Increase in Multidrug-resistant Tuberculosis (MDR-TB) in Alberta Among Foreign-born Persons: Implications for Tuberculosis Management

Richard Long, MD, Deanne Langlois-Klassen, PhD

ABSTRACT

OBJECTIVES: Globally, the prevalence of anti-tuberculosis drug resistance has been increasing. This study sought to identify trends in multidrug-resistant tuberculosis (MDR-TB) among foreign-born persons in Alberta, a major immigrant-receiving province of Canada.

METHODS: A retrospective cohort study design was used to investigate the prevalence of MDR-TB in foreign-born culture-positive TB cases between 1982 and 2011. Relevant demographic, clinical and laboratory data were abstracted from the TB Registry, individual medical records and the Provincial Laboratory for Public Health.

RESULTS: Of the 2,234 foreign-born culture-positive TB cases in Alberta in 1982-2011, 27 (1.2%) had MDR-TB. Overall, MDR was associated with age <65 years ($p=0.025$), TB relapse/retreatment, and diagnosis and arrival in the last decade (2002-2011). The prevalence of MDR-TB in 2002-2011 was 2.1%, a significant increase from 0.65% in 1982-1991 ($p=0.022$) and 0.56% in 1992-2001 ($p=0.009$). Only immigrants from the Philippines and Vietnam showed a significant increase in the prevalence of MDR-TB between the first two decades and the last. Compared to MDR-TB cases reported in the first two decades, those reported in the last decade were more frequently younger than 35 years of age, new active versus relapse/retreatment cases and diagnosed with non-respiratory versus respiratory TB. In 1992-2011, MDR-TB strains had unique DNA fingerprints.

CONCLUSIONS: Recent trends in the prevalence and clinical characteristics of foreign-born MDR-TB cases have important implications for TB case management in Canada. Early diagnosis of MDR-TB, using genotypic drug susceptibility testing, is suggested in foreign-born TB cases at increased risk of being MDR.

KEY WORDS: Multidrug-resistant tuberculosis; immigrants

La traduction du résumé se trouve à la fin de l'article.

Can J Public Health 2013;104(1):e22-e27.

The burden of tuberculosis (TB) in Canada is increasingly shifting to foreign-born persons and, in particular, to those who emigrated from high-incidence countries.^{1,2} Foreign-born persons accounted for 66% of the TB cases in Canada in 2010, nearly four times the proportion of foreign-born cases reported in 1970.^{3,4} At the same time, resistance to one or more of the first-line anti-tuberculosis drugs (isoniazid, rifampin, pyrazinamide and ethambutol) is more common in foreign-born than Canadian-born cases. In 2006, the proportion of culture-positive foreign-born TB cases with resistance to one or more first-line drugs was more than twice that of Canadian-born cases (11% and 5%, respectively).⁵ The combination of a high burden of TB and increased drug resistance resulted in 80% of drug-resistant cases in Canada being foreign-born.⁵ Moreover, 83-95% of multidrug-resistant (MDR; resistance to at least isoniazid and rifampin) TB cases reported in Canada are foreign-born.⁶⁻⁸ Immigrants to Canada from the Western Pacific may be at a higher risk for MDR-TB due to Beijing/W strains of *Mycobacterium tuberculosis*.⁹

Drug resistance and especially MDR-TB are increasing globally, mainly on account of drugs being improperly prescribed (e.g., insufficient number of active agents in the regimen; suboptimal dosage), properly prescribed but unavailable (e.g., interrupted supply; prohibitive patient cost), inadequately supervised (e.g., erratic drug ingestion; omission of one or more active agents), or, more

rarely, malabsorbed.¹⁰⁻¹² Historically, high rates of drug resistance have been observed in countries with high rates of TB and widely available but poorly organized access to health care and medications.¹³ Unintentionally, the use of standardized regimens in these low- and middle-income countries in place of individualized regimens based upon drug susceptibility test results may have exacerbated the problem of drug resistance. In a systematic review and meta-analysis of the standardized treatment of previously untreated patients with culture-confirmed pulmonary TB, the cumulative incidence of acquired drug resistance with initially pan-sensitive strains was 0.8% (95% CI 0.5-1.0) compared to 6% (95% CI 4-8) with initially single drug-resistant strains and 14% (95% CI 9-20) with initially polydrug-resistant strains.¹⁴

Author Affiliations

Department of Medicine, University of Alberta, Edmonton, AB

Correspondence: Dr. Richard Long, TB Program Evaluation and Research Unit, Department of Medicine, Division of Pulmonary Medicine, University of Alberta, 8333 Aberhart Centre, 11402 University Avenue, Edmonton, AB T6G 2J3, Tel: 780-407-1427, Fax: 780-407-1429, E-mail: richard.long@ualberta.ca

Acknowledgements: The authors thank the staff of Alberta Health Services and the Provincial Laboratory for Public Health for their assistance with data abstraction. We also extend our gratitude to the staff of the TB Program Evaluation and Research Unit, University of Alberta, for their assistance in preparing this manuscript. This study was supported in part by a grant from the University Hospital Foundation.

