Antituberculous drug resistance in Manitoba from 1980 to 1989

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Objectives: To estimate the magnitude of antituberculous drug resistance and identify the risk factors for its development in tuberculosis patients in Manitoba over a 10-year period. As well, to examine the clinical course of the patients whose initial or subsequent isolates of *Mycobacterium tuberculosis* were resistant to one or more drugs.
Design: Comparison of drug-resistant and non-drug-resistant cases of tuberculosis.
Setting: Manitoba.
Patients: All people with tuberculosis reported to the Central Tuberculosis Registry of Manitoba between Jan. 1, 1980, and Dec. 31, 1989.
Main outcome measures: Of 1478 cases of active tuberculosis 1086 were culture positive, and drug susceptibility testing was performed in these cases. The clinical course, including outcome of treatment, of all drug-resistant cases was described.
Results: Of 1086 culture-positive cases of tuberculosis 77 (7.1%) were drug resistant. Odds ratios suggested that the risk of drug resistance was significantly higher among the immigrants than among the other Canadians. Compared with the other Canadians the risk of drug resistance was 9.9 times greater among the immigrants in whom tuberculosis developed within the first year after arrival in Canada and 5.4 times greater among the immigrants in whom it developed 2 to 5 years after arrival in Canada. Of the 71 patients with drug-resistant disease whose type of resistance was known 62% had never taken antituberculous drugs before and 38% had. Most (91%) of the 77 cases of drug-resistant disease were resistant to first-line drugs, especially isoniazid and streptomycin. Thirty-two (42%) of the 77 cases were resistant to two or more first-line drugs. Of patients with drug-resistant disease a subgroup of 10 had disease that became resistant to several drugs over the 10-year period. The outcome of treatment in these individuals was poor, and they presented a particular public health problem.
Conclusion: Resistance to one or more first-line antituberculous drugs continues to complicate the treatment of tuberculosis and may facilitate the spread of the disease.

Objectifs : Estimer l'ampleur de la résistance aux antituberculeux et identifier les facteurs de risque de son apparition chez les patients atteints de tuberculose au Manitoba au cours d'une période de 10 ans. Examiner, également, l'évolution clinique des patients dont les isolats initiaux ou subséquents de *Mycobacterium tuberculosis* étaient résistants à un médicament ou plus.
Conception : Comparaison des cas de tuberculose pharmacorésistante et non pharmacorésistante.
Contexte : Manitoba.
Patients : Toutes les personnes atteintes de tuberculose déclarées au Central Tuberculosis Registry of Manitoba entre le 1er janv. 1980 et le 31 déc. 1989.

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Principales mesures des résultats : Des 1 478 cas de tuberculose, 1 086 étaient positifs à la culture de la tuberculose, et des épreuves de sensibilité médicamenteuse ont été effectuées pour ces cas. On a décrit l'évolution clinique, y compris le résultat du traitement de tous les cas pharmacorésistants.

Résultats : Des 1 086 patients positifs à la culture de la tuberculose, 77 (7,1 %) étaient atteints d'une maladie pharmacorésistante. Le risque de pharmacorésistance, d'après les indices, était significativement plus élevé chez les immigrants que dans les autres Canadiens. Par comparaison avec les autres Canadiens, les immigrants qui ont contracté la tuberculose au cours de la première année suivant leur arrivée au Canada couraient 9,9 fois plus de risques d'être atteints d'une maladie pharmacorésistante, et ceux qui l'ont contractée 2 à 5 ans après leur arrivée au Canada couraient 5,4 fois plus de risques. Sur les 71 patients atteints de maladie pharmacorésistante dont on connaissait les antécédents thérapeutiques, 62 % n'avaient jamais reçu d'antituberculeux et 38 % en avaient reçu. Dans la plupart (91 %) des 77 cas de maladie pharmacorésistante, la résistance concerne les médicaments de choix, en particulier l'isoniazide et la streptomycine; 42 % des cas étaient résistants à deux médicaments de choix ou plus. Des patients dont la maladie était pharmacorésistante, un sous-groupe de 10 patients a produit des isolats devenus résistants à plusieurs médicaments pendant l'étude; leur traitement a donné de mauvais résultats, et ils constituaient ainsi une menace particulière à l'hygiène publique.

Conclusion : La résistance à un antituberculeux de choix ou plus continue de compliquer le traitement de la tuberculose, et elle peut favoriser la propagation de la maladie.

