ABSTRACT

Objective: To estimate the prevalence of resistance of *Mycobacterium tuberculosis* to first-line antituberculosis drugs in Canada.

Methods: M. tuberculosis isolates from one third of all culture-positive tuberculosis (TB) cases diagnosed between February 1, 1993 to January 31, 1994 in Canada were collected prospectively. Proportion of drug-resistant isolates and the factors related to drug resistance were measured.

Results: Of 458 study cases, 40 (8.7%) had resistance to at least one first-line antituberculosis drug, of which 5.9% had mono-resistance, 0.7% had multidrug-resistance(MDR-TB) – i.e., resistance to at least isoniazid and rifampin – and 2.2% had other patterns. The overall prevalence of resistance among the foreign-born cases was 10.6% with the highest level among those who resided in Canada for less than four years (15.5%).

Conclusions: Canada has a relatively low prevalence of antituberculosis drug resistance and a very low prevalence of MDR-TB. Some new immigrants to Canada may be at higher risk for drug resistance and their initial treatment needs to be tailored accordingly.

ABRÉGÉ

Objectif : Évaluer la prévalence de la résistance du *mycobacterium tuberculosis* contre le médicament antituberculeux de première ligne au Canada.

Méthodes : Le *mycobacterium tuberculosis* repère un tiers de tous les cas de cultures tuberculosis qui ont fait l'objet d'un diagnostic positif entre le 1er février 1993 et le 31 janvier 1994 au Canada; ces données ont été collectées de manière prospective. On a mesuré la proportion de repère des médicaments résistants et les facteurs reliés à la résistance du médicament.

Résultats : Sur 458 cas étudiés, 40 (8,7 %) se sont avérés résistants à au moins un médicament antituberculeux de première ligne dont 5,9 % se sont avérés résistants à un seul médicament et 0,7 % ont une résistance à plusieurs médicaments (MDR-TB) – c.-à-d. résistants à au moins deux médicaments : l'isoniazid et le rifampin – et 2,2 % avaient d'autres caractéristiques. La prévalence globale de la résistance parmi les cas venus de l'étranger était de 10,6 % dont le niveau le plus élevé a résidé au Canada pendant moins de quatre ans (15,5 %).

Conclusions : Au Canada, la prévalence de la résistance des médicaments antituberculeux est relativement faible. Certains nouveaux arrivants peuvent présenter un risque plus élevé de résistance aux médicaments et leur traitement initial doit être personnalisé en conséquence.

Drug Resistance Study of *Mycobacterium tuberculosis* in Canada, February 1, 1993 to January 31, 1994

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Reports from many countries around the world have documented an increasing prevalence of drug-resistant tuberculosis.[1-5] The last Canadian national drug resistance survey[6] conducted in 1975 reported a drug resistance prevalence of 6.3% among new cases. More recently, a drug resistance survey in Western Canada[7] reported a prevalence of 6.9%. Prevalence of drug resistance was reported to be higher among foreign-born patients[6-9] especially if they developed tuberculosis (TB) within the first few years of their arrival in Canada.[7-9]

Drug-resistant tuberculosis – i.e., resistance to one or more of the first-line antituberculosis drugs including isoniazid (INH), rifampin (RMP), streptomycin (SM), pyrazinamide (PZA) and ethambutol (EMB), and specifically multidrug-resistant tuberculosis (MDR-TB), i.e., resistance to at least isoniazid and rifampin – poses new challenges for both clinical management and TB control programs.[10-13]

In Canada from 1991 to 1996, about 2,000 active cases of TB (7 per 100,000 population) were diagnosed and reported annually[14] with more than 100 deaths per year attributed to TB.[15]

The epidemiology of TB in Canada has changed over the last 15 years. The proportion of foreign-born cases has increased from 35% in 1980 to 63% in 1996 while the proportion of cases occurring in the non-Aboriginal Canadian-born has decreased from 50% to 20% and the proportion of cases among Aboriginal Canadians has remained stable over this period.[14]

To provide a more recent estimate of the prevalence of antituberculosis drug resistance in Canada and to ascertain the potential risk factors related to drug resistance, a collaborative study was initiated by the interested investigators, the Laboratory Centre for Disease Control (LCDC), the provincial and territorial TB Control units, and the provincial and territorial TB laboratories.

METHODS AND MATERIALS

Study design

A descriptive study was designed to determine the prevalence of antituberculo-

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sis drug resistance among TB cases in Canada. Data were collected prospectively over a one-year period.

