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3   1   **Title page:**
4   2   **Title:** Children referred for Tuberculosis medical surveillance (TBMS) in Ontario, Canada:
5   3   results of clinical and diagnostic evaluation
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28   25   **The authors have no competing interests to declare.**
29   26
30   27   Supported by a grant from Paediatric Consultants, Hospital for Sick Children, Toronto.
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30 **Abstract**

31 BACKGROUND:

32 There are few data about the utility of the Canadian TB Medical Surveillance (TBMS) system

33 for detecting tuberculosis (TB) in children and adolescents.

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35 OBJECTIVE:

36 To assess the prevalence of TB infection and disease in TBMS-referred patients evaluated at

37 the SickKids TB Program.

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39 DESIGN/METHODS:

40 We retrospectively studied clinical records, radiographic findings and results of interferon

41 gamma release assays (IGRAs) of all TBMS-referred children evaluated at SickKids between

42 November 2012 and June 2016.

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44 RESULTS:

45 The median age of the 216 children, 40% of all Ontario pediatric TBMS referrals, was 10.0

46 years. Most were born in the Philippines (73%), and India (19%). Seventy-seven percent had a

47 history of prior treatment for TB and 16% were federal-sponsored refugees from high-TB-burden

48 settings. Negative IGRAs were found in 110/130 (85%) of those with prior TB treatment.

49 Thirty-one patients (14%) had any radiographic abnormality of whom 4 had changes thought to

50 be due to TB. No children were diagnosed with active TB at assessment or during follow up; 3

51 were treated for latent TB infection following IGRA testing at SickKids. A positive IGRA was

52 associated with contact with infectious TB (OR 5.97 [95% CI 2.03, 17.52]) and older age at first

53   clinic visit (OR 2.98 [95% CI 1.24, 8.30]), but not with radiographic abnormalities or history of

54   prior TB treatment.

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56   INTERPRETATION:

57   Most children were referred because of prior treatment for TB: few had evidence of infection or

58   prior disease. The TBMS process did not identify any children who required treatment for active

59   disease and requires improvement.

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63 **Introduction**

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65   Pediatric tuberculosis (TB) in Canada predominantly affects migrant children, children of

66 migrant parents, and indigenous children.[1] During the years 2006-2011, 33.7% of migrants to

67 Canada were younger than 25 .[2] Requirements for screening children and adolescents for TB

68 vary widely between immigrant-receiving-low-TB burden countries.[3] In Canada, all prospective

69 applicants for residency undergo an Immigration Medical Exam (IME), which includes a

70 medical history for all migrants and chest X-rays for those older than 11 years of age, but does

71 not include routine Tuberculin Skin Tests (TSTs) or IGRAs.[4] Those deemed to be at high risk for

72 reactivated or new incident TB are referred by Immigration, Refugees, and Citizenship Canada

73 for post-landing TB-medical-surveillance (TBMS).

74   Using cohort data from Ontario, Canada, Khan et al. have shown that for adults, current

75 TBMS screening is inefficient, identifying few cases of TB. [5] Adults are often referred for

76 TBMS because of abnormal chest radiographs; but chest radiographs are not required for

77 younger children. Recently, Yasseen et al. have shown that referral for TBMS in children and

78 adolescents was closely correlated with a past diagnosis of TB, and that the proportion of those

79 with a prior TB diagnosis was significantly different between countries with comparable TB

80 incidence rates.[6] It is unclear whether this reflected inaccurate diagnosis in some countries,

81 underdiagnosis in others, or a combination.

82   Referral for TBMS incurs financial and other costs for families. Being flagged with TB

83 concerns is often associated with fear of stigmatization and erroneously, fear of loss of

84 immigration status.[7]

85   The TB clinic at the Hospital for Sick Children (SickKids) is the principal facility used

86 by Toronto Public Health (TPH) to evaluate children notified to them for TBMS. The clinic

87   receives 40-80 TBMS referrals per year. Standardized demographic and clinical information is

88   collected at clinic entry. We examined records of a cohort of such children to ascertain reasons

89   for TBMS referral, the proportion of children who had evidence of TB infection or prior disease,

90   and to assess the utility of the TBMS process in detecting TB in children and adolescents.

