Prevalence of latent tuberculosis infection in Syrian refugees to Canada

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Abstract

Objectives Canada has accepted more than 25,000 Syrian refugees fearing persecution in their homeland. Canadian guidelines recommend screening recent refugees from high incidence countries for tuberculosis (TB) and latent TB infection (LTBI). The prevalence of TB in this population is unknown. A refugee clinic in Edmonton presented a unique opportunity to estimate prevalence of TB and LTBI in Syrian refugees arriving in Canada.

Methods In January 2016, 100 consecutive Syrian refugees were screened for TB with clinical assessment and LTBI using QuantiFERON Gold In-Tube assay (QFT-GIT). Patients with positive QFT-GIT were referred to Edmonton Tuberculosis Clinic (ETBC) for evaluation and, if appropriate, offered prophylaxis.

Results No cases of active TB were found. Valid QFT-GIT were measured in 99 of 100 individuals and of these, nine (9%) were positive using a threshold concentration of blood interferon- γ greater than 0.35 IU/L. Eight of the nine patients attended follow-up appointments; of these, seven began LTBI prophylaxis and all seven (78%) completed same.

Conclusion The 9% (95% confidence interval 3–15%) prevalence of LTBI was higher than expected in this population.

Résumé

Objectifs Le Canada a accepté plus de 25 000 réfugiés syriens fuyant la persécution dans leur patrie. Les lignes directrices canadiennes recommandent le dépistage de la tuberculose et de la tuberculose-infection latente (TBIL) chez les réfugiés récents des pays à forte incidence. La prévalence de la tuberculose dans cette population est inconnue. Une clinique pour les réfugiés d'Edmonton a représenté une occasion unique d'estimer la prévalence de la tuberculose et de la TBIL chez les réfugiés syriens arrivant au Canada.

Méthode En janvier 2016, 100 réfugiés syriens de suite ont subi des tests de dépistage de la tuberculose avec évaluation clinique et de dépistage de la TBIL à l'aide du test QuantiFERON Gold In-Tube Assay (QFT-GIT). Les patients séropositifs selon le QFT-GIT ont subi une évaluation à la clinique de tuberculose d'Edmonton (ETBC) et, le cas échéant, se sont fait offrir une prophylaxie.

Résultats Aucun cas de tuberculose active n'a été décelé. Des épreuves QFT-GIT valides ont été réalisées chez 99 personnes sur 100, et neuf d'entre elles (9 %) ont affiché des résultats positifs, soit un seuil de concentration supérieur à 0,35 UI/l selon le test sanguin interféron gamma. Huit patients sur neuf se sont présentés aux rendez-vous de suivi, sept ont commencé un traitement contre la TBIL en prophylaxie, et tous les sept (78 %) l'ont terminé.

Conclusion La prévalence de 9 % (intervalle de confiance de 95 %: 3–15 %) de la TBIL était plus élevée que prévu dans cette population.

Keywords Latent tuberculosis · Tuberculosis · Refugees · Syria

Mots-clés Tuberculose latente · Tuberculose · Réfugiés · Syrie

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Introduction

Tuberculosis (TB) remains a significant factor in global mortality. Although TB decreased dramatically over the twentieth century in Canada, the past decade has not seen any appreciable decline in incidence (Gallant et al. 2014). Re-activation of latent tuberculosis infection (LTBI) in foreign-born individuals now accounts for a majority of TB cases in the country (Public Health Agency of Canada 2015). Further reduction in Canada's TB incidence to meet global elimination goals must address this reservoir of LTBI in migrants (Greenaway et al. 2013; Lönnroth et al. 2015). Treatment for LTBI is broadly considered safe and can reliably prevent TB re-activation (Menzies et al. 2013). All new immigrants to Canada are screened for active but not latent TB as part of the immigration medical examination (IME) mandated by Immigration, Refugees and Citizenship Canada (IRCC) (Immigration Refugees and Citizenship Canada n.d.). Recent expert recommendations are to additionally screen for LTBI in immigrants from certain countries with high incidence of TB (Greenaway et al. 2013; Greenaway et al. 2011).