The incidence rate of tuberculosis remains high in both aboriginal (Canadian native Indian and Inuit) and immigrant populations despite a general decline in the rate in Canada over the last decade.[1,2] Resistance to antituberculous drugs may be contributing to the relatively high incidence rate of the disease in these populations. Drug resistance significantly complicates treatment and facilitates spread of the disease.[3,4] For aboriginal peoples language, culture and geographic barriers may interfere with effective treatment with antituberculous drugs and allow the emergence of drug resistance. Language and cultural barriers may interfere with effective treatment of disease in immigrants as well, but such people often are from countries where there may be a high prevalence of antituberculous drug resistance. Added to these considerations are recent reports from the United States of outbreaks of multidrug-resistant tuberculosis.[5-11]

The objective of the present study was to estimate the magnitude of antituberculous drug resistance and identify the risk factors for its development in tuberculosis patients in Manitoba over a 10-year period. In addition, we examined the clinical course of the patients whose initial or subsequent isolates of *Mycobacterium tuberculosis* were resistant to one or more drugs.

Methods

Demographic, clinical and mycobacteriologic data on all cases of active tuberculosis diagnosed in residents of Manitoba between Jan. 1, 1980, and Dec. 31, 1989, were extracted from the Central Tuberculosis Registry of Manitoba. Drug-resistant cases were identified through the records of the Mycobacteriology Laboratory, Health Sciences Centre, Winnipeg, where all provincial specimens are cultured. Additional clinical information on drug-resistant cases was obtained from patients' medical records. The drug susceptibility test results reported are those of the Laboratory Centre for Disease Control (LCDC), Ottawa.

Demographic data

The age at diagnosis of tuberculosis, sex, and immigrant and registered (treaty) Indian status were recorded. Treaty Indians are those registered with the Department of Indian and Northern Affairs according to the Indian Act of Canada. They were divided into those living on and off reserves. Canadian-born patients who were not treaty Indians were defined as "Canadians." For immigrants the country of origin and the date of arrival in Canada were also noted.

Clinical data

For each case the date of diagnosis (date on which the case was reported to the tuberculosis registry), type of disease (pulmonary, miliary, primary, pleurisy, other respiratory, nonrespiratory) and disease status (new active disease, reactivation) were recorded according to the Canadian Tuberculosis Reporting System, Statistics Canada.[12] A new active case is a case never 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 "never treated" (no history of antituberculous drug use) and "treated" (received antituberculous drugs either in the past or during treatment of the current episode or as prophylaxis for more than 3 months). Resistance was classified as "unknown" in patients whose drug use history was unknown.

The following details of treatment were noted: duration of drug treatment, whether the attending physician(s) responded to the antibiogram with an appropriate treatment adjustment, and surgery. Medical records were used to determine whether the patient had an alcohol problem. If the medical record indicated that the patient had failed to comply with the antituberculous drug therapy the patient was termed "noncompliant"; otherwise the patient was assumed to be compliant. Outcome was recorded. Those who completed a course of appropriate antituberculous drug therapy were considered cured. For those who died, the cause of death was determined.

Mycobacteriologic data

From 1980 to 1987 isolates were cultured on fresh Lowenstein-Jensen media in the Mycobacteriological Laboratory, Winnipeg, and sent to LCDC for analysis. Standard biochemical tests were used for speciation of each isolate.[13] The proportion method[13] was used to determine susceptibility to four first-line antituberculous drugs (isoniazid [INH], streptomycin [SM], ethambutol [EMB] and rifampin [RIF]) and four second-line drugs (para-aminosalicylic acid [PAS], cycloserine [CS], capreomycin [CM] and ethionamide [THA]). Drug concentrations were as follows: INH 0.2, SM 4.0, EMB 2.0, RIF 40.0, PAS 0.5, CS 30.0, CM 50.0 and THA 20.0 μg/mL. At all stages American Type Culture Collection (ATCC) controls were routinely used (Trudeau Mycobacterial Culture [TMC] 102, H37RV — susceptible to all drugs; TMC 303, 301, 330 and 331 — resistant to INH, SM, EMB and RIF respectively).

