Risk factors for drug-resistant tuberculosis at a referral centre in Toronto, Ontario, Canada: 2010–2016

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Abstract

Background: Drug-resistant tuberculosis (TB) poses a major public health concern worldwide. However, no studies have addressed risk factors for drug resistance in Ontario, which has its own unique profile of immigrants. We evaluated demographic and clinical risk factors for drug-resistant TB among patients treated at West Park Healthcare Centre, located in Toronto, Ontario (Canada).

Methods: All patients who were diagnosed with TB and treated at West Park Healthcare Centre between January 2010 and December 2016 were included in this retrospective cohort study. Characteristics of patients with isoniazid mono-resistant (INH-R) TB and multidrug resistant (MDR) TB were compared to patients with drug-susceptible TB with bivariate and multivariable logistic regression.

Results: Risk factors for INH-R TB included younger age (younger than 35 years), prior TB treatment, non-diabetic and birth in a non-South-East Asian country, but only the latter two factors were significant in multivariable analysis. On the other hand, we found younger generation (younger than 65 years), birth in European region, recent arrival to Canada (fewer than 120 months), prior treatment and human immunodeficiency virus (HIV) infection were associated with MDR-TB, among which younger age (younger than 35 years), more recent immigration (fewer than 24 months), prior treatment and HIV infection were significant in multivariable analysis.

Conclusion: These findings may be of use to TB clinicians in the province by informing the initial empiric antibiotic regimen prescribed while awaiting phenotypic drug susceptibility testing and assisting in decisions regarding whether to request rapid molecular drug susceptibility testing.

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Introduction

Drug-resistant tuberculosis (TB) poses a major public health concern worldwide. The two most common, clinically important forms of drug-resistant TB include isoniazid (INH) mono-resistant (INH-R) (resistant to INH) and multidrug-resistant (MDR) TB (resistant to at least INH and rifampin, RMP) (1,2). Drug resistance is identified either by genotypic methods or phenotypic culture-based drug susceptibility testing (DST), the latter being considered the gold standard (3). Identification of drug resistance is critical to guide appropriate selection of anti-mycobacterial drugs and to prevent further drug resistance. However, phenotypic DST can take weeks to report, and not all clinical settings perform rapid molecular DST routinely. Therefore, clinicians often start empiric TB treatment prior to the availability of phenotypic DST results, and may expand the initial empiric regimen, or may request rapid molecular DST, based upon an individual patient's risk factors for drug resistance.

Few studies have described risk factors for drug resistance in Canada. In British Columbia, age, foreign-born status, ethnicity, prior treatment, diagnosis outside of Canada and certain

birth country regions were associated with drug resistance from 1990–2001 (4). In Alberta from 1982–2011, age (younger than 65 years), prior treatment, arrival to Canada from 2002–2011, and recent emigration from Philippines and Vietnam were risk factors for MDR-TB in foreign-born persons (5). A national surveillance study found that age, foreign-born status, prior treatment, and certain World Health Organization epidemiological regions-of-birth were associated with drug resistance on a national level from 1997 to 2008 (1). However, no studies have addressed risk factors for drug resistance in Ontario, which has its own unique profile of immigrants (6) and has the highest burden of drug-resistant TB cases in Canada (7,8). There is also a need for more contemporary data, because risk factors may differ as immigration patterns change and as rates of drug-resistant TB, including primary MDR-TB, change world-wide.

The principal objective of this study was to evaluate possible demographic and clinical risk factors for drug-resistant TB among patients treated at West Park Healthcare Centre (WPHC) and to compare risk factors for INH-R TB against risk factors for MDR-TB. Additionally, the enrolled TB patients were reviewed according to the recent American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention (ATS/IDSA/CDC) statement (3), recommending rapid molecular testing for RMP +/- INH resistance be performed in the following patient sub-groups: 1) previous treatment; 2) born or lived for one or more years in a country with TB incidence of greater or equal to 20/100,000 or primary MDR prevalence of greater or equal to 2%; 3) contact with MDR; and 4) human immunodeficiency virus (HIV) infection.

Methods

The TB program at WPHC, located in Toronto, Ontario, is recognized as a referral centre for drug-resistant TB, and sees the majority of MDR-TB cases in the province (84% between 2000 and 2011) (9). All patients who were diagnosed with TB and treated at WPHC between January 2010 and December 2016 were included in this retrospective cohort study. Chart review was used to identify patients for inclusion and to extract demographic and clinical characteristics. The study protocol was approved by the Joint Bridgepoint/West Park Healthcare Research Ethics Board. In light of the retrospective design, the requirement of informed consent was waived.