The Syrian civil war has caused the external relocation of over 4 million individuals since 2011. The Canadian government brought 25,000 refugees displaced by this conflict to Canada over a 3-month period beginning in late 2015 (Citizenship and Immigration Canada 2015). All refugees received an IME in their country of last residence and Canadian Collaboration for Immigrant and Refugee Health (CCIRH) guidelines recommended screening for a number of communicable diseases on arrival (Pottie et al. 2011, 2016). LTBI screening was not included in CCIRH guidelines specific for the initial wave of Syrian refugees to Canada (Pottie et al. 2016). LTBI screening was not initially considered necessary because latest WHO estimates of active TB in Syria were a moderate 19 (6.2–39) per 100,000 (World Health Organization 2016a; Sikora 2016). However, political strife often increases TB incidence in displaced populations (Kimbrough et al. 2012). Refugees, as a subgroup of migrants, often may have elevated rates of TB due to poor nutrition, cramped housing and limited access to healthcare (Kimrough et al. 2012). These factors have been reported to varying degrees in all regional countries hosting Syrian refugees (Citizenship and Immigration Canada 2015).

In Edmonton, Canada, government-sponsored refugees are temporarily housed at the New Canadians Centre, an integrated centre that includes a health clinic, the New Canadians Clinic (NCC). At the clinic, all refugees are offered testing for certain infectious diseases; individuals from high incidence countries are additionally offered testing for LTBI (Rennert-may et al. 2016). QuantiFERON Gold-in-Tube assay (QFT-GIT) testing was added to the health screens of an early cohort of 100 Syrian refugees seen at the NCC (Campbell et al. 2015). This study aims to estimate the

prevalence of LTBI in Syrian refugees to Canada from the results of QFT-GIT screening in this group of government-sponsored refugees at the NCC.

Methods

Government-sponsored refugees to Edmonton are first received at the New Canadians Centre. This centre serves as temporary housing, supplies a settlement counsellor, arranges English classes and provides initial health services at an onsite clinic. Refugees are typically seen within 2 weeks of arrival at the NCC for a nurse-led health check-up. Patients are asked about their health priorities and mental health concerns. Screening for diseases is performed on an opt-out basis (Rennert-may et al. 2016). Routine testing for Syrian refugees included serology for hepatitis B (HBV), hepatitis C (HCV), human immunodeficiency virus (HIV), varicella (VZV), and haemoglobin electrophoresis. For those over 12 years of age, serology for syphilis and urine for gonorrhoea and chlamydia nucleic acid amplification were also performed. Serological testing for *Strongyloides stercoralis*, peripheral blood smears for malaria, and stool microscopy for ova and parasites were not requested at the NCC (Pottie et al. 2016).

At the first clinic visit, individuals were systematically screened for active TB using a detailed symptom inquiry with particular attention to the presence of fever, night sweats, cough persistent for more than 2 weeks, hemoptysis and lymph node swelling. Past history of active TB and bacille Calmette-Guérin (BCG) vaccination status were also sought. Patients determined to have a positive TB symptom screen at the NCC were referred directly to Edmonton Tuberculosis Clinic (ETBC), located offsite, and provided transportation for their first appointment (Fig. 1). Individuals referred to the ETBC clinic through these pathways receive a chest radiograph (CXR), provide three sputa for acid-fast bacilli (AFB) smear and culture and have a consult with an ETBC physician (Rennert-may et al. 2016). The IRCC requires TB follow-up in Canada for patients with an issue on the IME in their pre-arrival country. The issues prompting IRCC referral are either a prior history of TB, chest radiograph (CXR) with findings suspicious for TB or deferred CXR due to pregnancy. Patients with an IRCC referral were also directed to the ETBC for evaluation. Those who had previously deferred CXR for pregnancy that had normal findings in CXR performed at the ETBC were evaluated with symptom screen and subsequent LTBI testing with QFT-GIT similar to the general cohort. Patients with abnormal CXR on IME but active disease excluded by symptoms, new CXR and three sputa were also considered eligible for LTBI testing with QFT-GIT.