Disclaimer: The opinions, results and conclusions reported in this paper are those of the authors. No endorsement by the University of Alberta or Alberta Health Services is intended or should be inferred.

Conflict of Interest: None to declare.

Table 1. Estimated Proportion of MDR-TB Cases Among Incident TB Cases in the 27 High MDR-TB Burden Countries, 2008*†

WHO Region	Country	Source of Estimates	% MDR Among New TB Cases (95% CI)	% MDR Among Previously Treated TB Cases (95% CI)
Africa	DR Congo	model	1.8 (0.0-4.3)	7.7 (0.0-18.1)
	Ethiopia	DRS, 2005	1.6 (0.9-2.7)	11.8 (6.4-21.0)
	Nigeria	model	1.8 (0.0-4.3)	7.7 (0.0-18.1)
	South Africa	DRS, 2002	1.8 (1.5-2.3)	6.7 (5.5-8.1)
Europe	Armenia	DRS, 2007	9.4 (7.3-12.1)	43.2 (38.1-48.5)
	Azerbaijan	DRS,‡ 2007	22.3 (19.0-26.0)	55.8 (51.6-59.9)
	Belarus	model	12.5 (0.0-25.3)	42.1 (11.9-72.2)
	Bulgaria	model	12.5 (0.0-25.3)	42.1 (11.9-72.2)
	Estonia	DRS, 2008	15.4 (11.6-20.1)	42.7(32.1-53.9)
	Georgia	DRS, 2006	6.8 (5.2-8.7)	27.4 (23.7-31.4)
	Kazakhstan	DRS, 2001	14.2 (11.0-18.2)	56.4 (50.9-61.8)
	Kyrgyzstan	model	12.5 (0.0-25.3)	42.1 (11.9-72.2)
	Latvia	DRS, 2008	12.1 (9.9-14.8)	31.9 (24.9-39.9)
	Lithuania	DRS, 2008	9.0 (7.5-10.7)	47.5 (42.9-52.2)
	Republic of Moldova	DRS, 2006	19.4 (16.8-22.2)	50.8 (48.7-53.0)
	Russian Federation	DRS,‡ 2008	15.8 (11.9-19.7)	42.4 (38.1-46.7)
	Tajikistan	DRS,‡ 2008	16.5 (11.3-23.6)	61.6 (52.9-69.7)
	Ukraine	DRS,‡ 2002	16.0 (13.8-18.3)	44.3 (40.0-48.7)
	Uzbekistan	DRS,‡ 2005	14.2 (10.4-18.1)	49.8 (35.8-63.8)
Eastern Mediterranean	Pakistan	model	2.9 (0.0-8.0)	35.4 (0.0-75.1)
South-East Asia	Bangladesh	model	2.2 (0.0-5.6)	14.7 (0.0-39.6)
	India	DRS,‡ 2005	2.3 (1.8-2.8)	17.2 (14.9-19.5)
	Indonesia	DRS,‡ 2004	2.0 (0.5-6.9)	14.7 (0.0-39.6)
	Myanmar	DRS, 2007	4.2 (3.2-5.6)	10.0 (7.1-14.0)
Western Pacific	China	DRS, 2007	5.7 (5.0-6.6)	25.6 (22.6-28.3)
	Philippines	DRS, 2004	4.0 (3.0-5.5)	20.9 (14.8-28.7)
	Vietnam	DRS, 2006	2.7 (2.0-3.6)	19.3 (14.5-25.2)

Abbreviations: WHO=World Health Organization; MDR-TB=multidrug-resistant TB; CI=confidence interval; DR=Democratic Republic; DRS=drug resistance surveillance or survey data.

* This table is a modified version of Table 6 in the WHO publication Multidrug and Extensively Drug-Resistant TB (M/XDR-TB) 2010 Global Report on Surveillance and Response and is used with permission (See reference 12).

† The 27 high MDR-TB burden countries refer to WHO Member States that were estimated by the WHO in 2008 to have had an annual incidence of at least 4,000 MDR-TB cases and/or at least 10% of newly registered TB cases with MDR-TB.

‡ Estimates were based on subnational drug resistance data.

Drug-resistant TB and MDR-TB in particular represent grave threats to TB prevention and control. To treat it, one must use longer, more costly and often more toxic drug regimens. Presumably, low-incidence countries like Canada will not remain isolated from global increases in MDR-TB as emigrants from high MDR-TB burden countries (Table 1) may be infected with MDR strains prior to immigration and develop active disease after arrival in Canada.¹⁵ This study sought to identify trends in MDR-TB among foreign-born persons in a major immigrant-receiving province of Canada over the last 30 years.

