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We examined trends in resistance to first-line antituberculous agents for *Mycobacterium tuberculosis* strains isolated in Ontario, Canada from 1987 through 1998 (n = 8069). The proportions resistant were as follows: isoniazid, 9.6%; rifampin, 1.9%; streptomycin, 4.9%; ethambutol, 1.3%; and pyrazinamide, 1.7%. Resistance to isoniazid has increased markedly since 1990, whereas resistance to streptomycin, ethambutol, and pyrazinamide increased from 1997 through 1998. Resistance to both isoniazid and rifampin did not increase. The incidence of persistence and reactivation (early or late treatment failure) was 1–2 per 100 person-years (PY) in the first 7–12 months and 0.3–0.9 per 100 PY from 13 months to 5 years thereafter. For initially susceptible strains, the incidence of resistance to isoniazid was 0.11 per 100 PY and for rifampin was 0.06 per 100 PY in the first year and negligible thereafter, with an overall risk of 0.14% for isoniazid and 0.10% for rifampin. Resistance of *M. tuberculosis* to antituberculous agents, and in particular to isoniazid, is a growing problem in Ontario and is higher than elsewhere in Canada.

During the past 50 years, the incidence of tuberculosis in Ontario decreased dramatically. Similar trends have been observed in most industrialized countries, related primarily to improved social and economic conditions and to the development of effective antituberculous agents. However, since 1983, tuberculosis incidence in Ontario stabilized at slightly less than 800 cases each year and at a rate of about 8 per 100,000 [1, 2]. Several factors may be responsible. During this period, Ontario experienced large-scale immigration from tuberculosis-endemic regions. The HIV epidemic which began in Ontario in the late 1970s added a further obstacle to tuberculosis control, since tuberculosis infection among HIV-infected persons progresses more rapidly to clinical disease, a result of the deterioration of cellular immunity that develops in the later phases of HIV infection [3]. Finally, strains of *Mycobacterium tuberculosis* have demonstrated increasing resistance to antituberculous agents; in particular, an increasing number of isolates is resistant to the most important first-line drugs, isoniazid and rifampin. Outbreaks of multiple-drug–resistant tuberculosis (MDRTB) have been observed in the United States [4, 5]. This is potentially a serious problem, since patients infected with MDRTB may continue to transmit infection despite therapy, may be unable to achieve clinical cure, and may develop serious consequences (e.g., relapse or miliary disease). Thus, in spite of progress, tuberculosis remains an important public health problem.

The objectives of the present study were (1) to determine trends in susceptibility of *M. tuberculosis* isolates to first-line antituberculous agents during the period 1987–1998, (2) to determine the incidence of persistence and reactivation related to early and late treatment failure among persons in whom *M. tuberculosis* has been isolated, and (3) to determine the rate of resistance to isoniazid and rifampin among patients with initially susceptible strains of *M. tuberculosis*.

**Methods**

The present analysis is based on the results of susceptibility testing of *M. tuberculosis* strains either isolated at the Central Public Health Laboratory (CPHL) in Etobicoke, Ontario, or received from community hospital or other microbiology laboratories from January 1987 through December 1998.

**Laboratory methods.** Susceptibility testing of *M. tuberculosis* was carried out using the BACTEC radiometric method (Becton Dickinson, Sparks, MD). During the study period, almost all isolates of *M. tuberculosis* identified in the province of Ontario were
sent to CPHL for susceptibility testing. Some isolates were tested at a teaching hospital outside of Toronto during the study period and, for the past 2–3 years, at 2 regional public health laboratories. These sites tested ~6% of \( M. \) \textit{tuberculosis} isolates in Ontario from 1987 through 1998. All resistant isolates are sent to CPHL for confirmation and second-line drug testing, if indicated.

Usually only the initial isolate of a patient from whom multiple specimens were received was tested for drug susceptibility. However, isolates from the same patient underwent repeated susceptibility testing if >3 months elapsed since the previous isolate was tested. Furthermore, additional isolates obtained from different sites or on special request for clinical or other reasons were tested for susceptibility to antituberculous agents.

Isolates were tested initially against the following first-line antituberculous drugs (with threshold concentrations): isoniazid (0.1 mg/L), rifampin (2 mg/L), streptomycin (2 mg/L), ethambutol (2.5 mg/L), and pyrazinamide (100 mg/L). If the isolate was resistant to any 2 of these 5 drugs, it was tested for susceptibility to second-line agents.