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Materials and Methods

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93   We retrospectively analysed data from all children <18 years of age referred to the

94   SickKids' TB clinic for TBMS between November 29th, 2012 and June 9th, 2016, a sample for

95   whom we had consistent records. Data was obtained from a standardized initial clinic visit

96   assessment form, which records demographic and other data, as well as clinic letters, IME

97   records (if available) and chest radiograph reports. We excluded children referred to our clinic

98   who had not been identified by the TBMS system.

99   Chest radiographs were performed at SickKids for all patients at the first clinic visit and

100   reported by pediatric radiologists. Radiographs in which any abnormalities were described were

101   reviewed by a study pediatric radiologist (who was blinded to IGRA results) according to

102   standardized clinical case definitions for classification of intrathoracic TB disease.[8]

103   Follow up visits were scheduled at the discretion of the evaluating clinician.

104   Depending on availability and as part of clinical evaluation the QuantiFERON-TB Gold

105   (QFT) test, an IGRA, obtained in the majority of children, especially after 2015. Demographic

106   variables were presented as frequencies and proportions, and univariate analysis followed by

107   multiple logistic regression were used to identify risk factors for TB infection. All analyses were

108   conducted using the SAS software (Version 9.4). This study was approved by the research ethics

109   board at SickKids (REB #1000053061).

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Results

Patient characteristics

114   We included all 216 study-eligible children referred for TBMS at SickKids. Overall, 118

115 (55%) were male. The median age at time of first clinic visit was 10.0 years (Table 1). Children

116 born in the Philippines, 157 (73%), and India, 39 (18%), accounted for 91% of referrals. Of the

117 39 migrant children born in India, 37 (93%) were federally sponsored refugees of Tibetan

118 descent. The nine children born in Israel, Saudi Arabia, Italy and Lebanon, had migrated to the

119 Phillipines prior to migration to Canada. Ninety six percent of patients were recorded as having

120 received the Bacillus Calmette-Guérin (BCG) vaccine. Table 2 shows the numbers of migrant

121 children referred for TBMS in Ontario (aggregate data from Public Health Ontario) and the

122 proportion seen at the SickKids TB Clinic. The overall ages were younger than that for Ontario

123 in keeping with Toronto Public Health's policy of preferentially referring younger children to

124 SickKids as evaluation for TB at this age is more difficult.

125   The most common reasons for referral for TBMS included: past history of prior treatment

126 for TB [166 children (77%)] and referral under a refugee resettlement program involving high-

127 TB-risk communities [34 children (16%)]. Overall, 166 (77%) migrant children had a prior

128 diagnosis of TB made in the country of migration: of these 150 (90%) were diagnosed with

129 "Primary Complex TB" in the Philippines. In 102/166 (61%) instances the mother or both

130 parents had immigrated to Canada before the child's arrival: parents were often unsure of details

131 of symptoms prior to treatment. Based on IME reports and recorded history, 78 (47%) were

132 asymptomatic prior to diagnosis, another 80 (48%) had symptoms of cough, 36 (22%) fever 21

133 (13%) weight loss or poor appetite and 9 (5%) lymphadenopathy.

134 <u>Investigations prior to immigration</u>

135 There was some indication of chest radiographic findings at the time of TB diagnosis in 138 TB-

136 treated patients (Appendix 1): in 67 patients with recorded findings at the time of TB treatment

137 the descriptions were "abnormal" (57%), "primary complex or Kochs" (9%) and normal (16%);

138 12 patients (18%) were noted to have hilar changes. During the last 3 months of the study

139 period, 27 radiographs taken in the country of origin were reported by SickKids radiologists: of

140 these 4 (15%) were described as poor quality, 12 (44%) as normal, 7 (26%) as nonspecific lower

141 airway inflammation or peribronchial thickening; 1 had intrathoracic lymphadenopathy

142 suggestive of TB (Appendix 2). Seventy nine (37%) children had a TST performed: 38 with a