METHODS

A retrospective cohort study design was used to investigate the prevalence of MDR-TB in foreign-born culture-positive TB cases reported in the province of Alberta between 1982 and 2011. Study cases were identified through the provincial TB Registry and their demographic and clinical features abstracted. Laboratory data were abstracted from the Provincial Laboratory for Public Health, where all mycobacteriology in the province is performed. Demographic data included age at diagnosis, sex, country of birth, and year of arrival. Clinical data included disease type (new active versus relapse/retreatment as defined in the Canadian Tuberculosis Standards),¹ disease site (respiratory versus non-respiratory), and for MDR-TB cases, human immunodeficiency virus (HIV) sero-status. Laboratory data included susceptibilities to isoniazid, rifampin, ethambutol, and streptomycin on all initial isolates dating from 1982 and to pyrazinamide on all initial isolates dating from 1991. From 1982 to 1990, the resistance ratio method was used to determine susceptibilities.¹⁶ Strains with a resistance ratio of ≤ 2 were considered sensitive, while strains with a ratio of ≥ 8 were considered resistant. From 1991 to 2010, the BACTEC radiometric system

(BACTEC 460TB™, Becton-Dickinson Diagnostic Instrument Systems, Towson, MD), and from 2010 to 2011, the BACTEC non-radiometric system (BACTEC MGIT 960™, Becton, Dickinson and Company, Sparks, MD), were used to determine susceptibilities. All strains found to be resistant by BACTEC 460TB™ or BACTEC MGIT 960™ were retested using the resistance-ratio method to confirm drug resistance.

During the last two decades (1992-2001 and 2002-2011), all initial isolates of *M. tuberculosis* in Alberta were DNA fingerprinted using IS6110 restriction fragment length polymorphism, supplemented by spoligotyping in isolates with less than six copies of IS6110.¹⁷⁻¹⁹ The DNA fingerprints of MDR-TB isolates were compared to each other and to that of non-MDR-TB isolates.

As informed by the study results and in order to provide insight into the potential feasibility and cost-effectiveness of genotypic drug susceptibility tests for MDR-TB, estimated costs were calculated overall and for groups of foreign-born persons with a high prevalence of MDR-TB based on country of birth. Estimated laboratory costs for the genotypic drug susceptibility tests included consumables, miscellaneous laboratory supplies, laboratory personnel, and overhead costs but excluded the initial purchase of equipment, personnel training, and specimen shipping costs.²⁰ It was assumed that CAD \$1 was equivalent to US \$1.

The trends and related observations are summarized below, the two-sided p-values corresponding to the chi-square test or Fisher's exact test using a 5% level of significance. In the analysis, the potential association between calendar year of arrival in Canada (a proxy for calendar year of departure from the country of birth) and MDR-TB was of interest for three reasons: MDR strains of *M. tuberculosis* are a relatively recent and increasing phenomenon, rifampin therapy having been introduced in 1968;²¹ most foreign-born TB

Table 2. Characteristics of Foreign-born MDR and Non-MDR Tuberculosis Cases in Alberta, 1982-2011

Case Characteristic	Cases	MDR		RR	p-values
		n	%		
Overall	2234	27	1.21		
Age (years)					0.025
<35	766	13	1.70	6.07	
35-64	765	12	1.57	5.61	
>64	703	2	0.28	1.00	
Sex					0.89
Female	1130	14	1.24	1.05	
Male	1104	13	1.18	1.00	
Country of birth*					0.092
High MDR-TB burden†	1571	22	1.40	1.84	
Other	659	5	0.76	1.00	
Disease type‡					<0.0001
Relapse/Retreatment	151	10	6.62	7.88	
New active	2034	17	0.84	1.00	
Disease site					0.62
Respiratory	1560	20	1.28	1.23	
Non-respiratory	674	7	1.04	1.00	

Abbreviations: MDR=multidrug-resistant; RR=relative risk.

* The country of birth was unknown for four cases that were not MDR.

† The high MDR-TB burden countries that were associated with MDR-TB cases in this study were: Philippines (7 cases); China, including Hong Kong, Macau and Taiwan (4 cases); Vietnam (4 cases); India (3 cases); Ethiopia (2 cases); Pakistan (1 case); and Nigeria (1 case).

‡ Disease type was missing for 49 non-MDR cases.

cases result from infections that were acquired prior to immigration;¹⁹ and the genotypic profiles of *M. tuberculosis* strains among foreign-born persons largely reflect the *M. tuberculosis* epidemiology of their countries of birth/origin.^{22,23} These factors reasonably suggest that foreign-born persons who more recently departed their countries of birth would have higher rates of MDR-TB than longer-standing residents in Canada.

The reporting of this longitudinal data was approved by the Health Research Ethics Board of the University of Alberta.

RESULTS

Twenty-seven (1.2%) of the 2,234 culture-positive foreign-born TB cases in Alberta in 1982-2011 were MDR-TB cases (Table 2). Overall, MDR was associated with younger age (<65 years) and TB relapse/retreatment but not sex, country of birth, or disease site (Table 2).

There was a trend of foreign-born individuals who arrived in more recent calendar years having an increased risk of MDR-TB (Figure 1). In particular, the prevalence of MDR-TB was greatest in the most recent decade of diagnosis (2.11% in 2002-2011) and this was significantly higher than the prevalence in 1992-2001 (0.56%; $p=0.009$) and 1982-1991 (0.65%; $p=0.022$) (Table 3). For each decade of diagnosis, the prevalence of MDR-TB increased between 1.5 and 2.3 times when the analysis was limited to cases that arrived in the decade of diagnosis (Table 3). However, the association between prevalence of MDR-TB and decade of diagnosis was of borderline significance when limited to cases that arrived in the decade of diagnosis ($p=0.05$).