\textbf{Data management.} The following information was available for each isolate: patient name, the site from which the specimen was isolated, the laboratory (hospital or private laboratory) of primary isolation, lab number, date set up, and date reported. The antituberculous drug susceptibility database at the CPHL was in the database management program Q&A (Symantec, Cupertino, CA). We selected for analysis isolates received from January 1987 to December 1998. Data were analyzed by using SAS software (SAS, Cary, NC).

We eliminated from the database entries with atypical mycobacterial isolates, samples that showed no growth, isolates tested in the context of quality control, organisms isolated from a BCG site (an attenuated isolate of \( \text{Mycobacterium bovis} \)), and cancelled entries.

To link different specimens that were possibly received from the same person, we first corrected minor errors in the entry of the name (missing spaces, varied hyphenation, and minor spelling differences in first or last name) and then linked specimens manually. When it was not obvious that different entry of names represented different patients, we used information about the source, laboratory, the susceptibility result, the source of the specimen, and the dates received to decide whether 2 or more isolates were likely to have come from the same patient. We then reorganized the database according to patient rather than isolate (i.e., 1 entry for each patient).

\textbf{Data analysis.} We classified isolates according to the date the susceptibility testing was “set up.” Often, more than 1 isolate was received from the same patient within a short period. This may have occurred for several reasons: (1) several specimens were collected from the same site, (2) specimens were collected from different sites at the same or similar times, (3) patients were referred to another hospital for more specialized care where additional specimens were subsequently collected, (4) isolates in addition to primary specimens for culture were submitted for sensitivity testing, and (5) follow-up specimens collected after treatment was initiated were sometimes positive. To avoid “double counting” of isolates, we eliminated from the analysis any isolate from a given patient for which the testing was set up within a period of 3 months after setting up of the first specimen. Thus, after we received an isolate, we “counted” no subsequent isolate from the patient that was received in the next 91 days.

We calculated the number of isolates (overall and for each year of the 1987–1998 study period), the number of patients, and the number of patients by the number of isolates overall. We subsequently calculated, for each of the 5 first-line antituberculous drugs, the proportion of isolates that were resistant to each drug for each year. The number of sensitive strains tested at the 2 regional public health laboratories and 1 teaching hospital (as noted above) were added to the denominator for this purpose. For trend analysis and statistical testing, we aggregated, as appropriate, contiguous years for which the proportion of strains resistant was relatively stable. In the same way, we calculated for each year the proportion of isolates that were multi-drug resistant (i.e., resistant to both isoniazid and rifampin; MDRTB).

We calculated the incidence per 100 person-years of treatment failure (early or late) per quarter and per year among patients from whom \( M. \) \textit{tuberculosis} was initially isolated. The denominator was the person-time at risk, which we calculated as the sum of the periods of observation for each patient, from the date of the first isolate through 31 December 1998. The numerator was the number of patients with subsequent isolates after the 3-month period during the date \( M. \) \textit{tuberculosis} was first isolated. A similar approach was taken to determine the incidence of resistance to isoniazid and rifampin among patients with isolates that were initially found to be susceptible.

We carried out testing for statistical significance of differences in proportions using \( \chi^2 \) with Epi-Info (Version 6.04, May 1996; Centers for Disease Control and Prevention, Atlanta, and World Health Organization, Geneva, Switzerland). We also tested the statistical significance of the difference between the incidence of treatment failure among patients infected with susceptible strains and the incidence among patients infected with resistant strains [6].

\textbf{Results}

During the 12-year study period, 8069 \( M. \) \textit{tuberculosis} isolates in Ontario were available for analysis. Of these, 7513 isolates from 7182 patients were in the CPHL database; there was >1 isolate from 228 patients (3.2%); (2 isolates, 164 patients [2.3%]; 3 isolates, 48 [0.7%]; 4 isolates, 5 [0.1%]; and 5–9 isolates, 11 [0.1%]). The annual number of isolates, including those from the 2 regional public health laboratories and 1 teaching hospital, varied from 608 to 747 (mean, 672). The annual number of isolates increased 23% from 1987 to a peak in 1992 and then decreased to a stable incidence of ~650 isolates per year for the period 1995–1998 (table 1). Table 1 also shows the overall proportion of isolates resistant to each drug: isoniazid, 9.6%; rifampin, 1.9%; streptomycin, 4.9%; ethambutol, 1.3%; and pyrazinamide, 1.7%.

