cmajOPEN

Research

Prevalence of tuberculosis infection and disease in children referred for tuberculosis medical surveillance in Ontario: a single-cohort study

Catherine Yang BHSc, Abdool S. Yasseen III MSc, Jennifer Stimec MD, Elizabeth Rea MD MSc, Valerie Waters MD MSc, Ray Lam NP, Shaun K. Morris MD MPH, Ian Kitai MBBCh

Abstract

Background: There are few data about the utility of the Canadian tuberculosis medical surveillance system for detecting tuberculosis in children and adolescents. We sought to assess the prevalence of tuberculosis infection and disease in children and adolescents referred by the tuberculosis medical surveillance program who were evaluated at The Hospital for Sick Children (SickKids) tuberculosis program.

Methods: We retrospectively studied clinical records, radiographic findings and results of interferon-γ release assays (IGRAs) of all children less than 18 years of age referred by the tuberculosis medical surveillance program and evaluated at SickKids between November 2012 and June 2016.

Results: The median age of the 216 children was 10.0 years. Most were born in the Philippines (157 [72.7%]) or India (39 [18.0%]). Of the 216, 166 (76.8%) had a history of prior treatment for tuberculosis, and 34 (15.7%) were federal-sponsored refugees from settings with a high tuberculosis burden. Negative IGRA results were found in 110/130 (84.6%) of those with prior tuberculosis treatment. Thirty-one children (14.4%) had any chest radiographic abnormality, of whom 4 had changes thought to be due to tuberculosis. No child received a diagnosis of active tuberculosis at assessment or during follow-up; 3 (1.4%) were treated for latent tuberculosis infection following IGRA testing at SickKids. A positive IGRA result was associated with contact with infectious tuberculosis (odds ratio [OR] 5.97, 95% confidence interval [CI] 2.06–17.52) and older age at first clinic visit (OR 2.98, 95% CI 1.24–8.30) but not with radiographic abnormalities or history of prior tuberculosis treatment.

Interpretation: Most children were referred because of a history of prior treatment for tuberculosis; few had clinical or laboratory evidence of infection or prior disease. The tuberculosis medical surveillance process did not identify any children who required treatment for active disease and requires improvement.

In Canada, pediatric tuberculosis affects predominantly migrant children, children of migrant parents and Indigenous children.[1] During 2006–2011, 33.7% of migrants to Canada were younger than 25 years.[2] Requirements for screening children and adolescents for tuberculosis vary widely between immigrant-receiving countries with a low tuberculosis burden.[3] In Canada, all prospective applicants for residency undergo an immigration medical examination, which includes medical history-taking and, for those older than 11 years of age, chest radiography; it does not include routine tuberculin skin tests or interferon-γ release assays (IGRAs).[4] Those deemed to be at high risk for reactivated or new incident tuberculosis are referred by Immigration, Refugees and Citizenship Canada for postlanding tuberculosis medical surveillance. Using cohort data from Ontario, Khan and colleagues[5] showed that, for adults, current screening is inefficient, identifying few cases of tuberculosis. Adults are often referred for tuberculosis medical surveillance because of abnormal findings on chest radiography. Recently, Yasseen and colleagues[6] showed a close correlation between referral for tuberculosis medical surveillance of children and adolescents and a history of tuberculosis diagnosis. They

Competing interests: None declared.

This article has been peer reviewed.

Correspondence to: Ian Kitai, ian.kitai@sickkids.ca

***CMAJ Open* 2018. DOI:10.9778/cmajo.20180043**

reported that the proportion of migrant children with a prior diagnosis of tuberculosis was significantly different between countries with comparable tuberculosis incidence rates. It is unclear whether this reflects inaccurate diagnosis in some countries, underdiagnosis in others or a combination of the two. Referral for tuberculosis medical surveillance incurs financial and other costs for families. Being flagged with tuberculosis concerns is often associated with fear of stigmatization and, erroneously, fear of loss of immigration status.[7]

We examined records of a cohort of children referred for tuberculosis medical surveillance in Toronto to ascertain reasons for referral, the proportion of children who had evidence of tuberculosis infection of prior disease and the utility of the process in detecting tuberculosis in children and adolescents.