In this study, 100 consecutive eligible Syrian refugees seen at the NCC in January 2016 were additionally screened for LTBI. To be considered eligible for this extra screening,

Fig. 1 Pathway of TB care for Syrian refugees arriving in Edmonton

TB - Tuberculosis
 LTBI - Latent tuberculosis
 NCC - New Canadians Clinic
 IRCC - Immigration, Refugees and Citizenship Canada
 CXR - Chest radiograph
 AFB - Acid fast bacilli
 QFT-GIT - QuantiFERON Gold-in-Tube assay

* Symptom inquiry: fever, night sweats, cough >2 weeks, hemoptysis, lymph node swelling

** Not done if already performed as work up for symptoms

*** Unless under TB surveillance because of IRCC referral

patients had to be between 5 and 50 years of age without a history of previous TB disease or treatment and had to have consented to testing. QFT-GIT is not approved for children under 5 years and CCIRH guidelines are to only screen for LTBI in refugees under 50 (Greenaway et al. 2011; American Academy of Pediatrics Red Book 2009). Screening was done using the QFT-GIT as per manufacturer instructions with a positive result defined by interferon- γ concentration greater than 0.35 IU/mL. Blood for this test was drawn at the same time as other serologic screens indicated above. Patients with a negative QFT-GIT received no further TB follow-up unless high-risk radiographic scars, significant immune suppression,

or concerns of active TB were present. Patients with a positive QFT-GIT were referred to ETBC. At the ETBC, they received chest radiograph, provided sputum for AFB smear and culture, and had a consult with a physician. Patients with no positive findings for active tuberculosis but a positive QFT-GIT were offered prophylaxis for LTBI. Patients were offered either 9-month isoniazid (9H), 4-month isoniazid and rifampin (4HR), or 4-month rifampin (4R) depending on patient characteristics, anticipated tolerability, and personal preferences (Rennert-may et al. 2016).

The entire process from the NCC to the ETBC was facilitated by a combination of settlement counsellors fluent in the

refugees' language and by the ready availability of telephonic interpreters. Consent for testing was gained verbally via this translation as well as in writing. Patients were told explicitly that their immigration status was not affected by their participation in either screening or treatment. Parents consented for testing on behalf of their underage children. All medications, consults and interpretation services were provided free of charge to the refugees (Rennert-may et al. 2016). Ethics approval was provided by the University of Alberta Research Ethics Board.

Quantitative statistics included confidence interval (CI) of LTBI prevalence calculated from standard error and 95% level of confidence. Additionally, two-tailed independent *t* tests were performed comparing proportions of LTBI in relation to refugee camp stay, country of departure, gender, age, and IRCC referral. Annual rate of infection (ARI) was calculated for the group as well as the ≥ 25 -year and < 25 -year age cohorts separately: $ARI = 1 - (1 - LTBI \text{ prevalence})^{\left(\frac{1}{\text{mean age}}\right)}$.

Results

All 120 Syrian refugees seen at the NCC in January 2016 were evaluated and 100 of these were eligible and underwent additional LTBI screening with QFT-GIT testing (Figs. 2 and 3). Twenty individuals were excluded on age criteria. All patients had complete intake report forms. No refugees chose to opt out of testing. A valid QFT-GIT test result was achieved in 99/100 (99%) (Table 1). One QFT-GIT was invalid in a child where blood draw was unsuccessful. Individuals were on average seen at the NCC within 10 days of arrival in Canada. No patients reported history of previous TB. Including the 120 individuals seen in January, there were 378 Syrian refugees seen at the NCC over 2016.