The trends in resistance over the study period were different for the 5 first-line drugs studied. For isoniazid, the proportion of isolates resistant increased from 7.1% in the period 1987–1990, to 10.5% in 1991–1995, and to 11.2% in 1996–1998. This increase of 58% was statistically significant (\( P < 10^{-4} \)). Resistance to rifampin was relatively stable over the study period, at about 2%, with no obvious increasing or decreasing trend. However, resistance to streptomycin was stable at ~4%–5% of
isolates from 1987 through 1996 but increased to 6.4% in 1997–1998; this 39% increase was statistically significant (P < .007). The proportion of M. tuberculosis isolates in Ontario resistant to ethambutol also increased, from 1.5% in 1987–1996 to 2.3% in 1997–1998; the 52% increase was borderline significant (P = .06). Finally, resistance to pyrazinamide was 1.7% overall but, as for streptomycin, increased in the period 1997–1998; the increase of 71% in 1997–1998 compared with earlier years was statistically significant (P = .02). The proportions of isolates resistant to each of the 5 first-line antituberculous drugs are illustrated in figure 1.

The proportion of isolates resistant to ≥1 drug increased gradually over time, almost doubling over the 12-year study period. The proportion resistant to any drug increased from 8.2% to 14.1% (table 1). This increase appeared to occur in 3 “steps” and was statistically significant (P = .01).

The proportion of isolates resistant to both isoniazid and rifampin (referred to as multi-drug resistant or MDRTB) is also shown in table 1. Overall, 1.8% of isolates were resistant to both agents; no increasing or decreasing trend was observed, although the highest rate was observed in 1996.

The proportion of isolates resistant to the number of first-line antituberculous drugs is shown in table 2. The mean number of drugs resistant for each isolate overall was 1.5 and did not vary significantly over the study period. However, the proportion of isolates resistant to ≥2 drugs did increase steadily, from 3.1% in 1987 to 5.7% in 1998. The proportion of isolates received in 1995–1998 resistant to ≥2 drugs was 5.2%, compared with 3.9% previously; this increase of 33% was statistically significant (P = .008).

The incidence of treatment failure or reactivation appeared to decrease over the 47 quarters of observation after the initial isolate was obtained (figure 2). The incidence was 5.6 per 100 PY in the first quarter, 1.2–1.9 in quarters 2–4, 0.6–0.9 in years 2 and 3, and about 0.4 per 100 PY in years 4 and 5 after the first isolation. Overall, the incidence of persistence and reactivation among strains initially resistant to isoniazid or rifampin was 1.98 times greater than the incidence among isolates susceptible to both of the 2 principal antituberculous agents (figure 3); the difference was statistically significant (P < .0001).

With respect to the emergence of resistance (figure 4), for isoniazid, the incidence was 0.12 per 100 PY in the first year and from 0.00 to 0.02 from years 2–6. For rifampin, the incidence was 0.06 per 100 PY in the first year. The overall risk of developing resistance over the 12-year follow-up period was 0.14% (9 of 6470 patients) for isoniazid and 0.10% for rifampin (5 of 7075 patients).

Discussion

In the 12 years from 1987 through 1998, we found that 12.6% of M. tuberculosis isolates in Ontario were resistant to ≥1 first-line antituberculous drugs, with an increasing trend. The greatest increase observed was for isoniazid. Resistance increased markedly in the late 1980s and early 1990s; the rate observed since 1991 has been almost double the rate observed in 1986–1987. We also noted increased resistance to streptomycin, ethambutol, and pyrazinamide; however, this increase was relatively recent, having been documented in 1997 and 1998. Almost all isolates resistant to rifampin were also resistant to isoniazid. The incidence of treatment failure was highest in the first 18 months but decreased thereafter. Resistance to isoniazid and rifampin developed at a rate of ~0.10–0.15 per 100 PY in the first year but was low thereafter. Overall, the risk of developing resistance during the 12-year study period was 0.14% for isoniazid and 0.10% for rifampin.