Methods

Study design and data sources

Using a single-cohort study design, we retrospectively analyzed data from a convenience sample of all children less than 18 years of age referred to the tuberculosis clinic at The Hospital for Sick Children (SickKids), Toronto, for tuberculosis medical surveillance between Nov. 29, 2012, and June 9, 2016. The clinic is the principal facility used by Toronto Public Health to evaluate children notified to them for immigration tuberculosis surveillance. We obtained data from a standardized assessment form used at the initial tuberculosis clinic visit and designed to capture demographic variables, travel and immigration history, household characteristics in Canada, symptoms including those of tuberculosis and physical examination findings. The form collects this information in a uniform way but has not been formally assessed for accuracy. We also used clinic letters, supplementary case histories, immigration medical examination records and chest radiography reports. Information extracted included demographic variables, reasons for referral, past medical history, and imaging and investigation results before migration. Also collected was information about the care received at SickKids, including imaging, results of blood testing and tuberculin skin tests, treatments, referrals and follow-up information. We excluded foreign-born children referred to our clinic who had not been identified by the tuberculosis medical surveillance system.

Chest radiography was performed at SickKids for all children at the first clinic visit, and the radiographs were evaluated by pediatric radiologists. Chest radiographs in which any abnormalities were described were further reviewed by a study pediatric radiologist (J.S.) according to standardized clinical case definitions for classification of intrathoracic tuberculosis disease.[8] The radiologist was blinded to the initial radiograph interpretations, as well as the IGRA results, but was aware that the evaluation was of a possibly abnormal chest radiograph in the context of a concern for tuberculosis. Follow-up visits were scheduled at the discretion of the evaluating clinician. Depending on availability, the QuantiFERON-TB Gold test (Qiagen), an IGRA, was performed as part of the clinical evaluation in most of the children, especially after 2015.

Statistical analysis

We displayed demographic characteristics using summary statistics. We compared the referred children evaluated at SickKids and those evaluated by other Ontario providers using the χ^2 or Fisher exact test. We used uni- and multivariable logistic regression models to identify risk factors for a positive IGRA result. The variables entered into this analysis were age at first SickKids clinic visit, known infectious tuberculosis contact (a field in the clinic entry data form), chest radiograph abnormality on study radiologist review and history of prior tuberculosis treatment (obtained from the Public Health referral and entered into the clinic entry form). We conducted all analyses using SAS version 9.4 (SAS Institute).

Ethics approval

This study was approved by the Research Ethics Board at SickKids.

Results

Data quality

All variables analyzed as predictors of a positive IGRA result had complete data. Age at the time of tuberculosis treatment was missing in 1 case, and bacille Calmette–Guérin status was unknown in 4 cases.

Patient characteristics

We included all 216 study-eligible children referred for tuberculosis medical surveillance at SickKids during the study period. Of the 216, 118 (54.6%) were boys (Table 1). The median age at the time of the first clinic visit was 10.0 years. Children born in the Philippines (157 [72.7%] and India (39 [18.0%]) accounted for most of the referrals. Of the 39 children born in India, 37 (95%) were federally sponsored refugees of Tibetan descent. Nine children born in Israel, Saudi Arabia, Italy or Lebanon had migrated to the Philippines before migration to Canada. A total of 207 children (95.8%) were recorded as having received the bacille Calmette–Guérin vaccine. In keeping with Toronto Public Health's policy of preferentially referring younger children to SickKids (as evaluation for tuberculosis in this age group is more difficult), overall, children referred for tuberculosis medical surveillance in Ontario and seen at SickKids were younger than those seen elsewhere (Table 2).

