

Antituberculous drug resistance in western Canada (1993 to 1994)

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OBJECTIVES: To estimate the magnitude of antituberculous drug resistance and identify prospectively the risk factors for its development in tuberculosis (TB) patients in western Canada over a one-year period.

DESIGN: Comparison of drug-resistant and nondrug-resistant cases of TB.

SETTING: Western Canada.

PATIENTS: All people with TB reported to the TB registries of Manitoba, British Columbia, Alberta and Saskatchewan between February 1, 1993 and January 31, 1994.

MAIN OUTCOME MEASURES: Drug susceptibility testing was performed in all cases of culture-positive tuberculosis. Patients at risk for human immunodeficiency virus (HIV) infection were serotested.

RESULTS: Of 534 culture positive cases of TB, 37 (6.9%) were drug resistant. Odds ratios suggested that the risk of drug resistance was significantly higher among those with reactivation than among those with new disease, and among those born outside of Canada than among those born in Canada. Ninety per cent of the foreign-born patients with drug-resistant disease were from Asia. Of the 35 patients with drug resistance whose type of resistance was known, 76% had initial and 24% had acquired drug resistance. The initial resistance rate in Asian-born patients was 14%. Most

of the 37 drug-resistant cases were resistant to isoniazid (68%), streptomycin (49%) or both (22%). Twelve (32%) of the 37 cases were resistant to two or more first-line drugs. Of 14 patients who were HIV seropositive only one, a foreign-born patient, was drug resistant.

CONCLUSION: Antituberculous drug resistance is low among Canadian-born patients in western Canada, but not uncommon among those born outside Canada. Initial therapy of foreign-born patients should include four first-line drugs.

Key Words: *Canada, Drug resistance, Tuberculosis*

Résistance aux agents antituberculeux dans l'Ouest canadien

OBJECTIF: Estimer l'ampleur de la résistance aux agents antituberculeux et identifier de façon prospective les facteurs de risque pour son développement chez les patients tuberculeux dans l'Ouest canadien sur une période d'un an.

MODÈLE: Comparaison des cas de tuberculose pharmacorésistants et non pharmacorésistants.

CONTEXTE: L'Ouest canadien.

PATIENTS: Toutes les personnes atteintes de tuberculose signalées aux registres de la tuberculose du Manitoba, de la Colombie-Britannique, de l'Alberta et de la Saskatchewan entre le 1^{er} février 1993 et le 31 janvier 1994.

PRINCIPALES MESURES DES RÉSULTATS: Les tests de susceptibilité aux médicaments ont été pratiqués dans tous les cas

voir page suivante

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de tuberculose positifs à la culture. Les patients à risque pour le virus de l'immunodéficience humaine (VIH) ont été sérotestés.

RÉSULTATS: Des 534 cas de tuberculose positifs à la culture, 37 (6,9 %) étaient résistants aux médicaments. Le ratio d'incidence approché laissait à croire que le risque de pharmacorésistance était nettement plus élevé dans les cas de réactivation de la maladie que dans les nouveaux cas de tuberculose, et chez les individus nés à l'étranger plutôt que chez ceux nés au Canada. Quatre-vingt-dix pour cent des patients nés à l'étranger et démontrant une résistance aux antituberculeux provenaient d'Asie. Chez les 35 patients présentant une pharmacorésistance, et dont le type de résistance avait été identifié, il s'agissait d'une résistance primaire dans 76 %

des cas, et d'une résistance acquise dans 24 % des cas. Le taux de résistance primaire chez les patients nés en Asie était de 14 %. La plupart des 37 cas pharmacorésistants l'étaient à l'isoniazide (68 %), la streptomycine (49 %) ou les deux (22 %). Douze (32 %) des 37 cas étaient résistants à deux ou plus de deux médicaments de première ligne. Des 14 patients séropositifs, seulement un, né à l'étranger, était résistant aux antituberculeux.

CONCLUSION: Dans l'Ouest canadien, les cas de résistance aux antituberculeux sont peu nombreux chez les patients nés au Canada mais ne sont pas rares chez les patients nés à l'étranger. La thérapie initiale des patients nés à l'étranger devrait donc inclure 4 médicaments de première ligne.