Throughout the study period, all drug susceptibility testing was consistently performed at the Public Health Ontario TB and Mycobacteria Laboratory (Toronto, Ontario). The DST was performed according to Clinical Laboratory Standards Institute testing standards recommended methods (as available), using radiometric broth [BACTEC 460; Becton, Dickinson and Co., Franklin Lakes, New Jersey, United States (US)] until October 1, 2010, and nonradiometric broth (MGIT 960; Becton, Dickinson and Co.) thereafter (10,11). The first culture of *Mycobacterium tuberculosis* complex isolated from a patient was routinely tested for susceptibility to the four first-line drugs: INH; RMP; ethambutol; and pyrazinamide. Isolates resistant to INH at 0.1 mg/L were considered "resistant" herein, but were also tested at 0.4 mg/L and underwent moxifloxacin testing. Any isolate found resistant to RMP or any two of the first line drugs underwent DST to second line drugs. Second line susceptibility testing for the following drugs was performed during the study time period: rifabutin; amikacin; streptomycin; kanamycin; capreomycin; ofloxacin; ethionamide; and *p*-aminosalicylic acid. The DST for clofazimine was performed until October 1, 2010 and DST for moxifloxacin and linezolid started on October 1, 2010.

Characteristics of patients with INH-R TB and MDR-TB were compared with those patients with drug-susceptible (DS) TB (i.e. susceptible to the four first line drugs) using bivariate and multivariable logistic regression models. Statistical analyses were performed using GraphPad Prism 6.0 (GraphPad Software; La Jolla, California, US), StatPlus:macLE (AnalystSoft; Walnut, California, US) and Jamovi (Version 0.9, retrieved from https://www.jamovi.org). In bivariate analyses, many demographic characteristics (age, sex, birth country region and time from arrival in Canada) and clinical characteristics (known TB risk factors, location of TB and microbiologic results) were analysed for their possible association with drug-resistant TB, to be thorough and exploratory. Variables with a *p*-value less than 0.05 in bivariate analysis, and variables considered *a priori* to be clinically important (age, sex, birth country region, time from arrival in Canada and history of TB treatment) were selected for inclusion in the multivariable models. The multivariable models were restricted to foreign-born patients so that the association between time in Canada and drug resistance would be accurately studied. Patients were also divided into slightly different groups by DST (drug susceptible, non-MDR drug resistance and MDR/RMP resistance) to evaluate the recent recommendations for rapid molecular DST for rifampin put forth by the ATS/IDSA/CDC (3).

Results

Between 2010 and 2016, 485 patients with active TB were seen at WPHC, representing 11.1% of the total of 4,384 seen in Ontario (12). Among these WPHC patients, DST results were available in 82.9% (n=402/485) (**Table 1**). The other 83 patients (17.1%) did not have a phenotypic DST performed in Ontario (due to lack of culture confirmation or to a diagnosis made outside of Ontario), and were excluded from further risk factor analyses. The TB strains susceptible to the four first-line drugs accounted for 76.1% (n=306/402), strains INH-R accounted for 10.9% (n=44/402) and strains resistant to both INH and RMP +/- other drugs (MDR) accounted for 11.4% (n=46/402). Only four patients had mono-resistance to drugs other than INH (one to RMP and three to pyrazinamide), and two had poly-resistance to the first line drugs (but not MDR); six patients were excluded

from risk factor analyses. Extensively drug resistant TB (MDR with additional resistance to a fluoroquinolone and a second line injectable) was also rare at 1.0% (n=4/402).

