

Tuberculosis drug resistance in Canada, 1998 to 2000

Melissa D Phypers MSc, Linda Panaro MDCM MHSc FRCPC, Penny Nault

The emergence of drug-resistant strains of tuberculosis (TB) is a global threat to TB prevention and control efforts. A recent study conducted by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease found strains of TB resistant to first-line anti-TB drugs in all countries surveyed (1). The WHO estimates that 50 million people are infected with strains of drug-resistant TB (2).

Tuberculosis Prevention and Control (TBPC) in the Bureau of HIV/AIDS, STD and TB, Centre for Infectious Disease Prevention and Control, Health Canada, in collaboration with participating laboratories (representing all provinces and territories) in the Canadian Tuberculosis Laboratory Surveillance System, established a laboratory-based national surveillance system in 1998 to monitor TB drug resistance patterns in Canada.

DATA AND METHODS

A computerized database containing reported drug susceptibility test results on isolates of *Mycobacterium tuberculosis* and *Mycobacterium bovis* (bacille Calmette-Guerin and wild type) is maintained at TBPC. Provincial and territorial laboratories report their results on TB drug sensitivity testing for every patient for whom a specimen or an isolate has been received for each calendar year.

Data were collected either by manual completion and mailing of a standard reporting form or by electronic transmission to TBPC. Information collected included sex, year of birth, province or territory (originating and reporting), and susceptibility test results. Table 1 lists the first-line anti-TB drugs for which susceptibility testing was conducted and the

concentrations used by the participating laboratories. As noted in Table 1, the specific first-line anti-TB drugs and the number of these drugs for which routine susceptibility testing is carried out differ among the provinces and territories. Accordingly, the number of isolates included in the descriptive analyses varies. Isolates of *M. bovis* bacille Calmette-Guerin reported to the system were systematically excluded from this analysis. Every effort was made to eliminate duplicate specimens; only the most recent susceptibility test results for a given patient in the current reporting year were included for analysis. Linear trends were tested using χ^2 analysis for trend. All statistical analysis was conducted using SAS Version 8 (SAS Institute, USA).

TABLE 1
Concentrations for routine testing of first-line antituberculosis drugs

Antituberculosis drugs	Dose (mg/L)	Comment
Isoniazid	0.1	
Rifampin	2.0	
Ethambutol	2.5	British Columbia uses 4.0 mg/L concentration
Streptomycin	2.0	Routine testing is not performed for isolates from Quebec, Nova Scotia, New Brunswick, Prince Edward Island and for Nunavut isolates (tested in Quebec)
Pyrazinamide	100.0	Routine testing is not performed for isolates from British Columbia, Saskatchewan and the Yukon Territory

Tuberculosis Prevention and Control, Health Canada, Ottawa, Ontario

Correspondence and reprints: Melissa D Phypers, Senior Epidemiologist, Health Canada, Population and Public Health Branch, Centre for Infectious Disease Prevention and Control, Bureau of HIV/AIDS, STD and TB, Tuberculosis Prevention and Control, Brooke Claxton Building, Room 01010B-14, Tunney's Pasture, Postal Locator 0900B-1, Ottawa, Ontario K1Z 0L2.
Telephone 613-946-3920, fax 613-946-3902, e-mail Melissa_Phyppers@hc-sc.gc.ca

TABLE 2
Overall pattern of reported tuberculosis drug resistance in Canada, 1998 to 2000

	1998 total (%)	1999 total (%)	2000 total (%)	Mean prevalence (%)
Total number of isolates tested	1461 (100.0)	1416 (100.0)	1464 (100.0)	–
Any resistance to isoniazid	123 (8.4)	128 (9.0)	108 (7.4)	8.3
Any resistance to rifampin	19 (1.3)	19 (1.3)	17 (1.2)	1.3
Any resistance to ethambutol	22 (1.5)	20 (1.4)	20 (1.4)	1.4
Any resistance to streptomycin*	82 (5.7)	72 (6.5)	63 (5.5)	5.9
Any resistance to pyrazinamide*	23 (2.0)	27 (2.4) [†]	24 (2.1)	2.2
Monoresistance*	116 (7.9)	115 (8.1)	119 (8.1)	8.0
Multidrug-resistant tuberculosis	18.1 (1.2)	17 (1.2)	14 (1.0)	1.1
Other patterns	39 (2.7)	41 (2.9)	31 (2.1)	2.6
Total resistance to one or more drugs	173 (11.8)	173 (12.2)	164 (11.2)	11.7