Twenty-two (81.5%) of the 27 foreign-born MDR-TB cases reported over the three decades were from high MDR-TB burden countries (Table 2) (7 from the Philippines; 4 from China; 4 from Vietnam; 3 from India; 2 from Ethiopia; 1 from Pakistan; and 1 from Nigeria).¹⁵ Fifteen (68.1%) of these 22 cases were diagnosed in the last decade (2002-2011) and 13 (86.7%) of these 15 cases had also arrived in Canada during the 2002-2011 period (Table 3). All of the 13 MDR-TB cases that arrived and were diagnosed in the last decade were younger than 65 years at the time of diagnosis.

Figure 1. Number of foreign-born persons diagnosed with MDR-TB in Alberta by calendar year of arrival

Note: The number of cases is represented by the solid line and the trend in MDR-TB case counts by the dashed line.

The prevalence of MDR-TB among cases born in high MDR-TB countries increased from 0.7% in the first two decades (1982-2001) to 2.4% in the last decade (2002-2011) ($p=0.008$). A similar increase in prevalence was observed among cases born in high MDR-TB burden countries that had arrived in the decade of diagnosis (from 1.4% in the first two decades to 4.6% in the last decade; $p=0.016$). More specifically, a significant increase in the prevalence of MDR-TB between the first two decades and the last decade was only observed among cases born in the Philippines (from 0% to 4.1%, $p=0.017$) and Vietnam (from 0.4% to 3.5%, $p=0.040$). The prevalence of MDR-TB among cases in the last decade from the Philippines and Vietnam increased to 6.5% and 6.3%, respectively, if only TB cases that had arrived in 2002-2011 were considered (Table 3).

Compared to MDR-TB cases reported in the first two decades (1982-2001), those reported in the last decade (2002-2011) were more frequently younger than 35 years of age ($p=0.265$), new active versus relapse/retreatment cases ($p=0.102$) and diagnosed with non-respiratory versus respiratory disease ($p=0.068$) (Table 4). None of the MDR-TB cases with known HIV status were co-infected with HIV in either time period. Cases diagnosed in the first two decades were resistant to a mean of 3.1 first-line drugs out of an average of 4.5 drugs tested per case and, in the last decade, a mean of 3.5 first-line drugs out of an average of 5 drugs tested per case.

In 1992-2011, all but one of the MDR-TB isolates had unique DNA fingerprints. The exception was an isolate with an IS6110 low-copy-number that shared a DNA fingerprint with one non-MDR-TB isolate; a link between these cases could not be established through conventional contact tracing.

In Canada, the optimal cost-effectiveness of genotypic drug susceptibility tests requires that the subset of the foreign-born culture-positive TB cases at greatest risk for MDR-TB be identified. The results of the current study suggest that this subset would include individuals born in the Philippines or Vietnam who arrived in Canada in 2002 or later and who were aged <65 years, and especially aged <35 years, at the time of diagnosis. If this approach had been used in Alberta in 2002-2011, 116 TB cases would have been tested and 8 (53.3%) of 15 MDR-TB cases in the period potentially detected at an estimated laboratory cost of \$1740 to \$2088 per MDR case detected (Table 5). Expansion of the subset to include the 256 TB cases born in high MDR-TB burden countries would have poten-

Table 3. Prevalence of MDR-TB in Foreign-born TB Cases in Alberta, 1982-2011*

Foreign-born TB Case Grouping	Decade of Diagnosis			Total
	1982-1991	1992-2001	2002-2011	
TB cases	617	718	899	2234
MDR-TB cases	4	4	19	27
Group MDR-TB prevalence (%)	0.65	0.56	2.11	1.21
TB cases that arrived in the decade	200	239	406	845
MDR-TB cases that arrived in the decade	2	3	15	20
Group MDR TB prevalence (%)	1.00	1.26	3.69	2.37
TB cases born in HMTBC†	410	525	636	1571
MDR-TB cases born in HMTBC	3	4	15	22
Group MDR-TB prevalence (%)	0.73	0.76	2.36	1.40
TB cases born in HMTBC that arrived in the decade	164	187	281	632
MDR-TB cases born in HMTBC that arrived in the decade	2	3	13	18
Group MDR-TB Prevalence (%)	1.22	1.60	4.63	2.85
Philippine-born TB cases	54	91	170	315
Philippine-born MDR-TB cases	0	0	7	7
Group MDR-TB prevalence (%)	0	0	4.12	2.22
Philippine-born TB cases that arrived in the decade	27	39	108	174
Philippine-born MDR-TB cases that arrived in the decade	0	0	7	7
Group MDR-TB prevalence (%)	0	0	6.48	4.02
Vietnam-born TB cases	137	144	85	366
Vietnam-born MDR-TB cases	0	1	3	4
Group MDR-TB prevalence (%)	0	0.69	3.53	1.09
Vietnam-born TB cases that arrived in the decade	57	43	16	116
Vietnam-born MDR-TB cases that arrived in the decade	0	1	1	2
Group MDR-TB prevalence (%)	0	2.33	6.25	1.72

* Refers to culture-positive TB cases only.