In a recent (1980 to 1989) retrospective survey from the province of Manitoba, 7.1% of patients with culture-positive tuberculosis (TB) had disease caused by organisms that were resistant to antituberculous drugs. Risk of drug resistance was found to be significantly higher among foreign-born patients, especially if they developed TB within the first five years of arrival in Canada (1). Although aboriginal persons (Canadian native Indian and Inuit) were not at increased risk of drug resistance, they were over-represented in a poorly compliant subgroup that became increasingly drug-resistant over time. In the past decade the proportion of TB cases in foreign-born patients has increased in Canada, while the proportion in the aboriginal population has remained constant and the proportion in the Canadian-born nonaboriginal population has decreased (2). As well, regional differences in the proportion of TB cases in these three ethnic groups have developed; for example, in western Canada the majority of TB cases in British Columbia are found in the foreign born, while the majority of cases in Saskatchewan are found in aboriginal persons (2). In the present prospective survey we sought to determine the antituberculous drug resistance rate in western Canada, to confirm that the risk of drug resistance was higher in the foreign born compared with other ethnic groups and to ascertain whether regional differences in the ethnicity of TB patients might result from regional differences in drug resistance.

In the United States the strongest risk factor for human immunodeficiency virus (HIV)-associated multidrug-resistant TB (MDRTB) has been found to be place of residence, with most cases coming from New York City (3). If there was a problem with HIV-associated MDRTB in western Canada, one might expect to find it in Vancouver, British Columbia, where AIDS-related TB has been reported (4). In the present survey TB patients at risk for HIV were serotested.

METHODS

Demographic, clinical and mycobacteriological data were gathered on all cases of active TB diagnosed in residents of British Columbia, Alberta, Saskatchewan and Manitoba. Data were collected between February 1, 1993 and January 31, 1994 and were recorded prospectively by an on-site study nurse. Drug-resistant cases were identified through the records of the provincial mycobacteriology laboratories.

Demographic data: Age when diagnosed with TB, sex and ethnic status – foreign-born, aboriginal (registered [Treaty]

Indians, Métis and Inuit) and Canadian-born nonaboriginal – were recorded. Treaty Indians are those registered with the Department of Indian and Northern Affairs according to the Indian Act of Canada. Canadians who were not Aboriginal were defined as 'others'. For foreign-born patients the country of origin and the date of arrival in Canada were noted.

Clinical data: For each case the type of disease (respiratory, nonrespiratory, both) and disease status (new active disease, reactivation) were recorded according to the Canadian Tuberculosis Reporting System, Statistics Canada. A new active case is a case not previously reported. A reactivation is a recurrence of active disease in the same patient after a known period of inactivity. Patients from whom drug-resistant organisms were isolated were classified as having 'initial' drug resistance (no history of antituberculous drug use) or 'acquired' drug resistance (received antituberculous drugs in the past including prophylaxis for three months or more). Resistance was classified as 'unknown' in patients whose drug use history was unknown.

Resistance in patients with no history of prior antituberculous drug use was reported as 'initial' rather than 'primary' because it was anticipated that most of the drug-resistant patients would be foreign-born, precluding corroboration of their drug use history through records (5). 'Initial' resistance in Canadian-born Aboriginals and non-Aboriginals may be considered 'primary' (ie, resistance in a patient with no prior drug use with the information on drug use being collected in a standardized fashion and corroborated) because their drug use histories, in addition to being taken prospectively by a study nurse, were further corroborated through the records of the provincial tuberculosis registries.

Laboratory data: Isolates were processed with the radio-metric system (BACTEC 460, Becton-Dickinson Diagnostic Instrument Systems, Maryland). Details of this method have been described previously (6). In each provincial mycobacteriology laboratory the BACTEC system had been validated against the proportion method used by the Laboratory Centre for Disease Control, Ottawa, Ontario. Susceptibilities to four (isoniazid [INH], rifampin [RIF], ethambutol [EMB], and streptomycin [SM]) and, in some cases, five (pyrazinamide [PZA]) drugs were performed in duplicate with the radiometric method. Drug concentrations used were as follows: INH 0.1 µg/mL, RIF 2.0 µg/mL, EMB 7.5 µg/mL, SM 6.0 µg/mL and PZA 100 µg/mL.