The emergence of M. tuberculosis strains that are resistant to antituberculous drugs in Ontario is not unique. This trend has received increasing attention, in part due to the major outbreaks

Table 1. Number of Mycobacterium tuberculosis isolates obtained and the proportion resistant to first-line antituberculous agents, Ontario, Canada, 1987–1998.

<table>
<thead>
<tr>
<th>Year</th>
<th>n</th>
<th>INH</th>
<th>Rif</th>
<th>Stm</th>
<th>Eth</th>
<th>PZA</th>
<th>Any drug</th>
<th>MDRTB</th>
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</tr>
<tr>
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<tr>
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<td>14.5</td>
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<tr>
<td>1995</td>
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<tr>
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<tr>
<td>1998</td>
<td>637</td>
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<td>1.7</td>
<td>6.0</td>
<td>2.4</td>
<td>2.2</td>
<td>14.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Total</td>
<td>8069</td>
<td>9.6</td>
<td>1.9</td>
<td>4.9</td>
<td>1.3</td>
<td>1.7</td>
<td>12.6</td>
<td>1.8</td>
</tr>
</tbody>
</table>

NOTE. Data are percentages unless indicated otherwise. Eth, ethambutol; INH, isoniazid; MDRTB, multi-drug resistant (isoniazid and rifampin); PZA, pyrazinamide; Rif, rifampin; Stm, Streptomycin.

Figure 1. Proportion of Mycobacterium tuberculosis isolates resistant to individual antituberculosis drugs: isoniazid (●), streptomycin (○), rifampin (△), ethambutol (●), and pyrazinamide (△) by year of isolate. Ontario, Canada, 1987–1998.
of MDRTB in the United States. In these outbreaks, high mortality rates and nosocomial transmission were observed [4, 5].

There are several limitations to our study. Since no clinical information was available, we could not directly determine whether the resistance observed was “primary” (caused by initial infection with a resistant strain) or “acquired” (e.g., through ineffectual treatment regimens or poor compliance). Although we could identify recurrent disease for some patients by matching names, our analysis began only in 1987. Thus, we could not determine whether the patient had had an episode of tuberculosis before 1987 or one that occurred outside Ontario. In addition, because only limited demographic or other epidemiologic data were available to us, we could not characterize resistance patterns according to sex, age, country of birth, or region of residence.

We manually linked multiple isolates from the same person using primarily the patient’s name. Errors may have occurred in both directions; that is, isolates from the same person may have been judged to have been from different persons (e.g., as a result of spelling or transcription errors) and, conversely, isolates from persons with the same name may have been incorrectly considered as having been from 1 person. Although such errors certainly occurred, they were unlikely to be frequent, since the database was relatively small and most names distinct.

To examine patterns of incidence, we assumed that patients were “under observation” until 31 December 1998 and that, had the patient developed recurrent disease, the episode would have been diagnosed and the organism isolated and submitted to CPHL. We also assumed for this analysis that subjects remained in Ontario and did not die of other causes after the first isolate was obtained. Since these assumptions are incorrect, we almost certainly overestimated the person-time of observation (denominator) and underestimated the numerator used in our calculation. Thus, the incidence rates calculated represent minimum estimates.

The resistance to any antituberculous drug and to isoniazid appeared to occur in 3 distinct “steps.” We do not know the reasons for this pattern; it is possible that it is caused by statistical variation.

Our study observed an increase in resistant isolates of M. tuberculosis in Ontario for 4 of the 5 drugs examined and a near-doubling of resistance overall (8.2% of isolates in 1987, compared with 14.1% in 1998). Other regions in Canada have not experienced the high rates or the increasing trend in drug resistance observed in Ontario. The Canadian Drug Resistance Study [7, 8] found that, of 788 isolates from Canada outside Ontario in 1998, 9.6% were resistant to any drug and 0.8% were multiresistant or MDRTB; the proportions in Ontario were 14.1% and 1.7%, respectively. The difference in resistance to any drug was statistically significant ($P = .005$), but the difference in MDRTB was not.

Of M. tuberculosis strains received at the provincial laboratory in Quebec from 1987 through 1996 [9], 11.4% demonstrated resistance, compared with 12.3% in Ontario during the same period ($P = .02$). In contrast to Quebec, Ontario showed an increasing trend in resistance: in 1996, the rate was 14.3%, compared with 10.1% in Quebec ($P = .08$).