143 quantified measurement recorded, ($\geq$10mm in 31 and <10mm in 7); and 41 where the TST was

144 reported to be 'positive' (33) or 'negative'(8). No children had gastric aspirates prior to

145 immigration. Twenty-six (12%) had expectorated sputum: 85% were smear- and culture-

146 negative, 4% smear-negative culture-positive and 11% had an unknown result. In the 7 children

147 (3%) who had sputum induction, results were all smear and culture-negative. Other

148 investigations included: computed tomography scans (0.9%), lymph-node fine-needle-aspiration

149 (0.4%) and a mycobacterial urine culture (0.4%).

150   Of the 166 children who had TB/LTBI treatment prior to immigration, the median age at

151 initiation of treatment was 3.0 years. From IME records, 111(51%) children received triple

152 drug therapy with Rifampicin, (R) Isoniazid (I) and Pyrazinamide (Z). Three children (1%)

153 received therapy with RHZ and Ethambutol. Records suggest 16 children (7%) received RH, 1

154 child (0.5%) RZ, and 6 children (3%) Isoniazid monotherapy.

155

156 <u>Investigations and management at SickKids</u>

157   All children underwent chest radiographs at their first SickKids clinic visit, of these, 165

158 (76%) were reported as normal. The fifty-three radiographs which were noted to have possible

159 abnormalities or quality issues were subjected to a review by a study pediatric radiologist (Table

160 4). Twenty-two (42%) of the study-reviewed-radiographs were deemed normal: none of these

161 children had positive IGRAs. Twenty seven (12.5%) had questionable abnormalities, and 4

162 children had abnormalities according to a structured classification[8]: a 12 year old with an

163 enlarged intrathoracic lymph node, an 11 year old with upper lobe lucencies, a 13year old with a

164 possible granuloma, and an 8 year old with hilar changes.

165   In total, 176 (82%) children had an IGRA (60% of children before and 92% of children

166 after 2015) of which 24 (14%), 152 (86%), and 0 had positive, negative, and indeterminate result

167 respectively. Negative IGRAs were found in 110/130 (85%) of those with a history of prior

168 treatment for TB disease or infection. Twenty-nine children (13%) had a TST performed in

169 Canada, of these, 6 (21%) had induration >10mm: all 6 had a history of BCG vaccination. Three

170 children (1%) had expectorated sputum collected in clinic, all were smear and culture negative.

171 Three children (1%), all federally sponsored refugees without prior TB treatment, had positive

172 QFTs and were treated for latent TB infection (LTBI). No children were diagnosed with, or

173 treated for active TB at or following their SickKids assessment.

174 Of the the 114 patients first seen in the first 30 months of the study period, 95 (81%) had at least

175 one follow-up clinic evaluation and chest radiograph after a median interval of 3.5 months

176 from first visit and 69 (61%) had a second evaluation. Of those seen in the first 36 months

177 138/173 (80%) had at least one follow-up evaluation. For those 73 children (34%) officially

178 discharged, the mean length of follow-up was 10 (10.3) months No children were diagnosed with

179 new TB infection or disease during the follow-up period.

180

181   *Predictors of a positive IGRA*

182   On univariate analyses (Table 3), only contact with an infectious source case of TB and

183   age at treatment (<4, 5-16 yrs) were significantly associated with a positive IGRA. On

184   multivariate logistic regression (Table 3), older age at first clinic visit as a continuous variable

185   (OR 2.98 [95% CI 1.24, 8.30]) and contact with a known case of TB (OR 5.97 [95% CI 2.03,

186   17.52]) remained significant risk factors for a positive IGRA.

187

188

Discussion

189

190   We present data from a cohort of children refered for TBMS to a regional TB program

191   which receives >40% of all childhood TBMS referrals in Ontario. We found that most referrals

192   were made because of a past history of TB disease, that few of this chohort had evidence of TB

193   infection or past disease, and that the TBMS referral did not detect active TB in any referred

194   child.

