the total TB population, with a very high proportion of treaty individuals (75.3%) residing in both Winnipeg and reserves being infected. By contrast, the second most frequent fingerprint is type 2, infecting only 32 (5.1%) of the total population with TB. The top five fingerprint patterns in terms of prevalence are distributed as seen in figure 5.

The distribution of clustering by the distinct sub-populations is also graphically represented in figure 4. The treaty

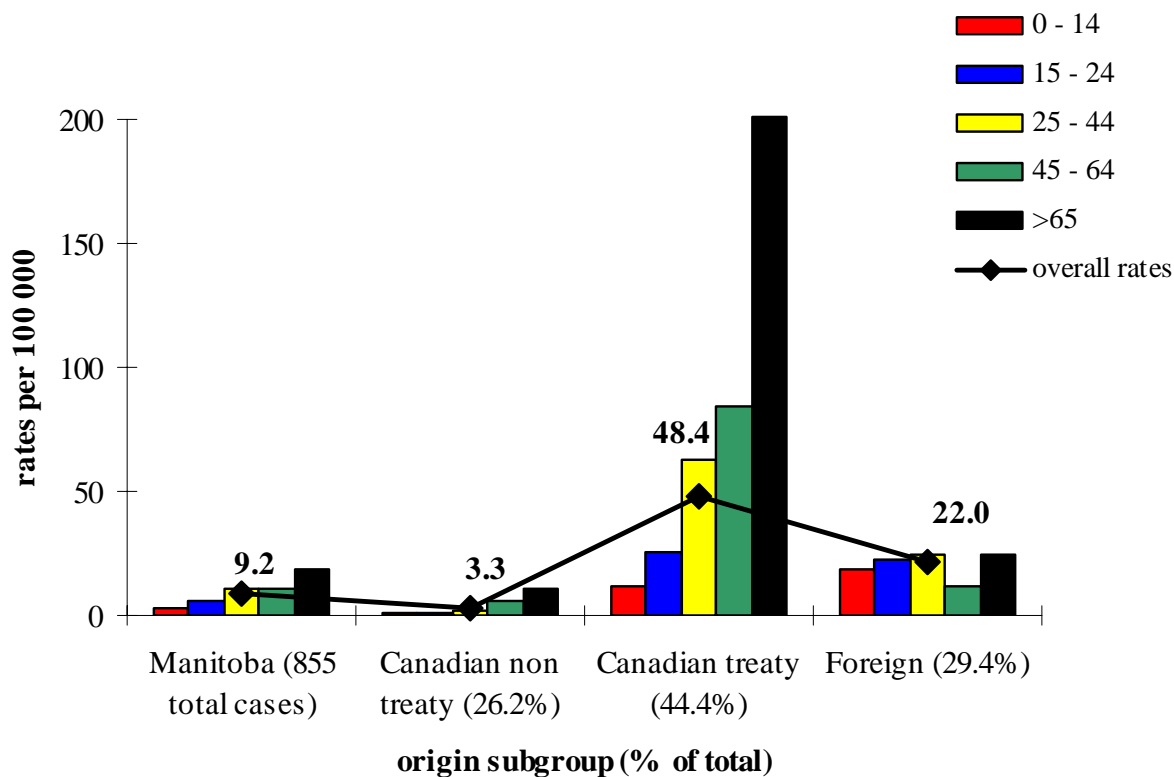


Figure 3
Tuberculosis incidence rates by age group and origin, 1992–1999.

subpopulation contributed 254 (59.6%) of clustered cases; in contrast, the FB population comprised the majority of unique cases (57.2%). Comparison of clustering among geographical subgroups also showed the highest proportion of clustering among the reserves and Winnipeg. Of the 162 FP1 cases, 93 (57.4%) lived in urban areas, and of these, 98.9% were in Winnipeg. Of the 69 (42.6%) living in rural areas, 92.8% resided on reserve land. Furthermore, Winnipeg presented the majority of unique fingerprint types, due to the large proportion of foreign-born persons residing in the city.