† HMTBC=High MDR-TB burden countries.

tially identified 13 (86.7%) of the MDR-TB cases diagnosed during the 2002-2011 period for an additional estimated laboratory cost of \$623 to \$748 per MDR-TB case detected (Table 5). Although MDR-TB was significantly associated with relapse/retreatment cases during the 30-year study period, MDR-TB was more frequent among new active TB cases in 2002-2011 ($p=0.102$). If the optimal subset for genotypic drug susceptibility testing was further defined to include only relapse/retreatment cases, 6 (75.0%) of 8 MDR-TB cases among Philippine- or Vietnam-born cases and 11 (84.6%) of 13 cases born in any high MDR-TB burden country would not have been tested.

DISCUSSION

The increased prevalence of MDR-TB among foreign-born TB patients in the past decade, the very high prevalence of MDR-TB among recent emigrants from the Philippines and Vietnam, and the trend towards younger, new active and non-respiratory MDR-TB cases have important implications for TB programming in Alberta and other major immigrant-receiving provinces of Canada (notably Quebec, Ontario and British Columbia). These implications relate to when a foreign-born TB case patient should be suspected of having MDR-TB and the need for a timely diagnosis of MDR-TB. If, prior to the availability of the drug susceptibility test results, a patient with MDR-TB is treated with a standard regimen of isoniazid, rifampin, pyrazinamide and ethambutol, their treatment cannot be expected to succeed. This is because the combination of pyrazinamide and ethambutol, assuming the isolate is susceptible to these drugs, is not a curative regimen. Moreover, our investigation demonstrates that resistance to pyrazinamide and/or ethambutol is not uncommon in MDR-TB isolates (43.5% and 55.6%, respectively, as per Table 4) and pyrazinamide is known to be ineffective at preventing resistance to companion drugs.^{1,24} Consequently, administration of the standard regimen to MDR-TB cases that are also resistant to either pyrazinamide or ethambutol is

Table 4. Characteristics of Foreign-born MDR-TB Cases in Alberta, 1982-2001 and 2002-2011

Case Characteristics	Time Period		p-values
	1982-2001 N=8 No. (%)	2002-2011 N=19 No. (%)	
Age (years)			0.265
<35	2 (25.0)	11 (57.9)	
35-64	5 (62.5)	7 (36.8)	
>64	1 (12.5)	1 (5.3)	
Sex			0.901
Male	4 (50.0)	9 (47.4)	
Female	4 (50.0)	10 (52.6)	
Disease type			0.102
New active	3 (37.5)	14 (73.7)	
Relapse/Retreatment	5 (62.5)	5 (26.3)	
Disease site			0.068
Respiratory	8* (100)	12 (63.2)	
Non-respiratory	0 (0.0)	7† (36.8)	
First-line drug resistance			0.451
Isoniazid	8 (100.0)	19 (100.0)	
Rifampin	8 (100.0)	19 (100.0)	
Pyrazinamide	2 (50.0)‡	8 (42.1)	
Ethambutol	3 (37.5)	12 (63.2)	
Streptomycin	4 (0.5)	8 (42.1)	

* One case was culture-positive from both pleural fluid and urine.

† Five cases were culture-positive from a cervical lymph node, one from an intra-thoracic lymph node and one from a vertebral body. The case of intra-thoracic lymph node TB is grouped here under "non-respiratory" as it had no co-existent respiratory disease and required an invasive procedure for diagnosis.

‡ Only 4 of the 8 MDR-TB cases were tested for susceptibility to pyrazinamide, with 2 (50.0%) of these cases having resistance.

essentially mono-therapy. If administered long enough, this treatment approach will produce resistance to the fourth drug ("amplified" resistance) given the selective advantage that a naturally occurring mutant, resistant to the fourth drug, has in the presence of mono-therapy.¹

Foreign-born persons contribute more than 82% of MDR-TB cases in low TB incidence high-income countries.^{6-8,25,26} Despite this commonality, the prevalence of MDR-TB cases among foreign-born individuals in these countries varies markedly due to differences in

Table 5. Estimated Costs of Targeted Genotypic Drug Susceptibility Testing Among Foreign-born TB Cases (Aged <65 Years at Diagnosis) That Arrived in Alberta in 2002-2011 and Were Diagnosed With TB During That Same Decade

Variables of Interest	Country of Birth		
	Philippines or Vietnam	Any High MDR-TB Burden Country	Any Country
TB cases	116	256	406
% of all TB cases	28.6	63.1	100.0
MDR-TB cases	8	13	15
% of all MDR-TB cases	53.3	86.7	100.0
NNT per MDR-TB case diagnosed	14.5	19.7	27.1
Laboratory cost per test*†	\$120 to \$144	\$120 to \$144	\$120 to \$144
Total laboratory costs in 2002-2011	\$13,920 to \$16,704	\$30,720 to \$36,684	\$48,720 to \$58,464
Laboratory costs per MDR case diagnosed	\$1740 to \$2088	\$2363 to \$2836	\$3248 to \$3898

Abbreviations: TB=tuberculosis; MDR-TB=multidrug-resistant TB; NNT=number needed to test.