The most common reasons for referral for tuberculosis medical surveillance were a history of prior treatment for tuberculosis (166 children [76.8%]) and referral under a refugee resettlement program involving communities at high risk for tuberculosis (34 children [15.7%]). Of the 216 children, 166 (76.8%) had a prior diagnosis of tuberculosis made in the country of migration, of whom 150 (90.4%) had received a diagnosis of "primary complex tuberculosis" in the Philippines. In 102 (61.4%) of the 166 instances, the mother or both parents had immigrated to Canada before the child; parents were often unsure of details of symptoms before treatment. Based on immigration medical examination reports and

Table 1: Characteristics of immigrant and refugee children referred to The Hospital for Sick Children for tuberculosis medical surveillance, November 2012 to June 2016

Characteristic	No. (%) of children			
	No IGRA done *n* = 40	IGRA result negative *n* = 152	IGRA result positive *n* = 24	Total *n* = 216
Sex				
Male	22 (45)	86 (43.4)	10 (58)	118 (54.6)
Female	18 (55)	66 (56.6)	14 (42)	98 (45.4)
Age, yr				
≤ 5	2 (5)	21 (13.8)	0 (0)	23 (10.6)
6–10	24 (60)	70 (46.0)	10 (42)	104 (48.1)
11–16	14 (35)	61 (40.1)	14 (58)	89 (41.2)
Country of birth				
Philippines	32 (80)	108 (71.0)	17 (71)	157 (72.7)
India*	3 (8)	32 (21.0)	4 (17)	39 (18.0)
Israel†	2 (5)	3 (2.0)	0 (0)	5 (2.3)
Saudi Arabia†	0 (0)	2 (1.3)	1 (4)	3 (1.4)
Russia	0 (0)	2 (1.3)	0 (0)	2 (0.9)
Nepal	0 (0)	2 (1.3)	0 (0)	2 (0.9)
Other†	3 (8)	3 (2.0)	2 (8)	8 (3.7)
Reason for medical surveillance referral				
History of prior treatment for tuberculosis	36 (90)	110 (72.4)	20 (83)	166 (76.8)
Refugee resettlement program (automatic referral)	0 (0)	31 (20.4)	3 (12)	34 (15.7)
Possible tuberculosis contact	1 (2)	3 (2.0)	0 (0)	4 (1.8)
Positive tuberculin skin test result on immigration	2 (5)	3 (2.0)	1 (4)	6 (2.3)
Abnormal chest radiograph on immigration	0 (0)	3 (2.0)	0 (0)	3 (1.4)
Other	1 (2)	2 (1.3)	0 (0)	3 (0.9)
Prior diagnosis				
Primary complex tuberculosis	31 (78)	101 (66.4)	18 (75)	150 (69.4)
Tuberculosis disease (site specific)	4 (10)	6 (3.9)	1 (4)	11 (5.1)
Pulmonary tuberculosis	2 (5)	6 (3.9)	1 (4)	9 (4.2)
Lymph node tuberculosis	2 (5)	0 (0.0)	0 (0)	2 (0.9)
Latent tuberculosis infection	1 (2)	2 (1.3)	1 (4)	4 (1.8)
No prior diagnosis	0 (0)	37 (24.3)	3 (12)	40 (18.5)
Symptoms in country of origin that led to diagnosis of tuberculosis disease				
None	13 (32)	56 (36.8)	9 (38)	78 (36.1)
Unknown	8 (20)	30 (19.7)	7 (29)	45 (20.8)
Known	19 (48)	66 (43.4)	8 (33)	93 (43.0)
Cough	17 (42)	57 (37.5)	6 (25)	80 (37.0)
Fever/headache	9 (22)	25 (16.4)	2 (8)	36 (16.7)
Weight loss/poor appetite	2 (5)	17 (11.2)	2 (8)	21 (9.7)
Lymphadenopathy	3 (8)	5 (3.3)	1 (4)	9 (4.2)
Cold- or "flu"-like symptoms	1 (2)	6 (3.9)	2 (8)	9 (4.2)
Abdominal pain	1 (2)	0 (0.0)	0 (0)	1 (0.5)
Vomiting	1 (2)	0 (0.0)	0 (0)	1 (0.5)
Diarrhea	1 (2)	0 (0.0)	0 (0)	1 (0.5)