In 1988 and 1989 isolates were first processed in the Mycobacteriology Laboratory with the radiometric system (BACTEC 460, Becton-Dickinson Diagnostic Instrument Systems, Towson, Md.). Details of this method have been described previously.[14] Screening susceptibilities to the four first-line drugs were performed in duplicate with the radiometric method. Drug concentrations used were as follows: INH 0.2, SM 6.0, EMB 7.5 and RIF 2.0 μg/mL. All isolates found to be resistant by the BACTEC system were then sent to LCDC for validation by the proportion method. We considered an isolate resistant if the results were confirmed by the proportion method. The BACTEC system had previously been demonstrated to be 100% sensitive in identifying resistance to first-line drugs.[14]

Statistical analysis

Statistical differences in the proportion of patients with drug-resistant disease were determined by the χ^2 test. Results were considered significant at a p level of less than 0.05. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated.[15]

Results

Over the study period 1478 cases of active tuberculosis were diagnosed in residents of Manitoba. Specimens from 1392 (94.2%) of these patients were submitted for culture: 1086 (78.0%) were culture positive (Table 1). In 86 (5.8%) of the cases cultures were not done. This proportion did not differ significantly by age, sex, ethnic status, residence or disease status. However, a greater proportion of patients with nonrespiratory tuberculosis (14.2%) had no specimen submitted for culture. Of the 1086 culture-positive patients 77 (7.1%) had drug-resistant organisms (42 immigrants, 19 Canadians and 16 treaty Indians).

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 the ORs and 95% CIs to indicate the likelihood that a culture-positive case of tuberculosis would be resistant to one or more antituberculous drugs. The ORs indicated that drug resistance was not influenced by age, sex, disease status or type of disease. On the other hand, the risk of antituberculous drug-resistant disease was significantly higher among the immigrants than among the Canadians (OR 4.0, 95% CI 2.5 to 7.9). Further analysis of the risk factors for antituberculous drug resistance among the immigrants revealed that the duration of residence in Canada was very important. An inverse relation between the risk of antituberculous drug resistance and the duration of residence in Canada was observed. Compared with the Canadians the risk of drug resistance was 9.9 times higher among the immigrants in whom tuberculosis developed within their first year in Canada and 5.4 times higher among the immigrants in whom it developed 2 to 5 years after immigration. The risk of resistance among the immigrants in whom tuberculosis developed after having resided in Canada for more than 5 years was similar to the risk among the patients born in Canada. The treaty Indians, whether living off or on reserves, had a risk for drug resistance similar to that of the Canadians.

A greater proportion of the patients with drug resistance were classified as "never treated" (57%)

than "treated" (35%) (Table 2). There was no significant difference between the three ethnic groups as to the type of resistance. Although 12 (29%) of the 42 immigrants with drug-resistant disease were treated in the past, only 3 of these were known to have received antituberculous drugs in Canada.

Table 1: Culture results and resistance to antituberculous drugs among patients in Manitoba with tuberculosis diagnosed from Jan. 1, 1980, to Dec. 31, 1989

Variable	Total no. of patients	Culture result;* no. of patients			No. of patients with drug-resistant disease	Odds ratio† (and 95% confidence interval)
		ND	Negative	Positive		
Age, yr						
0–19	282	17	99	166	7	1.0
20–39	477	15	94	368	34	2.3 (1.0–5.3)
40–59	300	25	56	219	15	1.7 (0.7–4.2)
≥ 60	419	29	57	333	21	1.5 (0.6–3.7)
Sex						
Male	781	40	150	591	44	1.0
Female	697	46	156	495	33	0.9 (0.6–1.4)
Ethnic status‡						
Canadian	612	47	122	443	19	1.0
Treaty Indian	479	12	97	370	16	1.0 (0.5–2.0)
Immigrant	387	27	87	273	42	4.0 (2.5–7.9)
Residence						
Canadian	612	47	122	443	19	1.0
Treaty Indian						
On reserves	348	7	75	266	14	1.2 (0.6–2.5)
Off reserves	131	5	22	104	2	0.4 (0.1–1.9)
Immigrant, time in Canada, yr						
≥ 10	99	7	23	69	3	1.0 (0.3–3.5)
6–9	60	8	10	42	4	2.3 (0.8–7.3)
2–5	107	8	27	72	14	5.4 (2.6–11.3)
≤ 1	90	4	18	68	21	9.9 (5.0–19.9)
Unknown	31	0	9	22	0	–
Disease status						
New, active	1328	80	274	974	65	1.0
Reactivated	150	6	32	112	12	1.7 (0.9–3.2)
Type of disease						
Pulmonary	889	24	100	765	52	1.0
Miliary	35	2	4	29	2	1.1 (0.2–4.4)
Primary	161	11	87	63	2	0.4 (0.1–2.9)
Pleuritic	91	6	38	47	3	0.9 (0.5–1.7)
Other respiratory	7	1	2	4	0	–
Nonrespiratory	295	42	75	178	18	1.5 (0.9–2.7)
Total	1478	86	306	1086	77	

*ND = not done.
†The first group for each variable is the reference category for calculating the ORs.
‡Canadian refers to patients born in Canada who were not treaty Indians; treaty Indian refers to native Indians registered with the Department of Indian and Northern Affairs.