Risk Factor Analysis

Analysis of risk factors for clustering using both bivariate and multivariate analysis is summarized in tables 1 and 2. Significant independent risk factors for clustering included gender, age, geographic residence and ethnic origin. Males are twice as likely to develop clustered TB than

females (table 2). Treaty status patients are at four times higher risk of developing clustered TB than those without treaty status (reference subgroup), while in comparison, foreign-born patients are at one-quarter the risk for developing clustered TB compared to the reference population. TB patients in the four age groups under age 65 had risks of developing clustered TB that ranged from 1.5 to 3.3 times that of those over the age of 65 (table 2). Residence on a reserve was significant in the bivariate analysis: these patients have a five times higher risk of having clustered TB than the patient group that lives in Winnipeg. In the multivariate model, however, controlling for the other variables revealed that residence is not a significant independent risk factor, although living in a rural non-reserve area is protective (table 2). Finally, there was no evidence that patients with pulmonary TB had a higher risk of developing clustered TB than those with extra pulmonary TB.

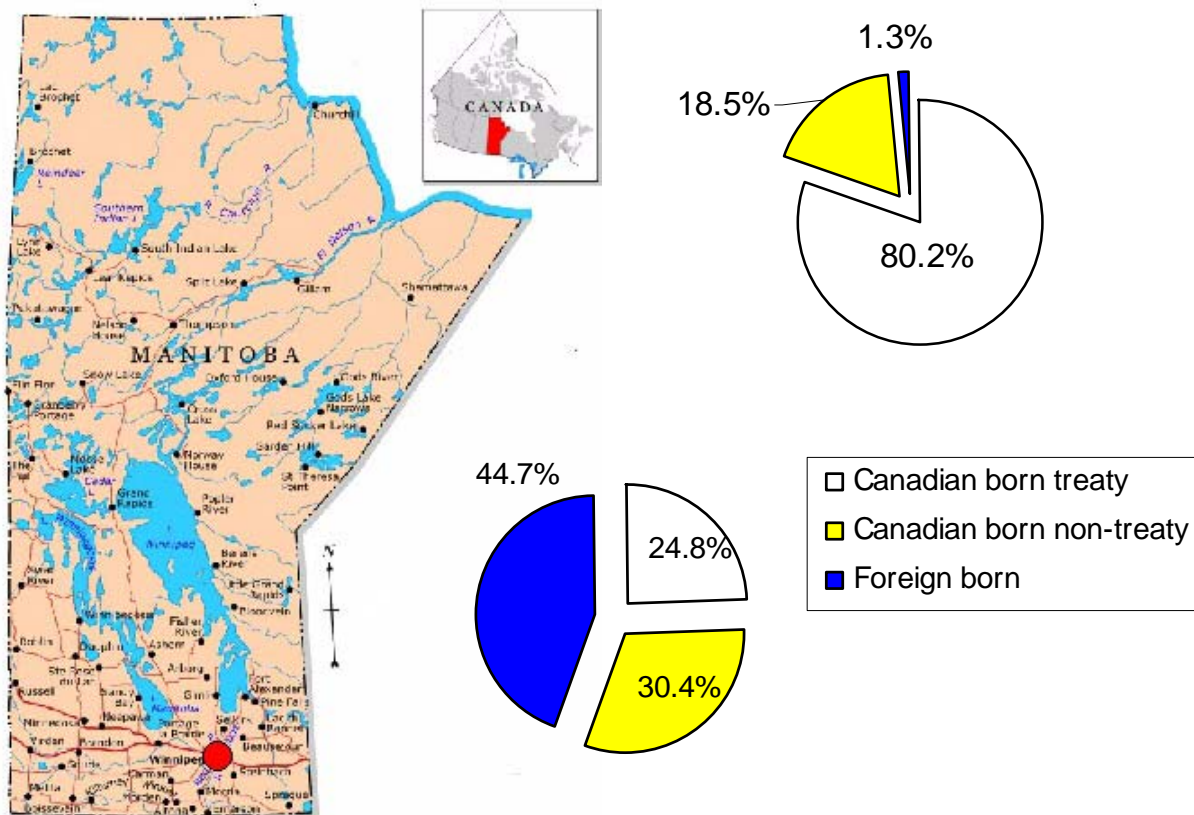


Figure 1
Geographic distribution of tuberculosis patients in Manitoba, 1992–1999. Top chart represents rural Manitoba, in contrast, the bottom depicts urban Manitoba.