Multidrug-resistant tuberculosis is defined as resistance to at least isoniazid and rifampin; *Because streptomycin and pyrazinamide are not part of the routine first-line drugs in some provinces and territories, denominators for any resistance to these drugs have been modified to reflect this (1998: streptomycin n=1450, pyrazinamide n=1174; 1999: streptomycin n=1110, pyrazinamide n=1130; 2000: streptomycin n=1142, pyrazinamide n=1144); [†]Includes two *Mycobacterium bovis* isolates for 1999 and four *M bovis* isolates for 2000

TABLE 3
Tuberculosis (TB) drug resistance reporting in Canada by province and territory, 1998 to 2000

	Alberta	BC	Manitoba	NB	Newfoundland	NS	NT	Nunavut*	Ontario	PEI	Quebec	Saskatchewan	YT	All of Canada
Susceptible	309	661	280	29	27	19	46	43	1545	7	716	144	4	3830
Monoresistant	22	53	16	1	0	2	0	1	164	0	84	5	0	348
Multidrug-resistant TB	1	7	4	0	0	0	0	0	32	0	5	0	0	49
Other patterns	8	13	7	0	0	0	0	0	74	0	5	4	0	111
Total isolates	340	734	307	30	27	21	46	44	1815	7	810	153	4	4338

*Nunavut began reporting isolates in 1999. BC British Columbia; NB New Brunswick; NS Nova Scotia; NT Northwest Territories; PEI Prince Edward Island; YT Yukon Territories

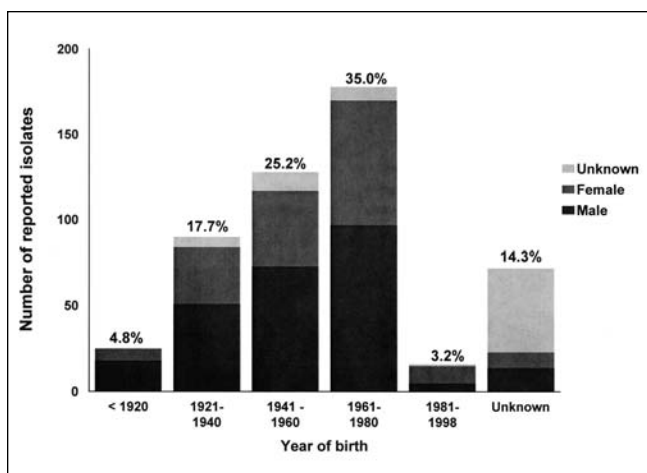


Figure 1) Number of reported tuberculosis drug-resistant isolates, 1998 to 2000 (n=509)

RESULTS

Table 2 shows the overall pattern of reported TB drug resistance in Canada from 1998 to 2000. No significant difference in the number of total isolates reported was found (χ^2 for trend, $P=0.82$). Patterns in the number of reported isolates resistant to one or more anti-TB drugs were stable (χ^2 for trend, $P=0.74$). The proportion of isolates classified as multidrug resistant (MDR) TB was also unchanged (χ^2 for

trend, $P=0.86$). In all three reporting years, resistance to isoniazid was the most common type of drug resistance (8.4%, 9.0% and 7.1%, respectively).

Table 3 shows the total number of isolates reported (1998 to 2000) by province and territory. The majority of isolates originated from Ontario, Quebec, British Columbia, Alberta and Manitoba. MDR TB was reported in the provinces of Ontario, British Columbia, Quebec, Manitoba and Alberta. The Yukon and Northwest Territories reported all isolates susceptible, as did the province of Prince Edward Island.