195   As shown in Table 2, our patients were geographically quite representative of all

196   pediatric TBMS referrals in Ontario though included more young children and fewer

197   adolescents. Very few of the 166 patients treated for TB had undergone diagnostic

198   microbiologic investigations in their country of origin and only onehad been culture- positive.

199   Pediatric TB is often paucibacillary and diagnosis is difficult. Investigations may be expensive

200   and difficult to access in many countries, but, in contrast over 40% of pediatric TB cases in

201   North America have positive cultures.[9,10]

202   In contrast to adults referred for TBMS,[5] only 1.4% of referrals for our cohort were due

203   to radiographic abnormalities. Upon evaluation in Toronto, most children had normal

204   radiographs and the remainder had minor or questionable changes: evidence of intrathoracic

205   lymphadenopathy or calcification, the hallmarks of childhood TB, [8] was rare. After review by a

206   second radiologist using a structured classification,[8] only 4 children were found to have

207   radiographic abnormalities suggestive of TB. Radiographic abnormalities often persist after

208   treatment for TB disease in children with only one third of children having normal chest

209   radiographs at the completion of treatment in a study in Texas.[10] The absence of such

210   abnormalities is evidence that many in this cohort did not ever have TB disease.

211

212

213   Only 15% of those with a past history of TB had a positive IGRA. IGRA test positivity

214   has been shown to persist in 87% of adults at the end of treatment for TB disease in Montreal,

215   Canada,[11] and was found in 70% of patients with a remote history of TB evaluated in a

216   Norwegian TB clinic.[12] In an United States study all QFT-positive health care workers treated

217   for LTBI were QFT-positive at the end of treatment.[13] Persistence of a positive TST has been

218   demonstrated 3-9 years following treatment for latent infection.[14] Given that both the TST and

219   IGRA depend on immunologic memory of TB, it is likely a much greater proportion of IGRAs

220   would remain positive if most children truly had TB infection or disease.

221   The most significant predictor of a positive IGRA was known contact with an infectious

222   source case, the most important known predictor of infection.[15] This further validates the IGRA

223   as a useful investigation and emphasizes the importance of taking a detailed contact history as

224   part of the screening process. Increasing age was weakly associated with IGRA positivity, which

225   has also been described elsewhere.[16]

226   The majority of our cohort were born in and/or migrated from the Philippines and had

227   been treated for TB. This study suggests that many children are treated without strong evidence

228   of disease. Frequently the IME recorded a diagnosis of "Primary Complex TB", but no child

229   with that diagnosis had microbiologically proven TB. Yasseen et al. have shown very different

230   rates of TB diagnosis in children immigrating from countries with comparable overall incidence

231   of TB:[6] 2.3% of children from the Philippines had a TB diagnosis as compared with 0.06% of

232   children immigrating from Pakistan. The 2016 TB incidence in these countries was 322/100,000

233   and 270/100,000, respectively.[17] Our study adds clinical detail to these data and confirms that,

234   based on chest radiograph findings and IGRA results, the majority of referred children had no

235 evidence of TB. The Canadian IME for children, which involves only a history and physical

236 exam generates most TBMS referrals because of a past history of TB diagnosis. We found that

237 for this cohort, prior TB diagnosis was a poor marker of past TB disease or LTBI, and that the

238 current TBMS process results in burdens to many families and health services without

239 identifying cases.

240   Our study identifies in detail several problems with the current TBMS system for

241 children. Firstly, the initial clinical TBMS visit had very limited utility in diagnosing TB. No

242 child was treated for TB disease as a result of our evaluation, and treatment for LTBI, prescribed

243 in 3 cases, resulted from IGRA testing which is currently not part of the IME or TBMS process.

244 Secondly, follow-up visits also failed to identify reactivated or incident cases. Thirdly, TB

245 contact is highly predictive of a positive IGRA highlighting the importance of conducting a

246 detailed history regarding contact with TB during the IME and post-immigration.