Sample size

The required sample size was estimated based on the prevalence of drug resistance reported from previous drug resistance surveys and the number of culture-positive TB cases reported in Canada in 1990[16] (1,274), the most recent national statistic available when the study was initiated. The Epi-Info 6.03 statistical package was used to calculate the sample size. It was determined that a sample size of 455 culture-positive cases was needed to detect a drug resistance level of 8% ± 2%, with a 95% confidence interval (CI).

Sample selection

Since the number of reported TB cases varied extensively among different provinces and territories, using a systematic sampling, one third of all culture-positive cases from Quebec, Ontario, Alberta and British Columbia; one half of cases from Saskatchewan and Manitoba; and all cases from Newfoundland, Prince Edward Island, New Brunswick, the Yukon, and the Northwest Territories were selected. This meant that only one half or one third of all cases from provinces with higher case loads were selected, whereas all cases from provinces with lower case loads were selected. Because this sampling method may not have provided a representative sample within the Canadian population, a random sample of cases from the original sample was selected so that one third of all culture-positive TB cases from each of the provincial/territorial laboratories, diagnosed between February 1, 1993 and January 31, 1994, were included in the analyses.

The enrolled cases were assigned a unique study number and their isolates were forwarded to the National Reference Centre for Tuberculosis (NRCT) at LCDC, where they were tested for resistance to the five first-line antituberculosis drugs: isoniazid (INH), rifampin (RMP), streptomycin (SM), pyrazinamide (PZA), and ethambutol (EMB). The radiometric modified proportion method of drug susceptibility testing of *M. tuberculosis* by the BACTEC 460 system was employed.

TABLE I
Distribution of Sex, Age, Disease Activity Status, and Ethnic Origin Among Study Cases and Drug-resistant Cases

	Number of TB Cases (%)		Number of Resistant Cases (%)		Prevalence of Resistance (95% CI)	
Total	458	(100)	40	(100)	8.7	(6.4, 11.8)
Sex						
Male	268	(58.5)	24	(60)	8.9	(5.9, 12.8)
Female	190	(41.5)	16	(40)	8.4	(5.1, 13.0)
Age (years)						
<15	14	(3.1)	0	(0.0)	0.0	
15-45	219	(47.8)	24	(60)	10.9	(7.3, 15.6)
>45	225	(49.1)	16	(40)	7.1	(4.3, 11.1)
Activity Status						
New	401	(87.6)	36	(90)	9.0	(6.5, 12.1)
Relapsed	50	(10.9)	4	(10)	8.0	(2.6, 18.2)
Unknown	7	(1.5)	0			
Ethnic Origin						
Foreign-born	255	(55.7)	27	(67.5)	10.6	(7.2, 14.8)
Canadian-born	194	(42.3)	12	(30)	6.2	(3.4, 10.3)
Aboriginal	86	(18.8)	2	(5)	2.3	(0.3, 7.5)
Non-Aboriginal	108	(23.5)	10	(25)	9.3	(4.8, 15.9)
Unknown	9	(2)	1	(2.5)	11.1	(0.5, 43.9)

TABLE II
Pattern of Drug Resistance in Canada

	Number of TB Cases	Prevalence of Resistance (95% CI)	
Total Number of Isolates	458		
Sensitive to All 5 Drugs	418		
Any Resistance	40	8.7	(6.4, 11.8)
SM	25	5.5	(3.6, 8.1)
INH	20	4.4	(2.8, 6.5)
PZA	7	1.5	(0.7, 3.3)
RMP	3	0.7	(0.2, 2.1)
EMB	1	0.2	(0.0, 1.4)
Mono-resistance	27	5.9	(4.0, 8.3)
SM	14	3.1	(1.7, 4.9)
INH	7	1.5	(0.7, 3.0)
PZA	6	1.3	(0.5, 2.7)
Multidrug Resistance*	3	0.7	(0.16, 1.77)
Other Patterns			
INH + SM	10	2.2	(1.11, 3.86)

* Resistance to at least INH & RMP

Comparative studies[17] have shown the reliability of the radiometric modified proportion method when compared to the conventional proportion method.

An isolate was defined as: 1) drug-resistant if it was resistant to one or more of the five drugs tested, or 2) drug-susceptible if it was sensitive to all drugs. Drug resistance was categorized as: 1) mono-resistance if the isolate was resistant to only one of the first-line antituberculosis drugs, 2) multidrug-resistance (MDR) if the isolate was resistant to at least INH and RMP, and 3) other patterns.