Our results also differed from those reported for western Canada. In Manitoba, 7.1% of isolates obtained in 1980–1989 were resistant to $\geq$1 drugs [10]. Among cases diagnosed in the 4 western Canadian provinces in 1993–1994, the rate of resistance was 6.9% [11] (about 8% in British Columbia, Alberta, and Saskatchewan, and 1.1% in Manitoba). The investigators noted a marked increase in the rate of initial resistance to isoniazid, compared with previous reports: 4.1% versus 1.5%–2.2% reported earlier [10, 12, 13]. The overall rate of resistance to isoniazid among strains that we tested in Ontario during 1993–1994 was 10.4%; that proportion is 2.2 times greater than the 4.7% of isolates reported from western Canada ($P = .0001$).

In Canada, resistance to antituberculous drugs has generally been higher among foreign-born patients [10–12]. In the western Canadian provinces in 1993–1994, resistance among isolates appeared to occur in 3 distinct “steps.” We do not know the reasons for this pattern; it is possible that it is caused by statistical variation.

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**Table 2.** Number of *Mycobacterium tuberculosis* isolates obtained and the proportion resistant to number of first-line antituberculous agents, Ontario, Canada, 1987–1998.

<table>
<thead>
<tr>
<th>Year</th>
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<th>5</th>
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<td>4.3</td>
<td>1.5</td>
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NOTE. Data are percentages unless otherwise indicated. * Mean number of drugs to which isolates were resistant.

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**Figure 2.** Incidence of persistence or reactivation among *Mycobacterium tuberculosis* isolates, Ontario, Canada, 1987–1998.
Figure 3. Incidence of persistence or reactivation among *Mycobacterium tuberculosis* isolates for those initially sensitive to both isoniazid and rifampin (■) and those initially resistant to either isoniazid or rifampin (●). Ontario, Canada, 1987–1998.

Figure 4. Incidence of resistance to isoniazid (■) and rifampin (●) among initially susceptible *Mycobacterium tuberculosis* isolates. Ontario, Canada, 1987–1998.

from foreign-born cases was 3.6 times higher than that among Canadian-born cases [11]. Among 753 cases of tuberculosis in immigrants in Alberta diagnosed from 1982 through 1994 [14], 17.4% were resistant to any drug. Resistance to specific agents was as follows: isoniazid, 9.9%; rifampin, 0.8%; streptomycin, 12.9%; ethambutol, 1.9%; and pyrazinamide, 1.9%. Resistance was particularly high among cases in persons born in Vietnam (30%), China (22%), and the Philippines (16%). Although no comparison group was presented, the proportions of cases resistant were far higher than those reported among unselected populations in other studies from western Canada [10, 11], especially for isoniazid or streptomycin. A recently published study from British Columbia and Alberta that analyzed strains isolated from 1989 through 1998 [15] observed a 3-fold greater rate of resistance among isolates from patients born outside Canada (305 [14.8%] of 2128) than rates among isolates from Canadian-born patients. In contrast to elsewhere in Canada, the rate of resistance among foreign-born cases diagnosed in metropolitan Montreal from 1992 through 1995 was similar to the rate in Canadian-born tuberculosis patients [16].

Although our database lacked demographic data, a recent review of reported tuberculosis cases in Ontario found that most cases of drug-resistant *M. tuberculosis* infection were in patients born in countries other than Canada that have a high incidence of tuberculosis and of drug-resistant tuberculosis [1]. The greater proportion of *M. tuberculosis* strains resistant to antimicrobial agents in Ontario, compared with the other Canadian provinces, may be related to higher immigration rates from countries where tuberculosis is endemic and resistant strains more common. We compared the immigration rates in Ontario with rates in the rest of Canada for 6 of the 8 countries (for 2 countries, immigration data were not readily available) that have reported rates of isoniazid-resistant *M. tuberculosis* strains higher than Ontario. These countries (India, Russia, Kenya, Argentina, Latvia, and Estonia) were selected from 28 for which there is national data on resistant tuberculosis [17, 18]. Fifty-five percent of the immigrants to Canada from these countries lived in Ontario, compared with 7% in Québec; the immigration rate in Ontario was twice that of the rest of Canada and 5.1 times that of Québec. Therefore, differential immigration of persons from countries with a high rate of tuberculosis resistance may help to explain the higher rates of resistance observed in Ontario.