The prevalence of LTBI measured by interferon- γ release assay (IGRA) in this sample of Syrian refugees was 9% (95% CI 3–15%) (Table 2). There were no active cases of TB

Fig. 2 Age histogram of Syrian refugees screened for LTBI at the NCC

Fig. 3 Cascade of care

identified during the initial assessment. In QFT-GIT-positive individuals, the median value was 1.98 IU/mL (range 0.50 to 15.30 IU/mL). Older individuals had significantly higher prevalence of LTBI ($p = 0.048$); in the < 25 cohort, the prevalence was 4% and in those ≥ 25 , it was 15%. ARI calculated from the overall average age and prevalence was 0.42%. The ARI of those < 25 and ≥ 25 was approximately equal: 0.39 and 0.44%, respectively. Using a higher threshold for QFT-GIT (e.g., 1.0 IU/mL), the prevalence of LTBI was 7% (7/99). There was no difference in LTBI prevalence between those individuals spending > 2 weeks in a refugee camp and individuals in camps 0–2 weeks ($p = 0.84$). No significant difference between gender and LTBI positivity was observed ($p = 0.40$). The prevalence of LTBI was higher in refugees who stayed in Lebanon (14%) instead of Jordan (6%) but this difference was not statistically significant ($p = 0.18$). Eight of nine patients completed chest radiographs and provided sputum to exclude active TB; seven individuals began prophylaxis (five started 9H, one started 4HR, and another 4R). All seven completed prophylaxis.

Discussion

The prevalence of LTBI measured by IGRA in this sample of Syrian refugees to Canada was 9% (95% CI 3–15%). No individuals in our study were found to have active TB on arrival. To our knowledge, this study represents the first sampling of LTBI in Syrian refugees arriving in a low incidence country since the beginning of the civil war.

The overall ARI calculated in our study was 0.42%: using revised Styblo's rule to estimate TB incidence from ARI

Table 1 Population characteristics of 100 Syrian refugees seen at NCC in January 2016

Characteristics	Values
Age (years, sd)	22 (15)
Gender	—
Male	49 (49%)
Female	51 (51%)
Weight	—
Adults BMI kg/m ² (mean, sd)	27 (6)
Children (< 18 years) mean growth percentile (mean, sd)	47 (26)
Underweight individuals	—
Adults BMI kg/m ² < 18.5	1 (2.2%)
Children growth percentile < 5%	3 (6.8%)
Diabetes mellitus (self-report)	1 (1%)
Tobacco use (> 18 years)	17 (34%)
Stay in refugee camp (> 2 weeks)	30 (30%) median 30 (range: 3–208)
Country of departure	—
Lebanon	35 (35%)
Jordan	65 (65%)
Turkey	0 (0%)
Time from Canadian arrival to NCC visit (days, sd)	9.9 (4.5)
Total IRCC referral for TB	4 (4%)
Referral for history of TB	0 (0%)
Referral for high risk lung scar	0 (0%)
Referral for deferred medical exam due to pregnancy	4 (4%)
BCG status	—
Vaccinated (self-report or scar noted)	62 (62%)
Undetermined (unsure self-report, scar not noted)	33 (33%)
Unvaccinated (self-report and scar not noted)	5 (5%)
Reported history of previous TB	0 (0%)
Confirmed active TB	0 (0%)
QFT-GIT	—
Valid	99 (99%)
Invalid	1 (1%)

suggests that TB incidence among the source population of Syrian refugees to be approximately 40 cases per 100,000 (Styblo 1980). LTBI prevalence was significantly higher in older individuals, as expected because of more time for potential exposure with more years lived and a reflection of a higher prevalence of TB in Syria in past decades (Pareek et al. 2016; Houben and Dodd 2016; Cookson et al. 2015). However, there were not significant differences in the ARI between the older and younger cohorts as anticipated if LTBI incidence had increased since the beginning of hostilities (Barr and Menzies 1994). This study did not demonstrate significant differences in LTBI between genders as has been found in other high risk populations (Ting et al. 2014). The Jordanian National TB Program found high rates of TB cases in refugees had significantly increased the TB incidence of Jordan (Cookson et al. 2015). The influx of Syrian refugees to Lebanon has also been linked with a recent rise in TB