For each case in the study, a questionnaire was completed by the provincial/territorial TB Control units. The same study number was assigned to the questionnaire. Data were collected on gender, age, ethnic origin (foreign-born, non-Aboriginal Canadian-born, and Aboriginal Canadian), TB sites (based on ICD-9 codes), and disease activity status (new disease, relapsed disease). The completed questionnaires were then forwarded to LCDC.

The definitions of new and relapsed disease were consistent with the definitions used in the Canadian Tuberculosis Reporting System. New disease was defined as a case of TB with no history or documentation of previously active tuberculosis and relapsed disease was defined as a case of TB with a history or documentation of previously active tuberculosis that became inactive. Foreign-born individuals were categorized, according to the WHO, as having been born in one of six geographical regions (the Americas, Europe,

TABLE III
Prevalence of Drug Resistance by Province/Territory

Province/Territory	Number of TB Cases (%)		Number of Resistant Cases (%)		Prevalence of Resistance (95% CI)	
Atlantic Provinces	24	(5.2)	2	(5)	8.3	(1.4, 24.9)
Quebec	107	(23.4)	13	(32.5)	12.1	(6.9, 19.4)
Ontario	152	(33.2)	14	(35)	9.2	(5.3, 14.6)
Manitoba	31	(6.8)	0	(0)	0.0	
Saskatchewan	20	(4.4)	1	(2.5)	5.0	(0.2, 22.2)
Alberta	37	(8.1)	2	(5)	5.4	(0.9, 16.7)
British Columbia	79	(17.2)	8	(20)	10.1	(4.8, 18.3)
Yukon & Northwest Territories	8	(1.7)	0	(0)	0.0	
Total	458	(100)	40	(100)	8.7	(6.4, 11.6)

South East Asia, Western Pacific, Eastern Mediterranean, and Africa).[18]

Case inclusion criteria

TB cases were entered into the study if: 1) the NRCT received a viable *M. tuberculosis* specimen for the case, 2) the sampling method had been followed, 3) the culture date was consistent with study time frame, February 1, 1993 to January 31, 1994, and 4) the epidemiological questionnaire was available.

Statistical analysis

The Epi-info version 6.04 statistical package was used to perform descriptive and univariate statistical analyses to determine the prevalence of drug resistance in the study population (i.e., culture-positive cases) and to compare frequency of occurrence of potential risk factors among resistant TB cases. For simple proportions, confidence intervals were obtained by Fisher exact method. For comparison of categorical data, χ^2 test or Fisher exact test (if the expected cell values were less than five) were calculated to determine the statistical significance. For comparison of continuous data, the student t-test was used. For all analyses, a p-value of ≤ 0.05 was considered to be significant.

RESULTS

During the study period, a total of 536 culture-positive TB cases were enrolled in the study. This was slightly in excess of all culture-positive cases that were reported to Statistics Canada in 1993.[19] Upon arrival to NRCT, 78 (14.6%) isolates were excluded from further analyses for the following reasons: 70 isolates did not contain viable *M. tuberculosis*, 6 cases were not selected according to the study sampling frame, and 2 cases were not selected within the study time period. These patients were similar to the 458 patients included in the study except they were more likely to be foreign-born (p = 0.006). However, the proportion of foreign-born cases as well as the distribution of sex, age, ethnic origin, and disease activity status among the final study population were similar to those of the total TB cases that were reported to Statistics Canada in 1993.[19]

Overall, resistance to one or more antituberculosis drugs was reported in 40 (8.7%) of the total 458 cases (Table I). Prevalence of resistance was similar among males and females. No drug resistance occurred in children younger than 15 years of age. The rate of resistance was 10.9% among patients aged 15-45 years and 7.1% for those over 45 years, however, the difference was not statistically significant (p = 0.16).

The overall prevalence of drug resistance was 9% among those with new disease and 8% among relapsed cases. Further analyses of data showed that among foreign-born cases, prevalence of drug resistance was 11% for the new cases and 8.3% for the relapsed cases. On the other hand among non-Aboriginal Canadian-born, these proportions were 8.6 and 14.3% respectively. However, these differences were not statistically significant. Both Aboriginal resistant cases were new TB cases.

Of the drug-resistant cases, 27 (67.5%) were foreign-born, 10 (25%) were non-Aboriginal Canadian-born, and 2 (5%) were Aboriginal Canadians. The prevalence of resistance was 10.6% among foreign-born cases versus 6.2% for the Canadian-born cases (p = 0.1). Further analysis showed that the prevalence of resistance among both foreign-born and non-Aboriginal Canadian-born cases were significantly higher than that of Aboriginal cases (p = 0.02 and p = 0.05).