Table 1: Phenotypic drug susceptibility test results among patients enrolled in the study

Drug susceptibility	n/N	%
Drug susceptibility test for first-line drug (n=402 with DST available)		
Sensitive to first-line four drugs	306/402	76.1
Mono-resistance to INH	44/402	10.9
Mono-resistance to RMP	1/402	0.2
Mono-resistance to EMB	0/402	0.0
Mono-resistance to PZA	3/402	0.7
Poly-resistance to first-line drugs	2/402	0.5
Multidrug resistance (INH and RMP)	46/402	11.4
Extensively drug-resistance	4/402	1.0
Any resistance to INH	92/402	22.9
Any resistance to RMP	47/402	11.7
Any resistance to EMB	21/402	5.2
Any resistance to PZA	24/402	6.0
Drug susceptibility test for second-line drug (n=46 with MDR-TB)		
Any resistance to EMB	20/46	43.5
Any resistance to PZA	20/46	43.5
Any resistance to RFB	41/46	89.1
Any resistance to AMK	3/45	6.7
Any resistance to SM	29/46	63.0
Any resistance to KM	6/41	14.6
Any resistance to CM	6/46	13.0
Any resistance to MXF	5/41	12.2
Any resistance to OFX	8/46	17.4
Any resistance to ETA	13/46	28.3
Any resistance to PAS	5/46	10.9
Any resistance to LZD	0/41	0.0
Any resistance to CLO	0/5	0.0

Abbreviations: AMK, amikacin; CLO, clofazimine; CM, capreomycin; DST, drug susceptibility test; EMB, ethambutol; ETA, ethionamide; INH, isoniazid; KM, kanamycin; LZD, linezolid; MDR, multidrug-resistant; MXF, moxifloxacin; OFX, ofloxacin; PAS, *p*-aminosalicylic acid; PZA, pyrazinamide; RFB, rifabutin; RMP, rifampin; SM streptomycin; TB, tuberculosis

The TB patients were divided into three groups based on DST: DS-TB (n=306); INH-R (n=44); and MDR (n=46) and their demographic characteristics are shown in **Table 2** and clinical characteristics in **Table 3**. Compared with patients with DS-TB (Table 2), in unadjusted analyses, patients with INH-R TB were significantly younger; odds ratio (OR) for age younger than 35 years=2.58, 95% CI 1.06–6.30, with reference age older than 65 years, and less likely to have been born in South-East Asia (OR 0.157, 95% CI 0.03–0.91). Patients with INH-R TB (Table 3) were also more likely to have been previously treated (OR 2.39, 95% CI 1.01–5.68), and less likely to have diabetes (OR 0.26, 95% CI 0.08–0.87) in unadjusted analyses. Compared with DS-TB patients, in unadjusted analyses, patients with MDR-TB (Table 2) were also significantly younger (younger than 35 years, OR 15.2, 95% CI 3.49–66.1) and more likely to have been born in Europe (OR 15.6, 95% CI 1.66–146.4) and had a significantly shorter time from arrival to Canada to TB diagnosis. These patients (Table 3) were more likely to have been previously treated (OR 5.74, 95% CI 2.77–11.9), more likely to have HIV infection (OR 4.76, 95% CI 1.29–17.5) and more likely to have only pulmonary TB and less likely to have pulmonary and extrapulmonary TB.

In multivariable analysis restricted to foreign born patients (**Table 4**), patients with INH-R TB were less likely to be from South-East Asia than DS-TB patients (OR 0.10, 95% CI 0.01–0.73), and less likely to have diabetes (OR 0.18, 95% CI 0.04–0.81). Risk factors for MDR-TB in multivariable analysis restricted to foreign born patients included age younger than 35 years old (OR 8.11, 95% CI 1.43–45.7), TB diagnosis less than 24 months after arrival in Canada (OR 4.11, 95% CI 1.21–13.9), history of TB treatment (OR 3.78, 95% CI 1.58–9.05) and HIV infection (OR 10.95, 95% CI 1.90–62.9).

In our evaluation of the 2017 ATS/IDSA/CDC recommendations for rapid molecular DST for rifampin, we found that patients with MDR/RMP resistance were significantly more likely to have had previous TB treatment (OR 5.39, 95% CI 2.57–11.3) and HIV infection (OR 4.26, 95% CI 1.06–17.0) than DS-TB patients in multivariable analysis (**Table 5**).