247   This study has several limitations. It is retrospective, though data was prospectively

248 collected at the time of first visit. Data from the countries of origin were sparse including

249 specific details about why children were treated for TB. Furthermore, most, but not all children

250 underwent IGRA testing at our centre, though this was related to availability of the test. Our

251 patient population was was geographically similar to that of Ontario TBMS referrals but with

252 more young children and fewer adolescents limiting generalisability, our data may also not be

253 generalizable nation-wide due to differing migration patterns in various Canadian provinces.

254   We have found that current IME/TBMS system did not identify children with TB disease

255 in this cohort either at first visit or at follow-up. Relying on a past history of treatment as the

256 major driver of TBMS results in over-referal of children from countries with high rates of

257 empiric treatment. Consideration should be given to approaches which may include pre- or post-

258   immigration tests of infection with TSTs or IGRAs, especially in populations at high risk for

259   infection.[16] We believe that a better system needs to be designed and assessed to find a balance

260   between identifying those at risk for TB, protecting public health, and minimizing undue burden

261   on children, families, and the health care system.

262

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Table 1. Characteristics of Immigrant and Refugee Children Referred to SickKids for TB Medical Surveillance, Toronto, November 2012 - June 2016

Characteristic	No IGRA done (n=40)	IGRA neg. (n=152)	IGRA pos. (n=24)	Total (n=216)
Sex				
Male	18 (45%)	66 (43%)	14 (58%)	118 (55%)
Female	22 (55%)	86 (57%)	10 (42%)	98 (45%)
Age (yr)				
<5	2 (5%)	21 (14%)	0 (0%)	23 (11%)
6-10	24 (60%)	70 (46%)	10 (42%)	104 (48%)
f11-16	14 (35%)	61 (40%)	14 (58%)	89 (41%)
Country of birth				
Philippines	32 (80%)	108 (71%)	17 (71%)	157 (73%)
India*	3 (7.5%)	32 (21%)	4 (17%)	39 (18%)
Israel**	2 (5%)	3 (2%)	0 (0%)	5 (2%)
Saudi Arabia**	0 (0%)	2 (1%)	1 (4%)	3 (1%)
Russia	0 (0%)	2 (1%)	0 (0%)	2 (1%)
Nepal	0 (0%)	2 (1%)	0 (0%)	2 (1%)
Other***	3 (7.5%)	3 (2%)	2 (8%)	8 (4%)
Medical surveillance referral reason				
Past history of prior treatment for TB	36 (90%)	110 (72%)	20 (83%)	166 (77%)
Automatic referral refugee resettlement program	0 (0%)	31 (20%)	3 (13%)	34 (16%)
Possible TB contact	1 (2.5%)	3 (2%)	0 (0%)	4 (2%)
Positive TST on immigration	2 (5%)	3 (2%)	1 (4%)	5 (2%)
Abnormal CXR on immigration	0 (0%)	3 (2%)	0 (0%)	3 (1%)
Other	1 (2.5%)	2 (1%)	0 (0%)	2 (1%)
Prior diagnosis				
Primary complex TB	31 (78%)	101 (66%)	18 (75%)	150 (69%)
TB disease (site specific)	4 (10%)	6 (4%)	1 (4%)	11 (5%)
-Pulmonary TB	2 (5%)	6 (4%)	1 (4%)	9 (4%)
-Lymph Node TB	2 (5%)	0 (0%)	0 (0%)	2 (1%)
Latent TB infection	1 (2.5%)	2 (1%)	1 (4%)	4 (2%)
No prior diagnosis	0 (0%)	37 (20%)	3 (12.5%)	40 (19%)
Prior symptoms in country of origin that led to diagnosis of TB disease				
None	13 (33%)	56 (37%)	9 (37.5%)	78 (36%)
Unknown	8 (20%)	30 (20%)	7 (29%)	45 (21%)
Known*	19 (48%)	66 (43%)	8 (33%)	93 (43%)
-Cough	17	57	6	80
-Fever/ headache	9	25	2	36
-Weight loss/ poor appetite	2	17	2	21
-Lymphadenopathy	3	5	1	9
-Cold- or flu-like symptoms	1	6	2	9
-Abdominal pain	1	0	0	1
-Vomiting	1	0	0	1
-Diarrhea	1	0	0	1

*Percentages do not always add up to 100 due to rounding error

Table 2: Comparison between the country of birth and age of immigration of all TBMS referred children in Ontario and those referred to SickKids between November 2012 and June 2016.

