Impact of interferon-γ release assay on the latent tuberculosis cascade of care: a population-based study

To the Editor:

Latent tuberculosis infection (LTBI) screening and treatment can have a significant impact on TB incidence if a high proportion of at-risk people successfully complete an adequate course of LTBI therapy [1–5]. Patient loss and dropouts occur at multiple points along the LTBI screening and treatment process, ultimately resulting in a minority of high-risk people completing LTBI therapy. To understand the public health impact of new screening and treatment strategies, we need to evaluate the impact of various interventions on the LTBI cascade of care.

Interferon-γ release assay (IGRA) guidelines were introduced in British Columbia (Canada) in 2010 with implementation of both QuantiFERON-TB Gold In-Tube test (QFT; Qiagen, Germantown, MD, USA) and T-SPOT.*TB* test (T-Spot; Oxford Immunotec, Marlborough, MA, USA) by the British Columbia Centre for Disease Control (BCCDC) Public Health Laboratory. Provincial recommendations include the use of IGRAs as an optional test in tuberculin skin test (TST)-positive people with bacille Calmette–Guerin (BCG) vaccination history and lower risk of TB exposure and/or progression to active TB [6]. This approach uses IGRAs as a "confirmatory" test in people with positive TSTs and has been described as the "sequential approach" to LTBI testing. Sequential LTBI testing is used in several low-incidence regions, and is presented as an option in some situations by the European Centre for Disease Prevention and Control, the National Institute for Health and Care Excellence (United Kingdom), and Canadian TB guidelines [5–7]. We performed this study to examine the impact of a sequential TST–IGRA testing on LTBI outcomes in publicly funded TB clinics. We sought to compare sequential testing with the historical TST-only strategy using in routine clinical data.

British Columbia is a Canadian province with an active TB incidence of 6.3 per 100 000 people [7]. The majority of TB cases (70%) are diagnosed in persons born outside of Canada, many of whom are from high TB incidence countries with potential BCG vaccination history [8, 9]. From the BCCDC provincial TB registry, we identified all individuals with a new positive (⩾10 mm) TST assessed at BCCDC clinics in 2004–2008 (the pre-IGRA period) and 2010–2014 (the post-IGRA period). No age-based exclusions were made. We excluded individuals with a first positive TST in 2009, as this was the year of IGRA rollout. A subanalysis was performed using the same two periods, but including only individuals with a history of TB contact or at least one comorbidity placing them at higher risk for active TB (HIV, silicosis, transplant or renal failure) [10]. Active TB incidence rates were calculated from the BCCDC provincial TB registry.

We extracted demographic and clinical characteristics at time of first positive TST, along with subsequent LTBI testing and treatment information. Both cohorts were followed for a maximum of 53 months. TST-positive individuals diagnosed with active TB within 30 days of first positive TST, or with a TST performed in active TB diagnostic workup were excluded.

We calculated frequencies of clinical and demographic characteristics and stratified by year and presence of an IGRA test result. IGRA results were classified as positive or negative according to manufacturer's standards, with equivocal results considered "negative" for the purposes of this study. Primary outcomes were the proportion of individuals starting LTBI treatment, the proportion of those starting who completed LTBI treatment and the incidence rate of active TB per 100 000 person-years follow-up. Between-group comparisons were performed using Chi-squared test of proportions using R (V3.2.3; www.r-project.org).

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To control for cohort changes over time, we compared TST-positive individuals with sequential IGRA testing in the post-IGRA period (controls) to TST-positive individuals in the pre-IGRA period (cases), using propensity score matching. The model included sex, age group, foreign birth, diabetes, HIV, cancer, immunosuppressive medications, renal failure, substance abuse, TST induration, BCG history and contact history. We matched on the propensity score using nearest-neighbour matching, with a ratio of 2:1 (controls: cases), sampling with replacement and a calliper width of 0.2 of the standard deviation of the logit of the propensity score using the R MatchIt package (V2.4-21).

22 748 patients with positive TSTs were included for analysis; 12 406 patients had a first positive TST in 2004–2008 and 10 342 had their first positive TST in 2010–2014. Of those with a first positive TST in 2010–2014, 6783 patients had TST only and 3559 patients had a TST and follow-up IGRA. The majority of IGRA tests (96%) were QFT and the remaining 4% were T-Spot.

Patients in the post-IGRA period (2010–2014) were older, more likely to be a contact, BCG vaccinated, foreign-born and more likely to have comorbidities than the pre-IGRA cohort (2004–2008). Those receiving IGRA testing in the post-IGRA period were more likely to be foreign-born (88.4% *versus* 82.7%), a close (17.3% *versus* 11.3%) or casual (16.0% *versus* 7.9%) contact, and have comorbid disease (12.0% *versus* 9.3%) than those receiving TST only in the post-IGRA period.

Overall, a lower proportion of clients with TST ⩾10 mm started LTBI therapy in the post-IGRA period (20.7%, n=2144) compared with the pre-IGRA period (29.8%, n=3699) (Chi-squared 243.9, p<0.001) (table 1).

Within the post-IGRA period, more IGRA-positive patients started therapy (63.0%, n=862) than those with TST only (17.9%, n=1216) (Chi-squared 1216.6, df=1, p<0.001) and a higher proportion of IGRA-positive individuals completed therapy (45.0%, n=616) compared with TST-positive only (13.5%, n=919) (Chi-squared 737.1, df=1, p<0.001). 2190 patients were TST-positive and IGRA-negative, with only 66 (3.0%) and 30 (1.4%) individuals starting and completing LTBI therapy, respectively.

Active TB incidence was similar in both the pre-IGRA period (61.2 per 100 000 person-years) and post-IGRA period (58.5 per 100 000 person-years) (table 1). No cases of active TB developed in those with a negative IGRA during the follow-up period.