Table 2: History of drug treatment among patients with drug-resistant tuberculosis, by ethnic status

Ethnic status	Total no. of patients	History;* no. (and %) of patients		
		Never treated	Treated	Unknown
Canadian	19 (25)	8 (42)	8 (42)	3 (16)
Treaty Indian	16 (21)	9 (56)	7 (44)	–
Immigrant	42 (55)	27 (64)	12 (29)	3 (7)
Total	77 (100)	44 (57)	27 (35)	6 (8)

*For definitions of never treated and treated see the Methods section.

Table 3 shows the distribution of resistance by individual drugs and combinations of drugs. Most common was resistance to INH (in 46 [60%] of the patients with drug-resistant disease) and SM (44 [57%]). In only 15 (19%) of the cases the isolates were resistant to PAS and in 8 (10%) to THA. There was no resistance to CS and CM, the other two second-line drugs tested. In the majority (70 [91%]) of the patients with drug-resistant organisms the isolates were resistant to one or more first-line drugs. In 15 (47%) of the 32 cases in which the isolates were resistant to two or more first-line drugs they were resistant to both INH and RIF. In 10 of these 15 the patient had received treatment in the past. Resistance to INH, SM and EMB was significantly more likely in the immigrants than in the treaty Indians or the Canadians ($p < 0.05$). Of the 974 patients with culture-positive new active tuberculosis, resistance was found to the following drugs: INH 24 (2.5%), SM 23 (2.4%), EMB 3 (0.3%) and RIF 5 (0.5%).

To examine the clinical course, patients with drug-resistant disease were divided into two groups.

Group 1: Those whose antibiogram did not change over the treatment period (67 patients).

Group 2: Those whose antibiogram did change (10 patients). With two patients the initial isolate was resistant to one drug and a subsequent isolate was resistant to one or more other drugs. With the other eight the initial isolate was not resistant but a subsequent isolate was resistant to one or more drugs.

Patients in group 2 were significantly more likely to have pulmonary disease than those in group 1 (10/10 v. 45/67). At the time of the final, most resistant culture 40% (18/45) of the group 1 patients had positive sputum smear results, as compared with 90% (9/10) of the group 2 patients at the time of their final, most resistant isolate. The treaty Indians, although not at increased risk of drug resistance, were over-represented in group 2 (6 of 10), as compared with group 1 (10 of 67). Of the patients in group 1, only two were noncompliant, and the mean duration of treatment was similar (approximately 12 months) regardless of the number of drugs to which the isolates were resistant. In contrast, 7 of the 10 patients in group 2 were noncompliant (each abused ethanol), and the mean duration of treatment was almost three times as great (35 months). The cure rate averaged 83% in group 1, and the rate was not influenced by the number of drugs to which the isolates were resistant. The cure rate in group 2 was 50%. Because of difficulties in establishing a cure 3 of the 10 group 2 patients underwent surgery for their pulmonary tuberculosis.

Of the 77 patients with drug-resistant disease 10 (13%) received treatment regimens that did not always take into account the antibiogram, and 10 (13%) died. Seven of the deaths were due to the tuberculosis. In five of the tuberculosis deaths, drug resistance was thought to have been a factor; of the five patients, three had received treatment that did not always take into account the antibiogram.

Discussion

Over the study period we found that 7.1% of the patients in Manitoba with culture-positive tuberculo-

Table 3: History of drug treatment among patients with drug-resistant tuberculosis, by drug*

Drug	Total no. of patients	History; no. (and %) of patients		
		Never treated	Treated	Unknown
Isoniazid	46 (60)	24 (52)	20 (43)	2 (4)
Streptomycin	44 (57)	23 (52)	17 (39)	4 (9)
Ethambutol	9 (12)	3 (33)	4 (44)	2 (22)
Rifampin	17 (22)	5 (29)	11 (65)	1 (6)
Para-aminosalicylic acid	15 (19)	9 (60)	5 (33)	1 (7)
Ethionamide	8 (10)	6 (75)	1 (12)	1 (12)
First-line drug				
One	38 (49)	24 (63)	11 (29)	3 (8)
Two	21 (27)	14 (67)	6 (29)	1 (5)
Three or more	11 (14)	1 (9)	9 (82)	1 (9)
Second-line drug only	7 (9)	5 (71)	1 (14)	1 (14)
Total	77 (100)	44 (57)	27 (35)	6 (8)

*When the resistance pattern varied over the study period the pattern of the final, most resistant isolate was used.