Contact Tracing

The largest cluster contained 162 cases that displayed FP1. Contact investigations were indicated on 121 of these cases, determining a total of 2195 contacts. 145 of those contacts presented with disease. Of the 145 contacts, 92 (63.5%) harbored the FP1 strain of TB. 4 (2.8%) had a fingerprint type other than FP1, and the remainder of cases did not have isolates available for typing purposes. Most exposures were from family members (57.5%) or friends (24.5%) in the home (71.7%). Preliminary social network analysis using software packages Ucinet and Pajek revealed the spread of TB from Winnipeg to reserve land and vice versa.

Discussion

The end of World War II marked the beginning of a sharp decline in TB incidence rates in Canada. Unfortunately,

the last 10 years have shown a leveling off of total incidence rates at approximately 7 per 100,000, with no appreciable decline (figure 2) [6,7,9]. Manitoba shares the same national trends [7,10]. Although rates have declined in every subpopulation, comparative rates among CB treaty individuals in Manitoba (48.4 per 100,000) are still more than ten times than those of the non-treaty subgroup (3.3 per 100,000), and more than two times those of the FB subgroup (22.0 per 100,000) (figure 3) [10,11,18]. Furthermore, whereas the overall majority of TB cases in Canada are attributed to immigration, the population distribution of tuberculosis in Manitoba is distinctly different than in the other provinces. While foreign-born cases represent 81% of Ontario TB patients, 48% of Quebec TB patients and 60% of TB patients in British Columbia, in contrast, they represent only 29% of the total TB cases in Manitoba between 1992 and 1999

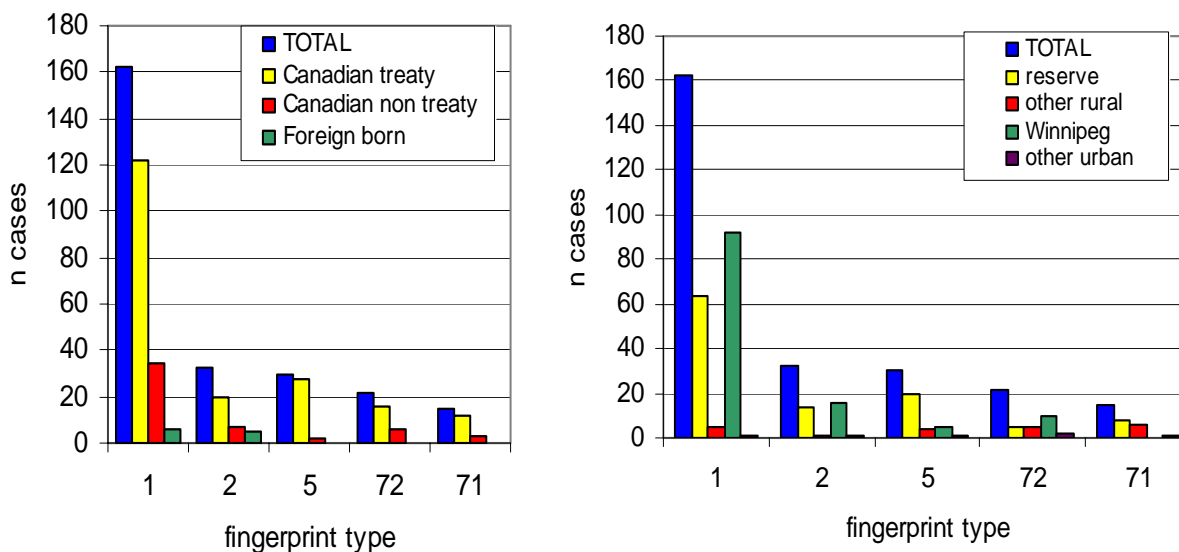


Figure 5
Distribution of the top five prevalent fingerprint types by (a) population subgroup and (b) geographic subgroup, 1992–1999.