Table 2: Demographic characteristics of all TB patients enrolled into the study

Demographic characteristic	All TB patients		DS-TB		INH-R TB		INH-R TB vs DS-TB			MDR-TB		MDR-TB vs DS-TB		
	(n=485)	%	(n=306)	%	(n=44)	%	OR	(95% CI)	*p*-value	(n=46)	%	OR	(95% CI)	*p*-value
Age, years														
Younger than 35 years	146	30.1	79	25.8	17	38.6	2.58	(1.06–6.30)	0.037	25	54.3	15.1	(3.49–66.11)	0.01
35–65 years	212	43.7	131	42.8	19	43.2	1.74	(0.73–4.14)	0.210	19	41.3	6.96	(1.58–30.6)	<0.001
Older than 65 years	127	26.2	96	31.4	8	18.2	1.0	reference[a]	N/A	2	4.3	1.0	reference[a]	N/A
Gender														
Sex, female	215	44.3	120	39.2	24	54.5	1.86	(0.99–3.51)	0.056	24	52.2	1.69	(0.91–3.15)	0.098
Country of birth														
Foreign-born	450	92.8	280	91.5	40	90.9	0.93	(0.31–2.80)	0.895	45	97.8	4.18	(0.56–31.53)	0.166
Canadian-born	35	7.2	26	8.5	4	9.1	1.0	reference[a]	N/A	1	2.2	1.0	reference[a]	N/A
Birth country WHO region														
African Region	43	8.9	27	8.8	3	6.8	0.72	(0.15–3.54)	0.688	2	4.3	1.92	(0.16–22.5)	0.602
Region of the Americas[b]	27	5.6	18	5.9	3	6.8	1.08	(0.22–5.44)	0.923	0	0.0	N/A	reference[a]	N/A
Eastern Mediterranean Region	49	10.1	29	9.5	5	11.4	1.12	(0.27–4.62)	0.875	2	4.3	1.79	(0.15–20.9)	0.641
European Region	21	4.3	10	3.3	0	0.0	1.0	reference[a]	N/A	6	13.0	15.6	(1.66–146.4)	0.016
South-East Asia Region	124	25.6	83	27.1	2	4.5	0.157	(0.03–0.91)	0.038	14	30.4	4.38	(0.55–34.9)	0.163
Western Pacific Region	186	38.4	113	36.9	27	61.4	1.55	(0.50–4.82)	0.446	21	45.7	4.83	(0.62–37.5)	0.132
Canada	35	7.2	26	8.5	4	9.1	1.0	reference[a]	N/A	1	2.2	1.0	reference[a]	N/A
Months from arrival to TB diagnosis[c]														
Less than 24 months	93	19.2	45	14.7	6	13.6	1.13	(0.42–3.01)	0.813	18	39.1	7.60	(3.09–18.6)	<0.001
24–120 months	141	29.0	80	26.1	16	36.4	1.69	(0.82–3.50)	0.157	19	41.3	4.51	(1.89–10.7)	<0.001
More than 120 months	213	43.9	152	49.7	18	40.9	1.0	reference[a]	N/A	8	17.4	1.0	reference[a]	N/A

Abbreviation: DS, drug susceptible; INH-R, isoniazid mono-resistant; MDR, multidrug resistant; N/A, not applicable; TB, tuberculosis; WHO, World Health Organization
[a] Reference means the control group which all other groups are compared to
[b] Excluded Canada
[c] Foreign-born only, three patients missing the date of arrival