In the United States, the number of reported tuberculosis cases decreased almost 4-fold from 1953 to 1985 but then increased 20% from 1985 to 1992 [19]. This was similar to the increase we observed in the number of isolates we received in Ontario from 1987 through 1992 (which increased from 608 to 747, or 23%). A nationwide survey in the United States of strains reported in the first quarter of 1991 [20] revealed an overall resistance rate of 14.2%, with the following drug-specific rates: isoniazid, 9.1%; rifampin, 3.9%; streptomycin, 5.7%; ethambutol, 2.4%; and pyrazinamide, 5.8%. In Ontario in 1991, the proportion of *M. tuberculosis* isolates resistant to isoniazid was 31% higher than in the United States. For the 4 other drugs, the proportions resistant were higher in the United States, varying from 46% higher for streptomycin to 350% higher for pyrazinamide. The proportion of strains resistant to both isoniazid and rifampin in 1991 was 2.0% in Ontario but 3.5% in the United States, or 75% higher.

A more recent analysis in the United States, covering the years 1993–1996 [21], reported a modest decrease in the proportion of strains resistant to first-line antituberculous drugs. Resistance to rifampin and ethambutol showed the greatest decline: for rifampin, from 3.6% in 1993 to 2.3% in 1996, and for ethambutol, from 4.3% in 1993 to 2.3% in 1996. In 1996, the rate of resistance for most of the 5 first-line drugs was approximately the same in the United States as in Ontario, with the exception of isoniazid (8.0% of strains resistant in the
United States vs. 12.0% in Ontario) and MDRTB (1.6% resistant in the United States vs. 2.3% in Ontario).

A recent international study reported resistance to antituberculous agents for countries with valid national data [17, 18]. Although rates of resistance were generally much higher in developing countries than in industrialized countries, the rate of \textit{M. tuberculosis} resistance varied greatly in all regions. Primary resistance to isoniazid is highest in Africa, Asia, and in parts of the United States and is low in Australia, England, and Japan. The proportion of strains resistant to isoniazid in Ontario of 10.8% in the period 1997–1998 was 1.2- to 2.6-fold higher than that of any of 8 industrialized countries for which data were available. In only 8 of the 28 countries presented was the proportion of strains resistant to isoniazid higher than that in Ontario.

In our analysis of the incidence of resistance among isolates found to be initially susceptible to isoniazid and rifampin, we observed that the risk for development of resistance to isoniazid and rifampin was highest in the first year after the initial isolate. This may reflect poor treatment compliance. However, we did not accord for competing mortality, failure to recognize disease, and out-migration of patients from the database, which may lead to an underestimation of incidence, especially in the later years. In countries that have adopted directly observed therapy (DOT) programs, a significant decrease in the rate of development of acquired resistance has been observed. Increased resistance has been reported wherever rifampin has been used. Therefore, programs to ensure that drug compliance is adequate, such as DOT, when indicated, are crucial to minimize the emergence of drug resistance [18].

The trends we observed in increasing resistance to first-line antituberculous agents, and in particular to isoniazid, have important clinical implications. The current Canadian Tuberculosis Standards [22] recommend that, in any region where \(\geq4\%\) of strains are resistant to isoniazid, 4-drug regimens be administered until the results of susceptibility testing are available.

Our study demonstrates that timely, complete, and accurate data on antituberculous drug resistance of \textit{M. tuberculosis} is useful to help guide treatment decisions. In addition, consistent monitoring of the drug susceptibility patterns will help in the development and evaluation of effective tuberculosis control programs, in particular to identify subpopulations at higher risk of resistant infection and develop guidelines concerning appropriate therapy.

Acknowledgments

We thank the laboratory technicians at CPHL who analyzed the specimens; Dr. Monika Naus (Public Health Branch, Ontario Ministry of Health), Dr. Paul Brassard (Montreal Regional Health Department) and Dr. Howard Njoo (Laboratory Centre for Disease Control, Health Canada), who reviewed an earlier version of the manuscript and provided useful advice; and Mark VandenNoort (Instructional Media Centre, Laboratories Branch) who helped in the preparation of the figures.

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