There were 297 pulmonary TB cases of which 30 exhibited resistance (10.1%), 123 with extra pulmonary TB of which 9 were resistant (7.3%), and 25 with both pulmonary and extra pulmonary TB. The difference between proportion of drug resistance among pulmonary and extra pulmonary cases did not achieve statistical significance.

The patterns of drug resistance among study population are shown in Table II. The highest level of resistance for individual drugs was to streptomycin (5.5%), followed by isoniazid (4.4%) and pyrazinamide (1.5%). Of the drug-resistant cases, 27 (5.9%) had mono-resistance, 3 (0.7%) had MDR-TB. The resistance to SM was significantly higher among foreign-born cases (7.1%) than among Aboriginal and non-Aboriginal Canadian cases, 0.0% and 5.6% respectively (p = 0.04)(not shown in Table II). The resistance to INH in foreign-born cases was 5.1% versus 2.3% for Aboriginal cases and 3.7% for non-Aboriginal Canadian-born cases. These differences were not statistically significant.

The prevalence of drug resistance varied widely between provinces/territories (Table III). Quebec, Ontario and British Columbia had the highest prevalence of drug resistance while Manitoba, the Yukon and Northwest Territories had the lowest. The overall drug resistance in the provinces of Quebec, Ontario and British Columbia (i.e., provinces with the highest reporting number of TB) was 10.3% which was significantly higher than the drug resistance level of 4.2% for the rest of Canada (p = 0.04). A high proportion of resistant cases in Quebec, Ontario and British Columbia occurred among foreign-born groups – 54%, 86%, and 63% respectively; and these proportions were not significantly different.

The prevalence of drug resistance among foreign-born cases varied between geographical regions (Table IV). More than 85% of the foreign-born drug-resistant cases were born in countries located in the Western Pacific, African, and South East Asian regions.

The five countries with the highest proportion of resistance are listed in Table V. The total resistant cases from these countries accounts for two thirds of foreign-born cases. Their overall drug resistance level of 15.1% is significantly higher than the Canadian national level of 8.7% (p = 0.04).

The mean duration of residence in Canada for foreign-born individuals with drug resistance was 6.3 years versus 10.6 years for those without drug resistance. This difference did not reach the significance level (p = 0.1). Table VI shows the trend of drug resistance among foreign-born cases in relation to the duration of their residence in Canada. The prevalence of drug resistance among those who lived in Canada less than four years (15.5%) was significantly higher than the average national level of 8.7% (p = 0.04).

TABLE IV
Prevalence of Drug Resistance Among Foreign-born TB Cases by WHO Geographical Region

	Number of TB Cases	Number of Resistant Cases	Prevalence of Resistance (95% CI)
African Region	27	4	14.8 (4.9, 31.9)
Western Pacific Region	125	15	12.0 (7.1, 18.6)
South East Asian Region	37	4	10.8 (3.5, 24.0)
Eastern Mediterranean Region	10	1	10.0 (0.5, 40.3)
American Region*	27	2	7.4 (1.3, 22.4)
European Region	29	1	3.4 (0.2, 15.8)
Total	255	27	10.6 (7.2, 14.8)

* Does not include Canada

TABLE V
Antituberculosis Drug Resistance Among Foreign-born Cases from the Five Countries with Highest Number of Drug Resistance

	Number of TB Cases	Number of Resistant Cases	Prevalence of Resistance (95% CI)
Vietnam	30	7	23.3 (10.8, 40.8)
Somalia	14	3	21.4 (5.8, 48)
China	31	4	12.9 (4.2, 28.3)
India	21	2	9.5 (1.6, 28.1)
Hong Kong	23	2	8.7 (1.5, 25.9)
Total	119	18	15.1 (9.5, 22.4)

TABLE VI
The Relationship Between Antituberculosis Drug Resistance and Duration of Residence in Canada Among Foreign-born Cases*

Duration of Residence (years)	Number of TB Cases	Number of Resistant Cases	Prevalence of Resistance (95% CI)
<4	97	15	15.5 (9.3, 23.7)
4-10	63	6	9.5 (3.9, 18.7)
>10	83	6	7.2 (3.0, 14.4)

* The cases for whom the duration of residence in Canada were not reported were excluded

DISCUSSION

In this study, resistance to antituberculosis drugs occurred in 8.7% of the 458 culture-positive TB cases. In the last national survey, Eidus[6] reported a resistance rate of 6.3% for new active cases – a rate lower than the 9% found in the present study (p = 0.07). Other Canadian studies have reported different rates of resistance from different parts of the country, ranging from 6.9% in Western Canada[7] to 16.2% in Montreal,[20] which indicate regional differences. The prevalence of drug resistance in this study is lower than those reported to WHO[1] by many countries including Australia (9.5%), USA (12.9%), Spain (12.9%), Netherlands (14%) and Portugal (16.5%).