Table 3: Clinical characteristics of all TB patients enrolled into the study

Clinical characteristics	All TB patients		DS-TB		INH-R TB		INH-R TB vs DS-TB			MDR-TB		MDR-TB vs DS-TB		
	(n=485)	%	(n=306)	%	(n=44)	%	OR	(95% CI)	*p*-value	(n=46)	%	OR	(95% CI)	*p*-value
TB risk factor														
History of TB treatment	70	14.4	26	8.5	8	18.2	2.39	(1.01–5.68)	0.048	16	34.8	5.74	(2.77–11.89)	<0.001
History of TB contact	102	21.0	64	20.9	7	15.9	0.72	(0.31–1.6)	0.442	9	19.6	0.92	(0.42–2.00)	0.833
History of known/ suspected DR-TB contact	4	0.8	1	0.3	1	2.3	7.09	(0.44–115.5)	0.169	1	2.2	6.77	(0.41–111.2)	0.179
Travel to high-incidence region	165	34.0	105	34.3	13	29.5	0.80	(0.40–1.60)	0.532	14	30.4	0.84	(0.42–1.63)	0.604
Resided in refugee camp	26	5.4	19	6.2	0	0.0	N/A	N/A	N/A	2	4.3	0.65	(0.14–2.87)	0.57
Homeless/ incarcerated	44	9.1	33	10.8	3	6.8	0.61	(0.18–2.96)	0.422	2	4.3	0.37	(0.08–1.62)	0.19
Illicit drug use	31	6.4	22	7.2	6	13.6	2.04	(0.78–5.35)	0.148	1	2.2	0.28	(0.03–2.18)	0.287
Regular alcohol consumption	172	35.5	117	38.2	13	29.5	0.68	(0.34–1.35)	0.267	17	37.0	0.95	(0.49–1.79)	0.868
Smoking (current/ previous)	145	29.9	98	32.0	15	34.1	1.10	(0.56–2.14)	0.784	16	34.8	1.13	(0.58–2.17)	0.71
Active malignancy	21	4.3	12	3.9	1	2.3	0.57	(0.07–4.50)	0.593	3	6.5	1.71	(0.46–6.30)	0.421
Immunosuppressive therapy	14	2.9	9	2.9	1	2.3	0.77	(0.95–6.21)	0.804	2	4.3	1.50	(0.031–7.17)	0.611
Diabetes	85	17.5	67	21.9	3	6.8	0.26	(0.08–0.87)	0.029	8	17.4	0.75	(0.33–1.68)	0.488
HIV infection	10	2.1	6	2.0	0	0.0	N/A	N/A	N/A	3	6.5	4.76	(1.29–17.5)	0.019
Distribution of TB														
Only pulmonary TB	280	57.7	176	57.5	28	63.6	1.29	(0.67–2.49)	0.442	34	73.9	2.09	(1.04–4.19)	0.038
Pulmonary + extrapulmonary TB	103	21.2	75	24.5	11	25.0	1.02	(0.49–2.13)	0.944	5	10.9	0.37	(0.14–0.98)	0.047
Only extrapulmonary TB	102	21.0	55	18.0	5	11.4	0.59	(0.22–1.55)	0.282	7	15.2	0.82	(0.34–1.92)	0.648
Cavity on chest radiograph	98	20.2	72	23.5	9	20.5	0.84	(0.38–1.82)	0.651	9	19.6	0.79	(0.36–1.71)	0.552
AFB test														
AFB positive smear in sputum	191	39.4	155	50.7	25	56.8	1.60	(0.80–3.20)	0.179	17	37.0	0.57	(0.29–1.08)	0.089

Abbreviations: AFB, acid-fast bacilli; DR, drug-resistant; DST, drug susceptibility test; INH, isoniazid; N/A: not applicable; MDR, multdrug resistant; WHO, World Health Organization

Table 4: Risk factors associated with isoniazid mono-resistant tuberculosis and multidrug resistant tuberculosis at West Park Healthcare Centre in foreign born patients

Risk factors	INH-R vs DS-TB			MDR vs DS-TB		
	OR	(95% CI)	p-value	OR	(95% CI)	*p*-value
Age, years						
Younger than 35 years	1.69	(0.54–5.26)	0.365	8.11	(1.43–45.7)	0.018
35–65 years	1.16	(0.44–3.06)	0.76	4.84	(0.94–24.7)	0.058
Older than 65 years	1.0	reference[a]	N/A	1.0	reference[a]	N/A
Gender						
Sex, female	1.36	(0.65–2.88)	0.408	1.57	(0.71–3.47)	0.265
Birth country WHO region						
African Region	0.46	(0.08–2.64)	0.384	0.45	(0.05–3.86)	0.468
Region of the Americas	1.0	reference[a]	N/A	N/A	N/A	N/A
Eastern Mediterranean Region[b]	0.90	(0.17–4.81)	0.909	1.0	reference[a]	N/A
European Region	N/A	N/A	N/A	4.29	(0.54–33.7)	0.166
South-East Asia Region	0.10	(0.01–0.73)	0.023	1.31	(0.25–6.95)	0.744
Western Pacific Region	1.50	(0.38–5.83)	0.558	1.97	(0.38–10.2)	0.415
Median month from arrival to TB diagnosis[c]						
Less than 24 months	1.10	(0.34–3.52)	0.861	4.11	(1.21–13.9)	0.023
24–120 months	1.26	(0.53–3.00)	0.588	2.48	(0.83–7.35)	0.101
More than 120 months	1.0	reference[a]	N/A	1.0	reference[a]	N/A
TB risk factor						
History of TB treatment	2.21	(0.73–6.15)	0.163	3.78	(1.58–9.05)	0.003
Diabetes	0.18	(0.04–0.81)	0.026	N/A	N/A	N/A
HIV infection	N/A	N/A	N/A	10.95	(1.90–62.9)	0.007
Distribution of TB						
Only pulmonary TB	N/A	N/A	N/A	2.76	(0.92–8.19)	0.067
Pulmonary and extrapulmonary TB	N/A	N/A	N/A	0.70	(0.17–2.77)	0.617