In subgroup analysis of high-risk clients, a total of 6185 individuals were identified. Similar patterns of therapy initiation and completion were noted. We did not detect any difference in outcomes in matched-propensity score analysis.

TABLE 1 Latent tuberculosis infection (LTBI) treatment and active TB outcomes of individuals testing positive in the tuberculin skin test (TST$^+$) in British Columbia Centre for Disease Control clinics, by year of first positive TST

	2004–2008	2010–2014			
	All TST$^+$	All TST$^+$	TST$^+$ only	TST$^+$ and IGRA$^+$	TST$^+$ and IGRA$^-$
Population	12 406	10 342	6783	1369	2190
LTBI treatment					
Started LTBI treatment (TST$^+$)	3699 (29.8)[¶]	2144 (20.7)[¶]	1216 (17.9)[f]	862 (63.0)[f]	66 (3.0)
Completed LTBI treatment (TST$^+$)	2158 (17.4)[+]	1565 (15.1)[+]	919 (13.5)[##]	616 (45.0)[##]	30 (1.4)
Completed LTBI treatment (started treatment)	2158 (58.3)[§]	1565 (73.0)[§]	919 (75.6)[¶¶]	616 (71.5)[¶¶]	30 (45.5)
Active TB					
Active TB cases in follow-up	22	19	17	2	0
Length of follow-up person-years	35 946	32 479	22 227	4019	6233
Incidence of active TB per 10^5 person-years	61.2 (35.6–86.8)	58.5 (32.2–84.8)	76.5 (40.1–112.8)	49.8 (0–118.7)	0
Active TB cases, untreated[#]	18	16	14	2	0
Follow-up, untreated, person-years	25 244	19 518	18 073	1445	6015
Incidence untreated active TB per 10^5 person-years	71.3 (38.3–104.2)	82.0 (41.8–122.1)	77.4 (36.9–118.0)	138.4 (0–330.2)	0

Data are presented as n, n (%) or rate (95% CI). IGRA: interferon-γ release assay [#]: any individuals in the study cohort who did not initiate therapy; [¶]: proportion of TST$^+$ individuals that started therapy pre-IGRA *versus* post-IGRA (Chi-squared 243.9, df=1, p<0.001); [+]: proportion of all TST$^+$ individuals who started that completed therapy pre-IGRA *versus* post-IGRA (Chi-squared 21.1, df=1, p<0.001); [§]: proportion of all individuals that completed LTBI therapy pre-IGRA *versus* post-IGRA (Chi-squared 126.1, df=1, p<0.001); [f]: proportion of TST$^+$ only *versus* TST$^+$/IGRA individuals that started LTBI therapy in 2010–2014 (Chi-squared 1216.6, df=1, p<0.001); [##]: proportion of TST$^+$ only *versus* TST$^+$/IGRA individuals that completed LTBI therapy in 2010–2014 (Chi-squared 737.1, df=1, p<0.001); [¶¶]: proportion of TST$^+$ only individuals who started LTBI therapy *versus* TST$^+$/IGRA individuals who started LTBI therapy, who completed LTBI therapy in 2010–2014 (Chi-squared 4.42, df=1, p =0.04).

In this study, physician-directed supplementary IGRA testing reduced the number of TST-positive individuals exposed to LTBI therapy without impacting active TB incidence. Similar findings have been shown in Israel and South Korea [11, 12]. Sequential TST–IGRA testing may result in significant improvement in the efficiency of LTBI screening and treatment programmes by avoiding unnecessary exposure to LTBI therapy in low-risk individuals while increasing the proportion completing LTBI therapy.

We cannot be certain that a subtle shift in clinic protocols and healthcare worker and client attitudes did not significantly influence the LTBI care continuum in the pre- and post-IGRA periods. Certainly, the completion rates in the post-IGRA period appear to be higher in both the TST- and TST–IGRA-positive groups. This could reflect the impact of IGRA screening and/or a shift in physician or client attitudes and clinic protocols; however, we believe that this is unlikely, given the large discrepancies in uptake in the TST-positive, TST–IGRA-positive and TST–IGRA-negative groups in the post-IGRA period.

In conclusion, our findings suggest that clinician-directed sequential TST–IGRA testing may reduce the number of people starting LTBI therapy without increasing active TB incidence. This sequential approach may be particularly relevant in countries with a large foreign-born population due to the effect of BCG vaccination on TST interpretation. We believe that confirmatory IGRA testing can focus clinical resources on those with higher risk of progression to active TB by avoiding LTBI treatment in low-risk individuals. Comparisons between an IGRA-only and sequential testing are needed to delineate the most appropriate approach to LTBI screening and treatment in low-incidence settings.

David Z. Roth[1,2], Lisa A. Ronald[2,3], Daphne Ling[4], Leslie Y. Chiang[2], Victoria J. Cook[2,3], Muhammad G. Morshed[5,6] and James C. Johnston[2,3]

[1]School of Public and Population Health, University of British Columbia, Vancouver, BC, Canada. [2]BC Centre for Disease Control, Vancouver, BC, Canada. [3]Division of Respiratory Medicine, University of British Columbia, Vancouver, BC, Canada. [4]Centre for Health Evaluation and Outcome Sciences, Vancouver, BC, Canada. [5]Department of Pathology and Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada. [6]BC Centre for Disease Control Public Health Laboratory Medicine, University of British Columbia, Vancouver, BC, Canada.

Correspondence: James Johnston, Provincial Tuberculosis Services, BC Centre for Disease Control, 655 West 12th Avenue, Vancouver, BC, V5Z 4R4 Canada . E-mail: James.Johnston@bccdc.ca

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