	Ontario (n=508)	SickKids (n=216)	p value
Country of birth			
Philippines	393 (77.4%)	157 (72.7%)	0.76
India	55 (10.8%)	29 (13.4%)	0.37
China	8 (1.6%)	0 (0.0%)	0.11
Saudi Arabia	6 (1.2%)	3 (1.4%)	0.53
Nepal	4 (0.8%)	2 (0.9%)	0.58
Other	42 (8.3%)	25 (11.6%)	0.16
Age at immigration/ age at first clinic visit			
0-4	20 (3.9%)	13 (6%)	0.24
5-10	149 (29.3%)	114 (52.8%)	<.0001
11-17	339 (66.7%)	89 (41.2%)	<.0001

Table 3. Predictors of a positive IGRA (Quantiferon-Gold (QFT®))

Characteristic	Quantiferon result		Univariate Analysis		Multiple Logistic Regression	
	NEG	POS	OR (95%CI)	p value	OR (95%CI)	p value
Age at first visit (years)						
≤10	91	10	Reference			
11 to 17	61	14	0.48 (0.20, 1.15)	0.1203		
Continuous (Older)					2.98 (1.24, 8.30)	0.024
Age at treatment (years)						
≤4	76	9	2.81 (1.07, 7.43)	0.0412		
5 to 16	33	11	Reference			
Known TB contact						
NO	138	16	Reference		Reference	
YES	14	8	4.93 (1.79, 13.55)	0.0034	5.97 (2.06, 17.52)	0.001
Abnormal chest X-ray**						
NO	132	20	Reference			
YES	20	4	0.76 (0.23, 2.45)	0.7479		
Prior treatment						
NO	42	4	Reference			
YES	110	20	1.91 (0.61, 5.91)	0.3234		
Total**	152	24				

* On second review

** Only 176 children underwent IGRA testing.

POS = Positive; NEG = negative OR = Odds ratio

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Table 4: Findings on initial SickKids radiographs

	n =	IGRA + (%)
Any abnormality	53	4 (8%)
Abnormal on second review:	31	4 (13%)
Suggestive of TB*		
Intrathoracic Lymphadenopathy	3	1 (25%)
Parenchymal disease	1	0 (0%)
Questionable abnormalities		
Peribronchial thickening	13	1 (8%)
Nodule/vessel	6	1 (17%)
Atelectasis	4	0 (0%)
Other**	4	1 (25%)

 * Using criteria of Graham et al. (2012)

** Other includes: possible pleural thickening (2), question of calcified nodule (1), possible lucencies (1)

Appendix 1: Chest radiographic information from the Immigration Medical Exam (IME) in children who were treated for TB

Available information	All treated patients (n=138)	CXR at time of diagnosis (n=67)
"Abnormal"	51 (37.0%)	38 (56.7%)
Hilar changes	14 (10.1%)	12 (17.9%)
"Primary complex/ Kochs"	13 (9.4%)	6 (9.0%)
Normal	52 (37.7%)	11 (16.4%)
Peribronchial thickening	1 (0.7%)	
Parenchymal/Pneumonia	4 (2.9%)	
Other	3 (2.2%)	

*Other: cyst, blunting of angles

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Appendix 2: Results of review by SickKids radiologist of available chest radiographs taken from the country of origin

Outside Films	n=27
Poor quality	4 (14.8%)
Normal: 2 views	11 (40.7%)
Normal: single view	1 (3.7%)
Nonspecific lower airway inflammation	7 (25.9%)
Airspace disease without lymphadenopathy	2 (7.4%)
Possible bronchiectasis	1 (3.7%)
Intrathoracic lymphadenopathy	1 (3.7%)
Total	27

*Median interval from outside chest radiograph and SickKids chest radiograph was 0.91 years.