Abbreviations: DS, drug susceptible; HIV, human immunodeficiency virus; INH-R, isoniazid mono-resistance; MDR, multidrug resistant; N/A, not applicable; TB, tuberculosis; WHO, World Health Organization

[a] Reference means the control group which all other groups are compared to

[b] The reference group for this analysis was patients from the Eastern Mediterranean Region because no patients with MDR-TB were from the Region of the Americas

[c] Three patients missing the date of arrival

Table 5: Criteria recommended by 2017 ATS Guidelines for rapid molecular drug susceptibility testing for rifampin[a]

Criteria	All TB patients[b]		DS-TB		Non-MDR/ RMP drug resistance		MDR/RMP-R TB		MDR/RMP-R TB vs DS-TB			MDR/RMP-R TB vs non-MDR/RMP drug resistance		
	(n=485)	%	(n=306)	%	(n=49)	%	(n=47)	%	OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Previous TB treatment	70	14.4	26	8.5	9	18.4	16	34.0	5.39	(2.57–11.3)	<0.001	2.21	(0.83–5.90)	0.112
Born or lived less than one year in higher risk country	428	88.2	264	86.3	43	87.8	45	95.7	2.72	(0.62–11.2)	0.184	3.02	(0.56–16.2)	0.197
Contact of MDR-TB	4	0.8	1	0.3	2	4.1	1	2.1	9.04	(0.54–148.7)	0.123	0.46	(0.03–5.60)	0.548
HIV infection	10	2.1	6	2.0	0	0.0	4	8.5	4.26	(1.06–17.0)	0.04	N/A	N/A	N/A

Abbreviations: ATS, American Thoracic Society; DS, drug-susceptible; HIV, human immunodeficiency virus; MDR, multidrug resistant; N/A, not applicable; R, resistance, RMP, rifampin; TB, tuberculosis
[a] Rapid molecular drug susceptibility testing for rifampin by drug resistance pattern (A) and multivariable analyses comparing MDR/RMP-R TB with drug susceptible TB (B) and non-MDR/RMP drug resistant TB (C)
[b] TB incidence of ≥20/100,000 or primary MDR prevalence of ≥2%

Discussion

We identified several risk factors for drug resistance among TB patients seen at our institution in Toronto, Ontario. Regarding INH-R TB, we found that young age (younger than 35 years), prior TB treatment, lack of diabetes and birth in a non-South-East Asian country were risk factors in bivariate (unadjusted) analysis, but only the latter two were significant in multivariable analysis. Prior TB treatment has been previously reported as a risk factor for INH-R TB, even after adjustment for possible confounders (13). Somewhat surprisingly, we found a significant association between diabetes and INH-R TB in both bivariate and multivariable analysis, with the former appearing "protective" against the latter. Most previous studies have not included diabetes in their assessment of risk factors for drug resistance; and a study from British Columbia did not find an association between the two variables (4). Additionally, some reports, including a recent meta-analysis, have described a positive association between diabetes and MDR-TB (14). Given that no prior studies reported a negative association between INH-R TB and diabetes, and the lack of a plausible biologic explanation for this finding, we suspect that this association might be spurious. While we did control for age in our multivariable model, there could be residual confounding by age, as INH-R TB was more common in younger patients, who generally have a lower prevalence of diabetes. This association could also have been found by chance, and may be related to multiple testing; future study on this association is needed. Interestingly, in our population, foreign birth (OR 0.93 95% CI 0.31–2.80) was not associated with INH-R TB. Although other North American studies have found foreign birth to be a risk factor for INH-R or mono-resistant TB (1,4,13), only one of these studies adjusted for potential confounders and no association was found (13).