[9,18]. It is well established that the foreign-born and Aboriginal groups seem more susceptible to tuberculosis than others within Canada [6,9]. In Manitoba, however, these sub-populations are sustaining the steady level of incidence. Our data demonstrates that TB in Manitoba is a multifaceted problem that can be examined in two distinct, parallel categories. These categories are Canadian TB, where the source of the strains and the patients is Canadian, and foreign TB, where both the patients and strains are from outside Canada.

The major single contributor to the current burden of incident cases is the treaty status subpopulation. The treaty subgroup, with 44.4% of all tuberculosis cases in Manitoba, comprises the largest group of cases, despite the fact that they represent only 8.9% of Manitoba's population. This figure is probably an underestimate of all Aboriginal individuals

who have not claimed treaty status. Moreover, the incidence rate of TB among the treaty status population (48.4 per 100,000) was higher than both the provincial rate (9.2 per 100,000) and the national rate of (5.9 per 100,000) by five and eight times respectively. Certain northern First Nation communities have TB incidence rates that are markedly elevated (up to 496.3 per 100 000 person-years). Statistical analysis showed the treaty subgroup to be at relatively high risk for the development of TB, with significant independent risk factors for clustering to include male gender, treaty status, and under age 65.

More than 75% of the treaty status population group was clustered together by the FP1 strain. Contact tracing revealed only 92 (57%) confirmed epidemiological links within this cluster, living in both Winnipeg and reserve land. Although using both molecular and conventional techniques verifies that linked cases are most likely linked,

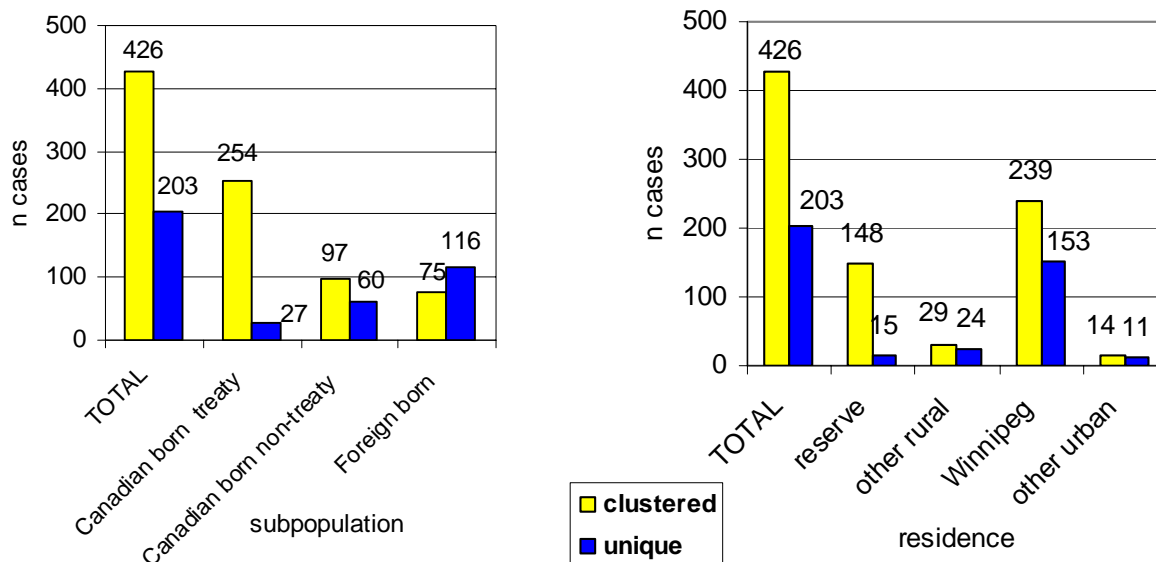


Figure 4
Clustering of fingerprint patterns for (a) population subgroups, (b) geographic subgroups, 1992–1999.

there are limitations to using these techniques [19]. Firstly, transmission can occur through brief, casual contacts, leading to patients having the same fingerprint pattern, yet no definable connection. Secondly, identical RFLP patterns can be obtained from patients that are not linked through recent transmission/reinfection, but due to reactivation. Thirdly, the strain can be inherent in a population, with an unidentifiable source.