sis had disease that was resistant to antituberculous drugs. This proportion is only slightly higher than the rate of resistance last reported in the Canadian population (6.3% in 1975).[16] In our study, only ethnic status increased the risk of drug resistance. The relative risk of drug resistance was four times greater among the immigrants than among the Canadians. Moreover, the earlier the tuberculosis developed in the immigrants after their arrival in Canada, the more likely the disease was to be drug resistant. The immigrants with tuberculosis that developed after they had resided in Canada for more than 5 years did not have an increased risk of drug resistance. In the last Canadian survey of drug resistance Eidus and associates[16] found that immigrant patients who had resided in Canada for less than 12 years were more likely to have drug-resistant disease than those who had lived in Canada for more than 12 years before the onset of disease. There was no difference in resistance between those who had lived in Canada for less than 5 years and those who had lived in Canada for 5 to 12 years before the onset of disease.

Because 64% of the patients in whom drug-resistant tuberculosis developed soon after immigrating to Canada denied ever having been treated ("never-treated" resistance), we must assume that they had been infected with a drug-resistant strain in their country of origin or that their history was unreliable. That a substantial number of the immigrant 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 recent immigrants (i.e., those in whom tuberculosis develops within the first 5 years after their arrival in Canada) be treated with four drugs until susceptibility testing allows a more individualized regimen. This will ensure that at least two of the drugs will be effective when the bacterial population is large. Resistance to three or more drugs occurred almost exclusively in those who reported having taken antituberculous drugs in the past ("treated" resistance) (Table 3).

Of the 77 patients with drug-resistant organisms 70 (91%) had disease resistant to one or more first-line drugs. However, the rates of resistance to INH and SM (2.2% and 2.1% respectively) among those never treated were similar to the rates in earlier surveys (1.5% and 2.7% in the study by Armstrong[17] and 2.2% and 2.1% in the survey by Eidus and associates[16]).

Thirty-two (42%) of the 77 patients with drug-resistant disease had isolates resistant to two or more first-line drugs. This high rate of multidrug resistance supports a general policy of treatment with four antituberculous drugs until the drug susceptibility test results are known. Resistance to both INH and RIF (in 15 of the 32) was worrisome, since disease resistant to these two drugs is particularly difficult to cure.[3] We did not observe any outbreaks of multidrug-resistant tuberculosis, as have recently been reported in the United States.[5-11] Such outbreaks are likely to occur, since multidrug-resistant disease is especially difficult to treat. Disease resistant to both INH and RIF may become more prevalent owing to wider dissemination of the human immunodeficiency virus — an agent known to facilitate the spread of tuberculosis.

A number of observations were made about the clinical course of the patients with drug-resistant disease. First, although there was a high prevalence of drug resistance in the immigrants, all were cured over approximately 12 months even though some may have had multidrug-resistant disease. Presumably this was because they were compliant. Second, the 10 patients with a changing antibiogram presented a major clinical and public health problem. Most of these patients abused alcohol, did not comply with treatment and had disease resistant to multiple drugs. Only 5 of the 10 were cured, after an average of 35 months of treatment. This extended period of treatment, together with the positive sputum smear results for 9 of the 10 on their final, most resistant isolate, made this group a particular public health hazard. The treaty Indians, although not at increased risk of drug resistance, were over-represented in this group.

Two additional observations were made about the course of the patients with drug-resistant disease. First, the mortality rate in this group was higher than the mortality rate that has been reported for tuberculosis in the Canadian population[18] (9% v. 5%). In more than half of the deaths in our study drug resistance was judged to have been a factor. An increased mortality rate among patients with drug-resistant tuberculosis is a reflection of the greater difficulty in achieving a cure and has been reported by others.[19,20] Second, in 13% of the patients with drug-resistant disease the antituberculous drug regimen did not always take into account the antibiogram. This oversight was usually due to a failure by health care personnel to follow up the drug susceptibility test results.

These observations about the clinical course of the patients with drug-resistant disease have convinced us of the need to promote universal, directly observed therapy in populations identified to be at high risk for drug-resistant disease. Particular attention has to be paid to drug susceptibility test results. Furthermore, it is recommended that known drug-resistant disease be managed by those most experienced with tuberculosis.[21] For treaty Indians the patients' social support system may have to be used

to ensure compliance with directly observed therapy.[22] Failing these measures, isolation or restriction of freedom may be necessary in the interests of the larger community.[23,24]

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Administering medicines

For, in diseases of the mind, as well as in all other ailments, it is an art of no little importance to administer medicines properly: but, it is an art of much greater and more difficult acquisition to know when to suspend or altogether to omit them.

— Philippe Pinel (1745-1826)
A Treatise on Insanity, *Sect. I (tr. by D.D. Davis)*