We found several risk factors for MDR-TB in our population that have been described previously in North America, including younger generation, prior treatment (5), more recent arrival to Canada (1) and HIV infection. HIV infection is controversial; a meta-analysis found that most North American studies reported an association. There was no significant association for MDR-TB overall when studies from all world regions were included; yet there was an association with primary MDR-TB (15). In the bivariate analysis, we also found that patients with only pulmonary TB were more likely to have MDR-TB, but patients with pulmonary and extra-pulmonary were less likely. It is possible that the distribution of TB was confounded by the time when they were diagnosed, as patients with MDR-TB were more likely to have recently arrived to Canada and, therefore, may have had less advanced disease. In fact, the overall fraction of pulmonary involvement (pulmonary plus pulmonary and extra-pulmonary) was similar among DST categories (DS 82.0% (n=251/306), INH-R 88.6% (n=39/44) and MDR 84.8% (n=39/46)).

Regarding regions of birth, there was no significant association in multivariable analysis, but birth in Europe (OR 15.6, 95% CI 1.66–146.4) was a risk factor for MDR-TB in bivariate analysis, and the lack of significance in multivariable analysis in our study could have been due to the small numbers of cases analysed.

Given the growing number of immigrants in Canada (5.5 million in 2000 to 7.9 million in 2017) (16,17) and the worldwide epidemic of DR-TB, the prevalence of DR-TB in Canada has the potential to increase (8). One of the many challenges posed by DR-TB in low burden countries is the delay between TB diagnosis and culture-based DST, which can prolong the time to appropriate treatment initiation, increase morbidity and prolong infectiousness. However, in such regions, universal rapid molecular testing may not be cost-effective, and may lead to high numbers of false positives (18). Therefore, targeted testing, based on risk factors, is often used. The most recent ATS/IDSA/CDC guidelines for TB diagnosis (3) suggest that rapid molecular testing for RMP +/- INH resistance be performed in the following

patient sub-groups: 1) previously treated; 2) born or lived for at least one year in a country with TB incidence of greater or equal to 20/100,000 or primary MDR prevalence of at least 2%; 3) contact with MDR; and 4) HIV infection. Our results support the application of these guidelines in Ontario regarding patient sub-groups (patient subgroups 1 and 4).

While we did not find a significant association between RMP-resistance and a history of contact with MDR-TB (patient sub-group 3), the OR was high and our numbers were small, and it seems logical that these patients may be at risk and should be tested. However, our data raises questions about the potential benefits and costs of "targeted" testing for patients in sub-group 2 in a geographical region such as ours (Toronto, Ontario) where the majority of TB patients are immigrants. Perhaps in Ontario and similar regions, this criterion could be modified such that only patients from a higher risk country, who are also of younger age and/or have recently immigrated, would be tested. Targeted testing for patients from very high-risk countries (i.e. European Region) may also be considered.

Strengths and limitations

Given WPHC's status as a referral center for complicated and drug-resistant TB cases in Ontario, it is not surprising that our proportions of drug-resistant cases (10.9% INH-R and 11.4% MDR) were higher than provincial (8.5%/1.4%) (7) and national (6.2%/1.2%) (18) rates in 2016. Our higher than average population of drug-resistant cases presented an opportunity to study patient characteristics in detail; however, the number of drug resistant cases in our study was still relatively low. Furthermore, we may not have had the power to detect a significant association between some true risk factors and drug resistant TB. Additionally, there could be selection bias in our study population, since DS-TB cases with less severe TB disease or with fewer comorbidities might have been less likely to be referred to our specialized center. Another potential limitation to our study is that it is representative of patients in the Toronto region (which sees the majority of TB in the province; 76% in 2016) (19), and may not represent the characteristics of patients from other Ontario cities, who may be less likely to be referred to our institution. Additionally, we did not have detailed information regarding all countries where an individual resided in before coming to Canada. Finally, we tested many patient characteristics for their association with drug resistant TB, and we may have found associations that were spurious due to multiple testing.

Conclusion

We summarize risk factors for INH-R and MDR-TB among patients seen at our institution in Toronto, Ontario. These findings may be of use to TB clinicians throughout the province by informing the initial empiric antibiotic regimen they prescribe while awaiting phenotypic DST, and by assisting them in their decision regarding whether to request rapid molecular DST. These findings may also guide policy makers and laboratory personnel regarding targeted application of molecular DST in the province.

Authors' statement

TH — Data collection, statistical analysis, writing original draft, review and editing
NS, PD, JM and HS — Data collection
TM and SB — Data collection, statistical analysis, writing original draft, review and editing

Conflict of interest

None.

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