Note: IGRA = interferon-γ release assay.
*Thirty-seven children born in India were federally sponsored refugees of Tibetan descent.
†Nine children born in Israel, Saudi Arabia, Italy or Lebanon had migrated to the Philippines before migration to Canada.

Table 2: Comparison between country of birth and age at immigration/first clinic visit of children referred for tuberculosis medical surveillance and evaluated at The Hospital for Sick Children and those evaluated elsewhere in Ontario, November 2012 to June 2016

Variable	No. (%) of children: Elsewhere *n* = 292*	No. (%) of children: Hospital for Sick Children *n* = 216	*p* value
Country of birth			
Philippines	236 (80.3)	157 (72.7)	0.04
India	26 (8.8)	39 (13.4)	0.1
China	8 (2.7)	0 (0.0)	0.02
Saudi Arabia	3 (1.0)	3 (1.4)	0.7
Nepal	4 (1.4)	2 (0.9)	0.8
Other	15 (5.1)	25 (11.6)	0.02
Age at immigration/first clinic visit, yr			
≤ 4	7 (2.4)	13 (6.0)	0.06
5–10	35 (11.9)	114 (52.8)	< 0.001
11–17	250 (85.0)	89 (41.2)	< 0.001

*Aggregate data from Public Health Ontario.

recorded history, 78 (47.0%) of the 166 children were asymptomatic before diagnosis, 80 (48.2%) had cough, 36 (21.7%) had fever, 21 (12.6%) had weight loss or poor appetite, and 9 (5.4%) had lymphadenopathy.

Investigations before immigration

There was some indication of chest radiographic findings at the time of tuberculosis diagnosis in 138 tuberculosis-treated children (Supplementary Table A1, Appendix 1, available at www.cmajopen.ca/content/6/3/E365/suppl/DC1). Among 67 children with recorded findings at the time of tuberculosis treatment, the descriptions were "abnormal" (38 [57%]), "primary complex/Kochs" (6 [9%]) and "normal" (11 [16%]); 12 children (18%) were noted to have hilar changes. During the last 3 months of the study period, 27 radiographs obtained in the country of origin were reviewed by SickKids radiologists, of which 12 were described as normal (Supplementary Table A2, Appendix 1). Seventy-nine children (37%) had had a tuberculin skin test performed: for 38, a quantified measurement was recorded (≥ 10 mm in 31 and < 10 mm in 7), and for 41, the result was reported to be "positive" (33) or "negative" (8). Gastric aspirate was not obtained in any of the children. In 26 children (12%), a sputum sample was obtained via expectoration: 23 specimens (88%) were smear and culture negative, and 1 specimen (4%) was smear negative and culture positive; in 3 cases (12%), the result was unknown. In 7 children (3.2%), a sputum sample was obtained via induction; all the specimens were smear and culture negative. Other investigations included computed tomography scans (2 children [0.9%]), lymph node fine-needle aspiration (1 [0.5%]) and urine culture for *Mycobacterium* (1 [0.5%]).

The median age at initiation of treatment among the 166 children who had treatment for tuberculosis or latent tuberculosis infection before immigration was 3.0 years. Immigration medical examination records showed that 111 children (66.9%) received triple-drug therapy with rifampin, isoniazid and pyrazinamide, and 3 children (1.8%) received therapy with rifampin, isoniazid, pyrazinamide and ethambutol. Records suggested that 16 children (9.6%) received rifampin and isoniazid, 1 child (0.6%) received rifampin and pyrazinamide, and 6 children (3.6%) received isoniazid monotherapy.