MDR-TB was demonstrated in only 0.7% of TB cases. A recent survey of MDR-TB from Alberta and British Columbia reported the same rate (0.7%) with all cases having MDR-TB on the initial isolate being foreign-born.[21] Based on the WHO report,[1] this is similar to the reported figure from Australia and New Zealand (0.7%) but lower than those reported from USA (2%) and among many European countries including England (1.9%), Spain (2%) and Portugal (3.7%).

Resistance was highest to streptomycin and isoniazid, probably because these drugs have been in use the longest. The prevalence of resistance to other first-line antituberculosis drugs including pyrazinamide, rifampin, and ethambutol were all low, justifying their use in the initial treatment of TB. The sample size of the present study was not sufficient for a precise calculation of resistance for individual antituberculosis drugs.

There was no case of drug resistance among children 14 years of age and younger in our data (Table I). Children are less likely to produce sputum or to be culture-positive and therefore are underrepresented in the study population.[19]

Surprisingly, our data did not show that resistance was more frequent among relapsed cases than among new cases. However, stratified analyses of the data showed that among foreign-born cases, the proportion of resistance was 11% and 8.3% among new and relapsed cases respectively, whereas the corresponding figures for non-Aboriginal Canadian-born cases were 8.6 and 14.3%. It is probable that, due to lack of documentation of prior antituberculosis drug use and because of recall bias, some relapsed foreign-born cases might have been misclassified as new cases.

55.6% of TB cases and 67.5% of resistant cases were among the foreign-born, who constitute only 17% of the total population of Canada. Prevalence of drug resistance was 10.6% among foreign-born and 6.2% among Canadian-born cases, a difference that did not achieve statistical significance. Whereas a survey from Montreal[20] showed no difference in the prevalence of drug resistance between the foreign-born and Canadian-born (16.3% and 15.9%), a Western Canada survey[7] demonstrated a significantly higher preva-

lence of resistance in foreign-born cases as compared to Canadian-born cases (11% and 3.1% respectively).

Further stratification of data showed a significantly lower prevalence of resistance among Aboriginal cases (2.3%) as compared to other groups. This low prevalence of resistance among Aboriginal cases was also shown in the Western Canada study.[7]

The likelihood of drug resistance among foreign-born cases decreased as the duration of residence in Canada increased (Table VI), with more than 50% of drug-resistant cases having resided in Canada for less than four years. These findings are consistent with those of previous drug resistance surveys in Canada.[6-9]

The recent changes in immigration patterns might have contributed to the high proportions of TB and resistant TB cases among new immigrants. The number of immigrants from areas of the world where the prevalence of TB and drug resistance are high, has increased over the past 20 years. As a result, a large pool of infected individuals or previously inadequately treated TB cases with resistant strains, may have immigrated to Canada with later progression to active resistant TB.

More than 85% of the foreign-born resistant cases were born in countries located in the Western Pacific, African, and South East Asian regions. Five countries, including China, Vietnam, Somalia, Hong Kong, and India, were stated as the birthplace for 66.6% of the foreign-born drug-resistant cases. The findings in this study are consistent with other drug-resistant surveys[7,9] and reflect the rate of resistance prevailing in those geographical areas.

CONCLUSION

This study demonstrated that Canada has a relatively low prevalence of antituberculosis drug resistance, including MDR-TB. Foreign-born TB cases from some regions of the world may have a higher risk of developing drug-resistant TB, especially if they develop TB within the first three years of arrival in Canada. It is recommended that initial therapy of foreign-born TB cases, especially those from countries with high prevalence of TB, include at least four first-line drugs until susceptibility testing allows a more individualized regimen. Furthermore, adequate treatment of TB cases must be assured to prevent development of drug resistance. Since treatment of TB cases with antituberculosis drugs is the mainstay of TB control, drug resistance studies should be repeated at regular intervals to assess the trends and pattern of drug resistance. This information may be used as an indicator of the effectiveness of TB control programs in Canada and as a guide to the clinical management of TB cases.

Although the study sample size was sufficient to produce a meaningful estimate of the overall prevalence of antituberculosis drug resistance in Canada, further studies with larger sample size are required to allow for precise subgroup analyses.

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