* The estimated laboratory costs for the genotypic drug susceptibility tests include consumables (\$10 to \$30 per sample tested), miscellaneous laboratory supplies (\$10 per sample tested), laboratory personnel (\$80 per sample tested), overhead costs (\$20 to \$24 per sample tested). Costs for the initial purchase of equipment, personnel training, or specimen shipping costs were not included in the cost estimates. It was also assumed that CAD \$1 was equivalent to US \$1.

† CDC. Report of Expert Consultations on Rapid Molecular Testing to Detect Drug-resistant Tuberculosis in the United States. Available at: <http://www.cdc.gov/tb/topic/laboratory/rapidmoleculartesting/MolDSTreport.pdf> (Accessed October 3, 2012).

the countries from which the majority of new immigrants arrive (i.e., immigration patterns). For example, the prevalence of MDR-TB in this study (1.4% in 1992-2011) was similar to that of the United States (1.7% in 1993-2009).²⁷ However, foreign-born persons in Alberta had a markedly lower prevalence of MDR-TB than those in Italy (1.6% and 6.2% in 2008-2010, respectively).²⁵ This difference reasonably relates to Italy receiving a larger proportion of foreign-born persons from higher MDR-TB incidence countries, such as the Ukraine and Moldova, than Canada (data not shown).

The finding that MDR-TB cases in this study had unique DNA fingerprint patterns argues against the likelihood of local transmission that progressed to culture-positive disease. Importantly, local transmission also does not appear to be responsible for the four Canadian-born MDR-TB cases that occurred in the 30-year study period (data not shown). Two of these Canadian-born cases had unique DNA fingerprints on account of being infected with MDR strains while traveling abroad; the other two started with an initially susceptible isolate and became drug-resistant during treatment.^{6,7,28}

The challenge of suspecting and diagnosing MDR-TB in foreign-born TB patients is great given the increasing proportion of younger, new active MDR-TB cases in recent years. These trends, which presumably reflect the ongoing transmission of MDR isolates from MDR source cases to susceptible contacts in their country of origin,²⁹ dictate that being a new active case (as opposed to a relapse/retreatment case which is well known to carry a risk of drug resistance)¹ does not reliably exclude, or make less likely, the probability of MDR-TB. This contrasts with the usual predictors of MDR-TB, namely: failed treatment with a standard four-drug regimen; previous TB treatment, particularly if it was associated with program or patient non-adherence; treatment of isoniazid-resistant TB in the past; or exposure to a patient who is known to have infectious MDR-TB.¹ The shift toward non-respiratory disease further complicates matters as a diagnosis of MDR-TB cannot be made unless an appropriate specimen is submitted for culture. That is, the provision of an empiric treatment regimen in lieu of specimen collection through an invasive procedure increases the likelihood of a missed diagnosis of MDR-TB.

Genotypic drug susceptibility tests provide an unprecedented opportunity to diagnose MDR-TB prior to the commencement of treatment.³⁰ These tests, which have >98% sensitivity and specificity for rifampin,³¹ target the 81 bp region of the *rpoB* gene of *M. tuberculosis* known as the rifampin resistance determining region

where 95% of the rifampin-resistant conferring mutations are located. In Canada, the presence of such a mutation strongly suggests the presence of MDR-TB given that only 10% of foreign-born rifampin-resistant TB cases in 2006-2010 had isoniazid-susceptible disease (Custom Report; Canadian Tuberculosis Reporting System, Public Health Agency of Canada, Health Canada). Importantly, however, negative genotypic drug susceptibility test results should not supplant phenotypic drug susceptibility testing in the presence of a high clinical suspicion for MDR-TB.³²

The genotypic drug susceptibility tests that are currently available and recommended by the World Health Organization for the early detection of MDR-TB are i) line probe assays (two commercial kits are currently available: the INNO-LiPA Rif.TB test [Inno-genetics NV, Gent, Belgium] and the GenoType MTBDR_{plus} test [Hain Lifescience GmbH, Nehren, Germany])³³ and ii) the Xpert MTB/RIF test (GeneXpert [Cepheid, Sunnyvale, California, USA]).³⁴ The GenoTypeMTBDR_{plus} test and the Xpert MTB/RIF test are currently approved for use in Canada.³⁵

When attempting to identify the high-yield target population for genotypic drug susceptibility tests, both feasibility and cost-effectiveness analyses must at least take into account the performance characteristics of the tests³¹ as well as the patient's country of birth, year of arrival, age at diagnosis, and possibly disease type (new active versus relapse/retreatment). Even so, in practice, there are only three management options when faced with a possible MDR-TB case: i) delay treatment altogether until phenotypic drug susceptibility test results are available – not an acceptable option if the patient is very ill or highly infectious; ii) within reason, make certain that an empiric regimen is sufficiently surfeit to cover off the possibility of MDR-TB; or iii) use one of the genotypic drug susceptibility tests. Decisions about each of these options are best made by physicians experienced in the management of drug-resistant TB.¹