Investigations and management at SickKids

All children underwent chest radiography at their first SickKids clinic visit. The radiograph was reported as normal in 165 (76.4%). Among the 53 radiographs that were noted to have possible abnormalities or quality issues, the study pediatric radiologist deemed 22 as normal; none of these children had a positive IGRA result (Table 3). Twenty-seven radiographs had questionable abnormalities, and 4 children had abnormalities according to a structured classification:[8] a 12-year-old with an enlarged intrathoracic lymph node, an 11-year-old with upper lobe areas of lucency, a 13-year-old with a possible granuloma and an 8-year-old with hilar changes.

In total, 176 children (81.5%) (92% of those evaluated in 2016 and 60% of those evaluated from 2012 to 2015) had an IGRA, of whom 24 (13.6%) had a positive result and 152 (86.4%), a negative result. Negative IGRA results were found in 110/130 (84.6%) of those with a history of prior treatment for tuberculosis disease or infection. Twenty-nine children (13.4%) had a tuberculin skin test performed in Canada, of whom 6 (21%) had induration greater than 10 mm; all 6 had a history of bacille Calmette–Guérin vaccination. Three children (1.4%) had expectorated sputum collected in clinic; all

Table 3: Findings on radiographs obtained at the initial Hospital for Sick Children clinic visit

Finding	No. of children	No. (%) with positive IGRA result
Any abnormality	53	4 (8)
Abnormal on second review	31	4 (13)
Suggestive of tuberculosis*		
Intrathoracic lymphadenopathy	3	1 (33)
Parenchymal disease	1	0 (0)
Questionable abnormality		
Peribronchial thickening	13	1 (8)
Nodule/vessel	6	1 (17)
Atelectasis	4	0 (0)
Other†	4	1 (25)

Note: IGRA = interferon-γ release assay.
*Using criteria of Graham and colleagues.[8]
†Includes possible pleural thickening (2 children), question of calcified nodule (1 child) and possible areas of lucency (1 child).

specimens were smear and culture negative. Three children (1.4%), all federally sponsored refugees without prior tuberculosis treatment, had a positive QuantiFERON-TB Gold test result and were treated for latent tuberculosis infection. No child received a diagnosis of or was treated for active tuberculosis at or following assessment at SickKids.

Of the 114 children initially seen in the first 30 months of the study period, 95 (83.3%) had at least 1 follow-up clinic evaluation, including chest radiography, after a median interval of 3.5 months from the initial visit, and 69 (60.5%) had a second clinic evaluation and chest radiography. A total of 138 (79.8%) of the 173 children seen in the first 3 years had at least 1 follow-up evaluation. For the 73 children (33.8%) officially discharged, the mean length of follow-up was 10 (standard deviation 10.5) months. New tuberculosis infection or disease was not diagnosed in any child during the follow-up period.

Predictors of positive interferon-γ release assay result

On univariate analyses, only contact with an infectious source case of tuberculosis and age at treatment (≤ 4 yr, 5–16 yr) were significantly associated with a positive IGRA result (Table 4). On multivariate logistic regression, older age at first clinic visit as a continuous variable (odds ratio 2.98, 95% confidence interval 1.24–8.30) and contact with a known case of tuberculosis (odds ratio 5.97, 95% confidence interval 2.06–17.52) remained significant risk factors for a positive IGRA result (Table 4).

Interpretation

We present data for a cohort of children referred for tuberculosis medical surveillance to a regional tuberculosis program that receives more than 40% of all such pediatric referrals in Ontario. We found that most referrals were made because of a history of tuberculosis disease, few of this cohort had evidence of tuberculosis infection or past disease, and evaluation did not detect active tuberculosis in any referred child.