Patients identified at risk for HIV infection (when this

TABLE 1
Culture results and resistance to antituberculous drugs among patients in western Canada with tuberculosis (TB) diagnosed from February 1, 1993 to January 31, 1994

Variable	Total patients	Patients with drug-resistant TB (%)	Odds ratio* (95% confidence interval)
Age range (years)			
0 to 19	38	3 (7.9)	1.0
20 to 39	180	16 (8.9)	1.1 (0.3-4.1)
40 to 59	121	6 (5.0)	0.6 (0.1-2.6)
60 or older	192	12 (6.3)	0.8 (0.2-2.9)
Unknown/missing	3	0	
Sex			
Male	303	15 (5.0)	1.0
Female	231	22 (9.5)	2.0 (1.0-4.0)
Ethnic status			
Aboriginal	160	6 (3.8)	1.0
Foreign-born	263	29 (11.0)	3.2 (1.3-7.8)
Other [†]	99	2 (2.0)	0.5 (0.1-2.7)
Unknown/missing	12	0	
Time since arrival in Canada			
Two years or less	78	11 (14.1)	1.0
Greater than two years	175	16 (9.1)	0.6 (0.3-1.4)
Unknown/missing	10	2 (20.0)	
Disease status			
New disease	465	28 (6.0)	1.0
Reactivation	62	9 (14.5)	2.4 (1.0-5.5)
Unknown/missing	7	0	
Type of disease			
Respiratory	400	26 (6.5)	
Nonrespiratory	115	11 (9.6)	
Both	17	0	
Unknown/missing	2	0	

*First group for each variable is the reference category for calculating odds ratios. [†]Canadian-born nonaboriginal patients

survey was conducted this did not include patients with a diagnosis of TB) were serotested (screening, enzyme-linked immunoabsorbent assay, and confirmatory test, Western blot antibody test) after obtaining informed consent (7). Appropriate pre- and post-test counselling was performed.

Statistical analysis: Statistical differences in the proportion of patients with drug-resistant isolates were determined by the χ^2 test. Results were considered significant at $P < 0.05$. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated (8).

RESULTS

Over the study period 534 cases of culture-positive tuberculosis were identified in residents of western Canada. Drug resistance occurred in isolates from 37 patients (6.9%; 29 foreign-born, six aboriginal and two others).

Table 1 shows the results of culture and drug resistance by age, sex, ethnic status, years since immigration, disease status and type of disease. It also shows ORs and 95% CIs to indicate the likelihood that a culture-positive case of tuberculosis would be resistant to one or more antituberculous drugs.

TABLE 2
Resistance to antituberculous drugs among tuberculosis patients from western Canada according to province and ethnic status

Province	Ethnic status				Total
	Aboriginal	Foreign-born	Other*	Unknown /missing	
Manitoba					
Resistant	0	1	0	0	1
Total	51	24	15	2	92
Percentage		4.2			1.1
Saskatchewan					
Resistant	4	1	0	0	5
Total	47	3	12	0	62
Percentage	8.5	33.0			8.1
Alberta					
Resistant	0	9	1	0	10
Total	16	80	24	0	120
Percentage	0	11.3	4.2		8.3
British Columbia					
Resistant	2	18	1	0	21
Total	46	156	48	10	260
Percentage	4.3	11.5	2.1		8.1
Total					
Resistant	6	29	2	0	37
Total	160	263	99	12	534
Percentage	3.8	11.0	2.0		6.9

*Refers to Canadian-born nonaboriginal patients

ORs indicated that drug resistance was not influenced by age, time since arrival in Canada or type of disease. On the other hand, in a univariate analysis the risk of antituberculous drug resistance was significantly higher among foreign-born patients than Aboriginals or others (OR 3.2, 95% CI 1.3 to 7.8). A borderline elevated risk of antituberculous drug resistance was seen between females versus males (OR 2.0, 95% CI 1.0 to 4.0) and among those with reactivation versus new disease status (OR 2.4, 95% CI 1.0 to 5.5). When a multiple logistic regression was performed on the same data, foreign-born ethnicity and reactivation disease status were confirmed to be independent risk factors for drug resistance.

The proportion of cases that were drug-resistant in each province was 1.1% in Manitoba, 8.1% in Saskatchewan, 8.3% in Alberta and 8.1% in British Columbia; the proportion in Manitoba was significantly less than in the other three provinces ($P < 0.05$) (Table 2). The most western provinces (Alberta and British Columbia) had the largest proportion of foreign-born TB patients (62%), and the most eastern provinces (Manitoba and Saskatchewan) had the largest proportion of TB patients who were aboriginal (64%). Drug resistance tended to be higher in British Columbia and Alberta (31 of 380, 8.2%) than in Saskatchewan and Manitoba (six of 154, 3.9%).