However, as clustering is assumed to reflect recent transmission within a population [16,19], supported by the considerable transmission between family and friends as illustrated by contact investigations, it is highly probable that there is an ongoing, propagating TB outbreak in this subpopulation. The presence of a high percentage of respiratory tuberculosis cases and the large number of positive smear results (data not shown) among FP1 patients suggests that TB in this population subgroup may be

transmitted more efficiently than in other subgroups. Potential factors contributing to increased risk in this subpopulation include: relative poverty, crowded housing, dense social networks, delays in diagnosis and treatment, increased susceptibility to infection due to poorer health status, and increased prevalence of substance abuse. Data on these variables was not available for analysis in the present study. In addition, while the HIV positive group was emerging as an at-risk group for TB in the US, it has not yet been recognized as a risk group in Canada [20]. Thus, the HIV status of tuberculosis patients was not routinely determined in Manitoba until 1997; therefore, complete data on this variable was not available for the current study [21].

The reason for the dominance of FP1 remains unknown, although it has been speculated that perhaps this strain was the first strain introduced to Manitoba. Host genetics,

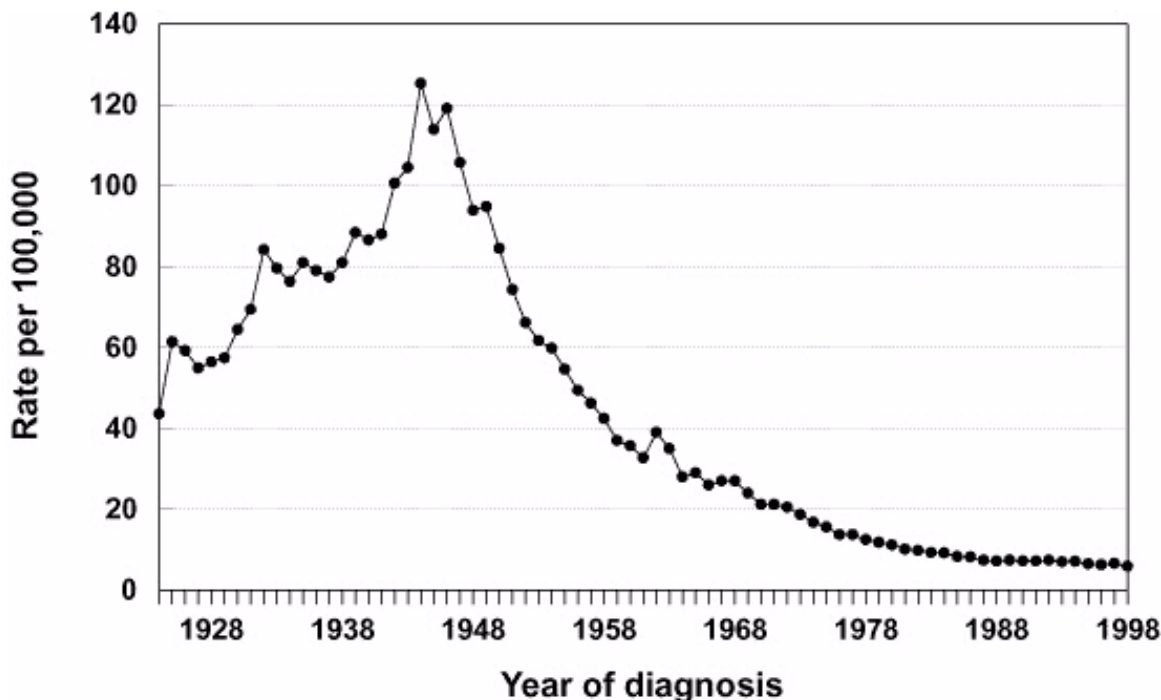


Figure 2
Reported new active and relapsed tuberculosis cases and incidence rate per 100,000 – Canada: 1928–1998.