REFERENCES

- Long R, Ellis E (Eds.). *Canadian Tuberculosis Standards*, 6th Edition. Ottawa, ON: Public Health Agency of Canada and the Canadian Lung Association/Canadian Thoracic Society, 2007. Available at: <http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tbstand07-eng.php> (Accessed March 7, 2012).
- Langlois-Klassen D, Wooldrage K, Manfreda J, Sutherland K, Ellis E, Phypers M, et al. Piecing the puzzle together: Foreign-born tuberculosis in an immigrant-receiving country. *Eur Respir J* 2011;38:895-902.
- Tuberculosis in Canada 2010 Pre-release. Public Health Agency of Canada. Minister of Public Works and Government Services Canada, 2012. Available at: <http://www.publichealth.gc.ca/tuberculosis> (Accessed September 24, 2012).
- PHAC. Tuberculosis among the foreign-born in Canada. *Can Commun Dis Rep* 2003;29:10-16.

5. Public Health Agency of Canada. Tuberculosis in Canada, 2007. Ottawa: Minister of Public Works and Government Services Canada, 2009.
6. Hersi A, Elwood K, Cowie R, Kunimoto D, Long R. Multidrug-resistant tuberculosis in Alberta and British Columbia, 1989 to 1998. *Can Respir J* 1999;6:155-60.
7. Long R, Nibert E, Chomyc S, van Embden J, McNamee C, Duran RR, et al. Transcontinental spread of multidrug-resistant *Mycobacterium bovis*. *Am J Respir Crit Care Med* 1999;159:2014-17.
8. Avendano M, Goldstein RS. Multidrug-resistant tuberculosis: Long term follow-up of 40 non-HIV infected patients. *Can Respir J* 2000;7:383-89.
9. Langlois-Klassen D, Kunimoto D, Saunders D, Chui L, Boffa J, Menzies D, et al. A population-based cohort study of *Mycobacterium tuberculosis* Beijing strains: An emerging public health threat in an immigrant-receiving country? *PLoS ONE* 2012;7:e38431. doi: 10.1371/journal.pone.0038431.
10. Iseman M. Drug therapy: Treatment of multidrug-resistant tuberculosis. *N Engl J Med* 1993;329:784-91.
11. Long R, Chui L, Kakulphimp J, Zielinski M, Talbot J, Kunimoto D. Post-sanatorium pattern of anti-tuberculosis drug resistance in the Canadian-born population of western Canada: Effects of outpatient care and immigration. *Am J Epidemiol* 2001;153:903-11.
12. Gandhi NR, Nunn P, Dheda K, Scharf HS, Zignol M, van Soolingen D, et al. Multidrug-resistant and extensively drug-resistant tuberculosis: A threat to global control of tuberculosis. *Lancet* 2010;375:1830-43.
13. Iseman MD, Sbarbaro JA. The increasing prevalence of resistance to anti-tuberculosis chemotherapeutic agents: Implications for global tuberculosis control. *Curr Clin Top Infect Dis* 1992;12:188-207.
14. Lew W, Pai M, Oxlade O, Martin D, Menzies D. Initial drug resistance and treatment outcomes: Systematic review and meta-analysis. *Ann Intern Med* 2008;149:123-34.
15. Multidrug and Extensively Drug Resistant TB (M/XDR-TB): 2010 Global Report on Surveillance and Response. Geneva, Switzerland: World Health Organization, 2010. Available at: http://whqlibdoc.who.int/publications/2010/9789241599191_eng.pdf (Accessed March 25, 2012).
16. Varelzdis BP, Grosset J, de Kantor I, Crofton J, Laszlo A, Felton M, et al. Drug-resistant tuberculosis: Laboratory issues: World Health Organization recommendations. *Tubercle Lung Dis* 1994;75:1-7.
17. van Emden JDA, Cave MD, Crawford JT, Dale JW, Eisenach KD, Gicquel B, et al. Strain identification of *Mycobacterium tuberculosis* by DNA fingerprinting: Recommendations for a standardized methodology. *J Clin Microbiol* 1993;31:406-9.
18. van Soolingen D. Molecular epidemiology of tuberculosis and other mycobacterial infections: Main methodologies and achievements. *J Intern Med* 2001;249:1-26.
19. Kunimoto D, Sutherland K, Wooldrage K, Fanning A, Chui L, Manfreda J, et al. Transmission characteristics of tuberculosis in the foreign-born and the Canadian-born population of Alberta, Canada. *Int J Tuberc Lung Dis* 2004;8:1213-20.
20. CDC. Report of expert consultations on rapid molecular testing to detect drug-resistant tuberculosis in the United States. Available at: <http://www.cdc.gov/tb/topic/laboratory/rapidmoleculartesting/MoldST-report.pdf> (Accessed October 3, 2012).
21. Sensi P. History of the development of rifampin. *Rev Infect Dis* 1983;5:S402-S406.
22. Gagneux S, DeRiemer K, Van T, Kato-Maeda M, de Jong BC, Narayanan S, et al. Variable host-pathogen compatibility in *Mycobacterium tuberculosis*. *Proc Natl Acad Sci U S A* 2006;103:2869-73.
23. Hirsh AE, Tzolaki AG, DeRiemer K, Feldman MW, Small PM. Stable association between strains of *Mycobacterium tuberculosis* and their human host populations. *Proc Natl Acad Sci U S A* 2004;101:4871-76.
24. Mitchison DA. The action of antituberculosis drugs in short course chemotherapy. *Tubercle* 1985;66:219-25.
25. Fattorini L, Mustazzolu A, Piccaro G, Pardini M, Filippini P, Giannoni F, et al. Drug-resistant tuberculosis among foreign-born persons in Italy. *Eur Respir J* 2012;40:4979-500.
26. Centers for Disease Control and Prevention (CDC). Trends in tuberculosis - United States, 2011. *JAMA* 2012;307:1791-93.
27. Taylor AB, Kurbatova EV, Cegielski JP. Prevalence of anti-tuberculosis drug resistance in foreign-born tuberculosis cases in the U.S. and in their countries of origin. *PLoS ONE* 2012;7:e49355.
28. Manns BJ, Fanning EA, Cowie RL. Antituberculosis drug resistance in immigrants to Alberta, Canada, with tuberculosis, 1982-1994. *Int J Tuberc Lung Dis* 1997;1:225-30.
29. Chaisson RE, Nuermberger EL. Confronting multidrug-resistant tuberculosis. *N Engl J Med* 2012;366:2223-24.
30. Falzon D, Jaramillo E, Schünemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J* 2011;38(3):516-28.
31. Ling DI, Zwerling AA, Pai M. Genotype MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: A meta-analysis. *Eur Respir J* 2008;32:1165-74.
32. Kalokhe AS, Shafiq M, Lee JC, Metchock B, Posey JE, Ray SM, et al. Discordance in *Mycobacterium tuberculosis* rifampin susceptibility. *Emerg Infect Dis* 2012;18:537-39.
33. O'Grady J, Maeurer M, Mwaba P, Kapata N, Bates M, Hoelscher M, et al. New and improved diagnostics for detection of drug-resistant pulmonary tuberculosis. *Curr Opin Pulmonary Medicine* 2011;17:134-41.
34. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010;363(11):1005-15.
35. Health Canada. Medical Device Active License Listing (MDALL). Available at: <http://www.hc-sc.gc.ca/dhp-mps/md-im/licen/mdlic-eng.php> (Accessed October 12, 2012).