Of the foreign-born patients, 68% (179 of 263) emigrated from five countries: China, India, Vietnam, Philippines and Hong Kong (Table 3). Most foreign-born patients who were drug-resistant (26 of 29, 90%) were from these countries. Rates of initial resistance among foreign-born TB patients

TABLE 3
Resistance to antituberculous drugs among foreign-born tuberculosis patients from western Canada according to country of origin

Country of origin	Total* (all provinces)
China	
Resistant	6 (5)
Total	48 (37)
Percentage	13 (14)
India	
Resistant	6 (6)
Total	42 (39)
Percentage	14 (15)
Vietnam	
Resistant	8 (5)
Total	36 (29)
Percentage	22 (17)
Philippines	
Resistant	4 (4)
Total	33 (31)
Percentage	12 (13)
Hong Kong	
Resistant	2 (2)
Total	20 (19)
Percentage	10 (11)
Total	
Resistant	26 (22)
Total	179 (155)
Percentage	15 (14)

*Figures in brackets refer to those not treated in the past

TABLE 4
Type of resistance among patients with drug-resistant tuberculosis by ethnic status

Ethnic status	Number of patients (total)	Type of resistance		
		Initial* (total)	Acquired [†] (total)	Unknown (total)
Aboriginal	6 (160)	2 (137)	4 (23)	0 (0)
Foreign-born	29 (263)	25 (233)	4 (28)	0 (2)
Other [‡]	2 (99)	1 (88)	1 (10)	0 (1)
Unknown/missing	0 (12)	0 (7)	0 (1)	0 (4)
Total	37 (534)	28 (465)	9 (62)	0 (7)

*Acquired Received antituberculous drugs in the past including prophylaxis if for three months or more. [†]Initial No history of antituberculous drug use. [‡]Refers to Canadian-born nonaboriginal

from each of these countries were China, five of 37 (14%); India, six of 39 (15%); Vietnam, five of 29 (17%); Philippines, four of 31 (13%); and Hong Kong, two of 19 (11%).

More patients with drug resistance were classified as having initial resistance (76%) than acquired resistance (24%) (Table 4). There was no significant difference among the three ethnic groups as to the type of resistance. Patients who had received antituberculous drugs in the past were significantly more likely to be drug-resistant than those who had never received them (15% versus 6%, $P < 0.05$).

Table 5 shows the distribution of resistance by individual drugs and combinations of drugs. Most common was resistance to INH (25 [67.6%]) of the patients with drug-resistant

TABLE 5
Type of resistance among patients with drug-resistant tuberculosis by drug*

Drug	Number of patients	Type of resistance (percentage)	
		Initial	Acquired
Isoniazid	25	19 (76.0)	6 (24.0)
Streptomycin	18	13 (72.2)	5 (27.8)
Ethambutol	4	4 (100.0)	
Rifampin	4	1 (25.0)	3 (75.0)
Pyrazinamide	2	1 (50.0)	1 (50.0)
Number of drugs			
One	25	20 (80.0)	5 (20.0)
Two or more	12	8 (66.7)	4 (33.3)
Total	37	28 (75.7)	9 (24.3)

*Drug susceptibility testing to pyrazinamide was performed on only 210 isolates

disease) and SM (18 [48.6%]). In the majority of the patients with drug-resistant organisms (25 [67.6%]), the isolates were resistant to only one drug. In four of the 12 cases (25%) in which the isolates were resistant to two or more drugs, the isolates were resistant to both INH and RIF. Only two patients, both foreign-born, were shedding organisms resistant to three or more drugs. Both denied having received antituberculous drugs in the past. Of the 465 patients with culture-positive new active tuberculosis, initial resistance was found to the following drugs: INH 19 (4.1%), SM 13 (2.8%), EMB four (0.9%) and RIF one (0.2%). Drug susceptibility to PZA was performed on only 210 isolates, all from Manitoba and Alberta. One patient of the 210 tested was found to be resistant (0.5%). Of patients who were serotested for HIV, 14 were found to be positive, 11 from British Columbia and three from the Prairie provinces. Only one, a foreign-born patient from Manitoba, was drug-resistant.