incidence in that country (Araj et al. 2016). Our measured LTBI prevalence is comparable to other IGRA-alone screening programs for refugees to low incidence countries (Campbell et al. 2015). Refugees to the USA from post-war Iraq (67 cases per 100,000) had 14.1% LTBI measured by IGRA screening (Centers for Disease Control and Prevention 2010; World Health Organization 2016b). A study of undocumented immigrants in Swiss healthcare centres measured 19% LTBI by IGRA (Bodenmann et al. 2009). An extensive study of all refugees to San Diego County using IGRA alone found a 21% LTBI (Bennett et al. 2014). The prevalence of LTBI in the mideast region has recently been estimated to be 16.3 (95% CI 13.4–20.5) (Houben and Dodd 2016).

The NCC, a single comprehensive centre for government-sponsored refugees, made Edmonton uniquely suited for this study. The existing physical and social infrastructure of the

Table 2 IGRA positivity (>0.35 IU/mL) in 99 IGRAs completed in Syrian refugees at the NCC

	Value N (%)	P value	95% CI
Total cohort	9 (9.1%)	–	3–15%
Age			
<25 years old	2 (3.8%)	0.048	–
≥25 years old	7 (15%)		
Gender			
Male	5 (10%)	0.40	–
Female	4 (7.8%)		
Country of departure			
Lebanon	5 (14%)	0.18	–
Jordan	4 (6.0%)		
Refugee camp stay			
0–2 weeks	3 (33%)	0.84	–
>2 weeks	6 (30%)		
IRCC referral			
Referral	0 (0.0%)	0.52	–
No referral	9 (9.5%)		

centre facilitated LTBI screening systematically with no additional staff required and relatively small additional expense. The IGRA-alone approach made screening this condensed cohort more feasible than other multistep options. Using a single blood test taken at the same time as routine screening while also addressing other patient health concerns appeared to lower drop-offs in the cascade of care. 99/100 complete test results in eligible individuals, as well as seven of nine eligible individuals starting and completing prophylaxis compares very favourably to rates reported in the literature (Greenaway et al. 2013; Bettache et al. 2012). IGRA has a greater specificity than TST (tuberculin skin test) in populations with high BCG vaccinations such as Syria, and recent consensus guidelines suggest this is the standard of care in this population (World Health Organization 2016c; Lewinsohn et al. 2017).

This study was limited by sample size. A primary reason was that Edmonton was a relatively minor destination for refugees, and operating within the NCC, focused on government-sponsored refugees, further limited numbers. The small sample size limited the precision in determining the prevalence in the whole cohort, as well as determining differences in factors relating to IGRA positivity, including country of departure, stay in refugee camp and gender. A main advantage of this study was that 100 unselected refugees at the NCC could be measured, limiting inclusion bias.

The 9% (95% CI 3–15%) prevalence of LTBI was higher than expected for this population. However, we feel that this prevalence is not high enough to indicate change to the current CCIRH guidelines for this cohort for several reasons. The found prevalence was not higher than the rate of LTBI found

in other refugee health centres, as discussed previously. The cost effectiveness of a screening program in this specific group is unknown. Although Canada has fulfilled its modified goal of 25,000 Syrian refugees, it is expected that up to 10,000 more Syrian refugees may arrive in the next several years. TB incidence in crisis populations often changes rapidly, so the prevalence likely will not remain static (Kimbrough et al. 2012). We suggest sampling a subsequent cohort in 1 to 2 years' time to re-evaluate the need for a screening program for future arrivals.

Compliance with ethical standards

Ethics approval was provided by the University of Alberta Research Ethics Board.

Conflict of interest The authors declare that they have no conflict of interest.

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