Received: March 28, 2012

Accepted: December 8, 2012

RÉSUMÉ

OBJECTIFS : La prévalence de la résistance aux médicaments antituberculeux augmente à l'échelle mondiale. Nous avons voulu cerner les tendances de la tuberculose multirésistante (TMR) chez les personnes nées à l'étranger vivant en Alberta, une province du Canada qui accueille un grand nombre d'immigrants.

MÉTHODE : Au moyen d'une étude de cohorte rétrospective, nous avons analysé la prévalence de la TMR entre 1982 et 2011 parmi les cas nés à l'étranger avec culture positive pour la tuberculose. Les données pertinentes (démographiques, cliniques et de laboratoire) ont été analysées à partir du Registre de la tuberculose, des dossiers médicaux des sujets et du laboratoire de santé publique provincial.

RÉSULTATS : Sur les 2 234 cas nés à l'étranger avec culture positive pour la tuberculose relevés en Alberta entre 1982 et 2011, 27 (1,2 %) avaient une TMR. Dans l'ensemble, la multirésistance aux médicaments était associée à l'âge de <65 ans ($p=0,025$), à la rechute ou au retraitement de la tuberculose, et au diagnostic et à l'arrivée au pays au cours de la dernière décennie (2002-2011). La prévalence de la TMR en 2002-2011 était de 2,1 %, en hausse significative par rapport à 0,65 % en 1982-1991 ($p=0,022$) et à 0,56 % en 1992-2001 ($p=0,009$). Seuls les immigrants des Philippines et du Vietnam ont affiché une augmentation significative de la prévalence de la TMR entre les deux premières décennies et la dernière. Comparativement aux cas de TMR déclarés dans les deux premières décennies, ceux déclarés au cours de la dernière décennie avaient plus souvent moins de 35 ans, étaient des nouveaux cas actifs plutôt que des cas de rechute ou de retraitement et présentaient un diagnostic de tuberculose non respiratoire plutôt que de tuberculose respiratoire. Les empreintes génétiques des souches de TMR relevées entre 1992 et 2011 étaient uniques.

CONCLUSION : Les tendances récentes de la prévalence et des caractéristiques cliniques des cas de TMR nés à l'étranger ont d'importantes conséquences pour la prise en charge de la tuberculose au Canada. Il est suggéré de faire le diagnostic précoce de la TMR, à l'aide de tests génotypiques de sensibilité médicamenteuse, chez les cas nés à l'étranger qui courent un risque accru de présenter une tuberculose multirésistante.

MOTS CLÉS : tuberculose multirésistante; immigrants