DISCUSSION

Over the study period we found that 6.9% of the patients in western Canada with culture-positive TB had disease that was resistant to antituberculous drugs. This proportion is very similar to the rate of resistance last reported in Manitoba (7.1% in 1993) (1) and in the Canadian population overall (6.3% reported in 1975) (9). Relative risk of drug resistance was 2.4 times greater among those with a reactivation than among those with new disease and 3.2 times greater among foreign-born patients than among Canadian-born. Previous surveys of antituberculous drug resistance in Canada suggested that the earlier TB developed in the foreign-born after their arrival in Canada the more likely the disease was to be drug-resistant (1,9). In the present study there was a tendency for the risk of drug resistance to be higher among foreign-born patients who developed TB within their first two years in Canada than in those in whom it developed more than two years after immigration. However, the difference was not statistically significant, probably because of the smaller numbers in this survey.

Among foreign-born TB patients, 68% were from five

Asian countries (China, India, Vietnam, Philippines and Hong Kong), reflecting the recent pattern of immigration to Canada, with increasing proportions of immigrants coming from Asian countries where TB morbidity rates are high (10). The majority of drug-resistant foreign-born patients (90%) was from these five countries. Together the rate of initial resistance among them was 14%, up from initial resistance rates of 7.6% (10) and 6.8% (11) reported in Asian immigrants to British Columbia in the early 1970s and 1980s, respectively.

Because 87% of the patients who developed drug-resistant TB after immigration to Canada denied being treated (initial resistance), we must assume that they have been infected with a drug-resistant strain in their country of origin or that their history was unreliable. That a substantial number of the foreign-born patients with disease resistant to the first-line antituberculous drugs denied previous treatment must be taken into account in the planning of antituberculous regimens for this group. It is recommended that foreign-born patients, particularly recent arrivals, be treated with four drugs until susceptibility testing allows a more individualized regimen. In most, but not all, this will ensure that at least two of the drugs will be effective when the bacterial population is large. Even this regimen would have been inadequate for two foreign-born patients who denied previous antituberculous drug use and yet were resistant to three or more first-line drugs. These cases illustrate the need for drug susceptibility testing of all isolates, particularly those from the foreign born.

On the other hand, according to the most recent American Thoracic Society/Centers for Disease Control and Prevention guidelines (12), rates of resistance in Canadian-born, aboriginal (3.8%) and nonaboriginal (2.0%) patients were sufficiently low (less than 4%) to warrant the use of only three drugs in the initial treatment regimen, INH, RIF and PZA.

British Columbia and Alberta had a greater proportion of foreign-born TB cases (62%), whereas Saskatchewan and Manitoba had a greater proportion of aboriginal TB cases (64%). This regional difference in the ethnicity of TB patients may have contributed to the higher, though not statistically significant, rate of resistance in British Columbia and Alberta (8.2%) compared with Saskatchewan and Manitoba (3.9%). A more likely explanation for this difference in resistance rates between regions was the unusually low rate of resistance in Manitoba in the study year (1.1%); a rate significantly less than that reported on average in the decade 1980 to 1989 (7.1%), but nevertheless consistent with the variability in the rate of resistance seen over that period (4% to 9%, unpublished data).

Rates of initial resistance to INH (4.1%) were higher than previously reported in Canada; rates in earlier surveys were 1.5% (1966) (13), 2.2% (1978) (9) and 2.2% (1993) (1). Rates of initial resistance to SM (2.8%) were unchanged from previous surveys: 2.7% (1966) (13), 2.1% (1978) (9) and 2.1% (1993) (1).

Twelve (32%) of the 37 patients with drug-resistant disease had isolates resistant to two or more first-line drugs. This

high proportion of multiple-drug resistance supports a policy of treating all TB patients who are from a country with a high prevalence of drug resistance, have had previous treatment with antituberculous medications or have had known exposure to a drug-resistant case with four antituberculous drugs until the drug susceptibility test results are known [12]. Four (11%) of the 37 drug-resistant patients were resistant to both INH and RIF. Outbreaks of disease resistant to these two drugs have been reported in association with HIV infection in the United States (3). These cases may be particularly hard to treat (14,15). No MDRTB was found in association with HIV infection in our survey; only one HIV seropositive TB patient was drug-resistant and he was foreign-born, consistent with an earlier report of TB in the HIV infected in British Columbia (4), in which almost all were Canadian-born non-aboriginal patients and none were drug-resistant.

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