Figure 1 illustrates the age and sex profiles of individuals for which drug-resistant isolates were reported to this system. Slightly more isolates were reported in male persons (51% male, 41% female, 8% unknown), with the largest cohort of individuals being born between the years of 1961 and 1980 (35%).

DISCUSSION

Over 90% of the TB isolates reported to this system originated from five provinces. The three largest provinces (Ontario, British Columbia and Quebec) consistently reported the majority of isolates and MDR TB in the three years of data collection. Since the initiation of this laboratory-based surveillance system, Saskatchewan, the Atlantic provinces and the three territories have not reported any MDR TB isolates. Overall, TB drug resistance was

unchanged over the three-year study period, with a mean prevalence of 11.7% of any drug resistance and a 1.1% mean prevalence of MDR TB.

Independent research across Canada has previously found evidence of TB drug resistance and MDR TB. In 1992 to 1995, 16.2% of the TB isolates in Montreal were resistant to one or more TB drugs, and 1.4% were MDR TB (3). Ontario's proportion of TB isolates resistant to any drug increased from 8.2% in 1981 to 14.4% in 1997 (4). The proportion of MDR TB hovered between 1.0% and 2.3% each year (4). Manitoba examined TB isolates from 1980 to 1989: 7.1% were resistant and 1.4% were MDR TB (5). Alberta and British Columbia examined their culture-confirmed TB cases from 1989 to 1998 and found that 10.3% were resistant to one or more drugs, and 6.6% were MDR TB (6). Further research in 1993 to 1994, including all of Western Canada, found that 6.9% of the TB isolates were drug resistant (7). All Canadian studies have noted foreign birth to be a significant factor associated with drug resistance (6-8).

In the latest report of the global TB drug resistance surveillance project, jointly conducted by the WHO and the International Union Against Tuberculosis and Lung Disease, the median prevalence of overall TB drug resistance among the participating countries in 1994 to 1997 was 11.1%, and the median prevalence of MDR TB was 1.7% (1). Further international studies indicate a higher incidence of drug-resistant TB in male individuals, those previously treated for TB and those older than 65 years (9,10). Resistance to isoniazid and rifampin was predominantly found in foreign-born individuals (10,11).

The results observed to date in this surveillance system are consistent with previous national data and international data with respect to drug resistance trends. However, one of the main weaknesses of Canadian Tuberculosis Laboratory Surveillance System is the lack of available epidemiological data. In addition to the originating province or territory, the only routinely collected information available is sex and year of birth. More epidemiological information on the TB cases from which the isolates were submitted would be desirable to examine critically and compare drug resistance patterns in Canada and internationally.

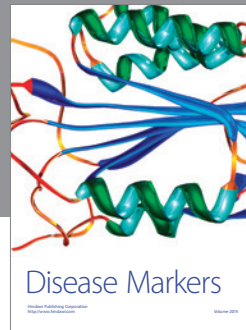
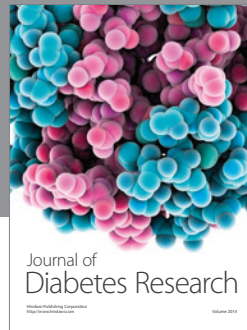
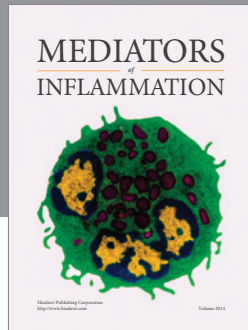
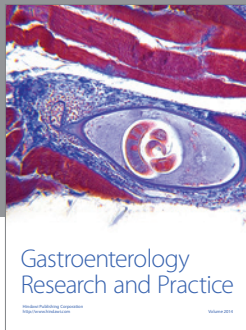
With growing worldwide concern regarding TB drug resistance, this surveillance system is vital to provide the

necessary data to monitor trends in TB drug resistance in Canada. The surveillance data collected to date indicate that the prevalence of TB drug resistance in this country is similar to that in the overall global situation. Although no significant difference was determined in the levels of TB drug resistance over time, several more years of collected data will be necessary to examine fully the unfolding trend of TB drug resistance in Canada.

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