strain virulence or a combination thereof may play a role [22,23]. Routine BCG administration to treaty status infants could have further fostered the natural selection of FP1 by increasing body protection against other susceptible strains through selective immunity. While it is difficult to disentangle social, economic and host risk factors from our analysis, we speculate that this particular strain may be more virulent than other strains introduced to the population. It is possible that this strain shares some features in common with putatively 'hyper virulent' strains CDC 1551 and/ or HN878 [24,25]. Bacterial virulence factors, their expression, regulation and mutation, and host immune system evasion mechanisms may play a role, and this remains to be studied [23].

Winnipeg and nine Aboriginal reserves of northern Manitoba appear to be the two reservoirs that maintain the bulk of clustered TB cases. Patients on reserves were found

more than six times as likely to have clustered TB compared to patients in Winnipeg using bivariate analysis. Sixty percent of Manitoba's entire population lives in Winnipeg and there is considerable mobility between Winnipeg and the reserve communities. Since neither geography nor physical distance can provide a barrier to stop the spread of this disease, the types of contact relationships are important factors in elucidating the spread of TB and differentiating active transmission versus reactivation.

The epidemiological separation between CB and FB tuberculosis cases is the result of many different characteristics. The dominance of unique (non-clustered) fingerprints among foreign-born individuals suggests that these patients may have contracted the disease outside the province and have subsequently imported tuberculosis into Manitoba through immigration. This was found true of

imported TB in province of Alberta [26]. The age distribution of cases in the foreign-born subgroup reflects the age distribution of immigrants, some of whom for unknown reasons progress to active TB after arrival into Canada. New arrivals into the country may for some time have limited close contact with Canadian-born individuals, which reduces the chance of spread from immigrants to the CB population. The small amount of clustering that does occur in the FB subpopulation may be explained largely by activation of infections acquired from common sources in the foreign country of origin. In Manitoba, FB TB patients reside largely in the Winnipeg area and spread of the disease from FB patients to CB individuals is very limited (data not shown).

While the foreign-born population may not seem to be actively spreading TB in Manitoba, incidence rates are still relatively high, and the number of FB cases reported annually is increasing. Screening procedures for immigrating individuals from countries with high or low prevalence of TB need further examination for effectiveness and cost-effectiveness [27].

In the present study, information derived from both conventional and molecular epidemiology methods allowed assessment of current trends and risk factors for subpopulation groups in Manitoba for contracting TB. Retrospective studies such as this one using stored RFLP data have shown invaluable to identify both clinical and epidemiological risk factors for clustering, and have been used extensively to study other populations within San Francisco, New York and the Netherlands [17,19,28,29]. This information helps assess the effectiveness and possible limitations of the Manitoba TB control programs. Elimination of TB has been defined as less than 1 case per 100,000 population per year [6,8]. By this standard, recent transmission to Canadian-born non-treaty status individuals has been nearly eliminated, reaching incidence rates of only 3.3 per 100,000. Complete elimination of TB in Manitoba has been targeted for 2010, with 5% reduction in incidence per year goal [6,8], but with the high incidence rates in the remaining two sub-populations, this will be a difficult task. Targeting and intensifying control measures in the immigrant and treaty status Aboriginal subpopulations should be a priority in striving for the goal of tuberculosis elimination in Manitoba.

Competing Interests

None declared.

Authors' Contributions

KB coordinated / drafted the final manuscript. AA carried out the data extraction, statistical analysis and initial draft. LE edited and participated/revised in statistical analysis. EH and AK provided the data, designed and supervised

the use of the data for the manuscript. All authors read and approved of the final manuscript.

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