In contrast to adults referred for tuberculosis medical surveillance,[5] only 1.4% of referrals among our cohort were because of radiographic abnormalities. On evaluation at SickKids, most children had normal radiographs, and the remainder had minor or questionable changes; evidence of intrathoracic lymphadenopathy or calcification, the hallmarks of childhood tuberculosis,[8] was rare. After review by a second radiologist using a structured classification,[8] only 4 children were found to have radiographic abnormalities suggestive of tuberculosis. Radiographic abnormalities often persist after treatment for tuberculosis disease in children, with only one-third of children having normal chest radiographs at the

Table 4: Predictors of a positive result of the interferon-γ release assay (QuantiFERON-TB Gold)

Characteristic	IGRA result; no. (%) of children		OR (95% CI)	
	Negative *n* = 152	Positive *n* = 24	Univariate analysis	Multiple logistic regression
Age at first visit, yr				
≤ 10	91 (59.9)	10 (42)	Reference	–
11–17	61 (40.1)	14 (58)	0.48 (0.20–1.15)	–
Continuous (older)	–	–	–	2.98 (1.24–8.30)
Age at treatment, yr				
≤ 4	76 (50.0)	9 (38)	2.81 (1.07–7.43)	–
5–16	33 (21.7)	11 (46)	Reference	–
Known tuberculosis contact				
No	138 (90.8)	16 (67)	Reference	Reference
Yes	14 (9.2)	8 (33)	4.93 (1.79–13.55)	5.97 (2.06–17.52)
Abnormal chest radiograph*				
No	132 (86.8)	20 (83)	Reference	–
Yes	20 (13.2)	4 (17)	0.76 (0.23–2.45)	–
Prior treatment				
No	42 (27.6)	4 (17)	Reference	–
Yes	110 (72.4)	20 (83)	1.91 (0.61, 5.91)	–

Note: CI = confidence interval, IGRA = interferon-γ release assay, OR = odds ratio.
*On second review.

completion of treatment in a study in Texas.[9] The absence of such abnormalities suggests that many in this cohort did not ever have tuberculosis disease. Few of the 166 children treated for tuberculosis had undergone diagnostic microbiologic investigations in their country of origin, and in only 1 child was the sputum sample culture positive. Pediatric tuberculosis is often paucibacillary, and diagnosis is difficult. Investigations may be expensive and difficult to access in many countries, but, in contrast, over 40% of pediatric tuberculosis cases in North America have positive culture results.[9,10] In addition, only 15% of children with a history of tuberculosis in our cohort had a positive IGRA result. Denkinger and colleagues[11] found that, in 87% of adults with a positive IGRA result in Montreal, positivity persisted at the end of treatment for tuberculosis disease, and IGRA positivity was found in 70% of patients with a remote history of tuberculosis evaluated in a Norwegian tuberculosis clinic.[12] In a US study, all health care workers with a positive result of the QuantiFERON-TB Gold assay treated for latent tuberculosis infection still had a positive result at the end of treatment.[13] Persistence of a positive tuberculin skin test result was shown 3–9 years following treatment for latent tuberculosis infection.[14] Given that both the tuberculin skin test and the IGRA depend on immunologic memory of *M. tuberculosis*, it is likely that a much greater proportion of IGRA results would have remained positive if most of our cohort truly had tuberculosis infection or disease. The most significant predictor of a positive IGRA result was known contact with an infectious source case, the most important known predictor of tuberculosis infection.[15] This further validates the IGRA as a useful investigative tool and emphasizes the importance of taking a detailed contact history as part of the screening process. Increasing age was weakly associated with IGRA positivity, which has been described elsewhere.[16]

Most of the children in our cohort were born in and/or migrated from the Philippines and had been treated for tuberculosis. Our findings suggest that many children are treated without strong evidence of disease. Frequently, the immigration medical examination recorded a diagnosis of "primary complex tuberculosis," but no child with that diagnosis had microbiologically proven tuberculosis. Yasseen and colleagues[6] showed very different rates of tuberculosis diagnosis in children immigrating from countries with comparable overall incidence of tuberculosis: 2.3% of children immigrating from the Philippines had a tuberculosis diagnosis, compared to 0.06% of those immigrating from Pakistan. The 2016 tuberculosis incidence in these countries was 322/100 000 and 270/100 000, respectively.[17] Our study adds clinical detail to these data and confirms that, based on chest radiograph findings and IGRA results, most of the referred children had no evidence of tuberculosis. The Canadian immigration medical examination for children, which involves only history-taking and a physical examination, generates most surveillance referrals because of a past diagnosis of tuberculosis. We found that, for this cohort, prior tuberculosis diagnosis was a poor marker of past tuberculosis disease or latent tuberculosis infection, and that the current process results in burdens to many families and health care services without identifying cases.

Limitations

Our study was retrospective, although some data were collected prospectively at the time of the first clinic visit. The validity of recorded data has not been formally assessed. Data from the countries of origin, including details about why children were treated for tuberculosis, were sparse. Furthermore, most, but not all, children had an IGRA at our centre, although this was related to availability of the test. Our cohort was fairly representative of all pediatric tuberculosis medical surveillance referrals in Ontario, although it included more young children and fewer adolescents. Since most of the children referred to SickKids and elsewhere in Ontario were born in the Philippines, our findings may not be generalizable nationwide owing to differing migration patterns in various Canadian provinces.

Conclusion

Our study identifies several problems with the current tuberculosis medical surveillance system for children. First, the initial clinical visit had limited utility in diagnosing tuberculosis. No child was treated for tuberculosis disease as a result of our evaluation, and treatment for latent tuberculosis infection, prescribed in 3 cases, resulted from the IGRA, which is currently not part of the immigration medical examination or tuberculosis surveillance process. Second, follow-up visits also failed to identify reactivated or incident cases. Third, contact with an infectious case of tuberculosis is highly predictive of a positive IGRA result, which highlights the importance of obtaining a detailed history regarding contact with tuberculosis during the immigration medical examination and after immigration. Ultimately, we found that the current system did not identify children with tuberculosis disease in this cohort, either at first visit or at follow-up. Relying on a history of treatment as the major driver of tuberculosis surveillance results in overreferral of children from countries with high rates of empiric treatment. Consideration should be given to approaches including pre- or postimmigration testing for infection with a tuberculin skin test or IGRA, especially in populations at high risk for infection.[16] Our findings suggest that a better system needs to be designed and assessed to find a balance among identifying those at risk for tuberculosis, protecting public health, and minimizing undue burden on children, families and the health care system.

References

1. Phypers M. Pediatric tuberculosis in Canada. *Can Commun Dis Rep* 2003;29:139-42.
2. Immigration and ethnocultural diversity in Canada: national household survey, 2011 [analytical document]. Cat. no. 99-010-X2011001. Ottawa: Statistics Canada; 2013. Available: http://www12.statcan.gc.ca/nhs-enm/2011/as-sa/99-010-x/99-010-x2011001-eng.cfm (accessed 2017 Apr. 23).
3. Alvarez GG, Gushulak B, Rumman KA, et al. A comparative examination of tuberculosis immigration medical screening programs from selected countries with high immigration and low tuberculosis incidence rates. *BMC Infect Dis* 2011;11:3.
4. Tuberculosis surveillance and screening in selected high-risk populations. In: *Canadian Tuberculosis Standards*. 7th ed. Ottawa: Public Health Agency of Canada; 2014. Cat. no. HP40-18/2014E-PDF. Available: www.phac-aspc.gc.ca/tbpc-latb/pubs/tb-canada-7/assets/pdf/tb-standards-tb-normes-ch13-eng.pdf (accessed 2017 Apr. 23).
5. Khan K, Hirji MM, Miniota J, et al. Domestic impact of tuberculosis screening among new immigrants to Ontario, Canada. *CMAJ* 2015;187:E473-81.

6. Yasseen AS 3rd, Rea E, Hirji MM, et al. Pediatric TB among the foreign-born: utility of the Canadian TB immigration medical surveillance program. *Int J Tuberc Lung Dis*. In press.
7. Yamada S, Caballero J, Matsunaga DS, et al. Attitudes regarding tuberculosis in immigrants from the Philippines to the United States. *Fam Med* 1999;31:477-82.
8. Graham SM, Ahmed T, Amanullah F, et al. Evaluation of tuberculosis diagnostics in children: 1. Proposed clinical case definitions for classification of intrathoracic tuberculosis disease. Consensus from an expert panel. *J Infect Dis* 2012;205(Suppl 2):S199-208.
9. Al-Dossary FS, Ong LT, Correa AG, et al. Treatment of childhood tuberculosis with a six month directly observed regimen of only two weeks of daily therapy. *Pediatr Infect Dis J* 2002;21:91-7.
10. Thampi N, Stephens D, Rea E, et al. Unexplained deterioration during antituberculous therapy in children and adolescents: clinical presentation and risk factors. *Pediatr Infect Dis J* 2012;31:129-33.
11. Denkinger CM, Pai M, Patel M, et al. Gamma interferon release assay for monitoring of treatment response for active tuberculosis: an explosion in the spaghetti factory. *J Clin Microbiol* 2013;51:607-10.
12. Dyrhol-Riise AM, Gran G, Wentzel-Larsen T, et al. Diagnosis and follow-up of treatment of latent tuberculosis; the utility of the QuantiFERON-TB Gold in-tube assay in outpatients from a tuberculosis low-endemic country. *BMC Infect Dis* 2010;10:57.
13. Pollock NR, Kashino SS, Napolitano DR, et al. Evaluation of the effect of treatment of latent tuberculosis infection on QuantiFERON-TB Gold assay results. *Infect Control Hosp Epidemiol* 2009;30:392-5.
14. Hsu KH. Tuberculin reaction in children treated with isoniazid. *Am J Dis Child* 1983;137:1090-2.
15. Saiman L, San Gabriel P, Schulte J, et al. Risk factors for latent tuberculosis infection among children in New York City. *Pediatrics* 2001;107:999-1003.
16. Lowenthal P, Barry PM, Flood J. High discordance between pre-US and post-US entry tuberculosis test results among immigrant children: Is it time to adopt interferon gamma release assay for preentry tuberculosis screening? *Pediatr Infect Dis J* 2016;35:231-6.
17. Tuberculosis country profiles. Geneva: World Health Organization; 2017. Available: www.who.int/tb/country/data/profiles/en/ (accessed 2017 Aug. 16).

Affiliations: Faculty of Medicine (Yang), Dalla Lana School of Public Health (Yasseen, Rea), Department of Pediatrics (Waters, Morris, Kitai) and Faculty of Nursing (Lam), University of Toronto, Toronto, Ont.; Children's Hospital of Eastern Ontario Research Institute (Yasseen), Ottawa, Ont.; Department of Diagnostic Imaging (Stimec) and Division of Infectious Diseases (Waters, Morris, Kitai), The Hospital for Sick Children; Toronto Public Health (Rea), Toronto, Ont.

Contributors: Ian Kitai and Shaun Morris contributed equally to the study. Ian Kitai conceived of the study and designed it with Shaun Morris, Catherine Yang and Elizabeth Rea, with assistance from all the other authors. Jennifer Stimec performed detailed review of chest radiographs. Catherine Yang modified the research protocol, performed data extraction and analysis, and drafted the manuscript. Abdool Yasseen contributed to data analysis. All of the authors contributed to interpreting the data and critically revising the manuscript for important intellectual content, gave final approval of the version to be published and agreed to be accountable for all aspects of the work.

Funding: This work was supported by a grant from Paediatric Consultants, The Hospital for Sick Children, Toronto. Catherine Yang received support for this work from the SickKids' Social Pediatrics Research Summer Studentship Program.

Supplemental information: For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/6/3/E365/suppl/DC1.