Title

Comparison of three tests for latent tuberculosis infection in high-risk people in the USA: an observational cohort study.

Journal

The Lancet Infectious Diseases, 22(1)

Authors

Ho, Christine

Feng, Pei-Jean

Narita, Masahiro

et al.

Publication Date

2022

DOI

10.1016/S1473-3099(21)00145-6

Peer reviewed

HHS Public Access

Author manuscript

Lancet Infect Dis. Author manuscript; available in PMC 2023 January 01.

Published in final edited form as:

Lancet Infect Dis. 2022 January ; 22(1): 85–96. doi:10.1016/S1473-3099(21)00145-6.

Comparison of three tests for latent tuberculosis infection in high-risk people in the USA: an observational cohort study

Christine S Ho,
Division of Tuberculosis Elimination, US Centers for Disease Control and Prevention, Atlanta, GA, USA

Pei-Jean I Feng,
Division of Tuberculosis Elimination, US Centers for Disease Control and Prevention, Atlanta, GA, USA

Masahiro Narita,
TB Control Program, Public Health—Seattle and King County, Seattle, WA, USA

Jason E Stout,
Division of Infectious Diseases and International Health, Department of Medicine, Duke University Medical Center, Durham, NC, USA

Michael Chen,
Division of Tuberculosis Elimination, US Centers for Disease Control and Prevention, Atlanta, GA, USA

Lisa Pascopella,
Tuberculosis Control Branch, Division of Communicable Disease Control, Center for Infectious Diseases, California Department of Public Health, Richmond, CA, USA

*Tuberculosis Epidemiologic Studies Consortium
California Department of Public Health, Richmond Jennifer Flood, Lisa Pascopella (includes San Francisco Department of Public Health, Julie Higashi; County of San Diego Health and Human Services Agency, Kathleen Moser, Marisa Moore [CDC]; and University of California San Diego Antiviral Research Center, Richard Garfein, Constance Benson); *Denver (CO) Health and Hospital Authority* Robert Belknap, Randall Reves; *Duke University (Durham, NC)* Jason Stout (includes Carolinas Medical Center [Charlotte, NC], Amina Ahmed; Vanderbilt University Medical Center [Nashville, TN], Timothy Sterling, April Pettit; Wake County Human Services [Raleigh, NC], Jason Stout); *Emory University (Atlanta)* Henry M Blumberg (includes DeKalb County Board of Health, Alawode Oladele); *University of Florida (Gainesville)* Michael Lauzardo, Marie Nancy Séraphin; *Hawaii Department of Health (Honolulu)* Richard Brostrom; *Maricopa County Department of Public Health (Phoenix, AZ)* Renuka Khurana; *Maryland Department of Health (Baltimore)*, Wendy Cronin, Susan Dorman; *Public Health—Seattle and King County* Masahiro Narita, David Horne; *University of North Texas Health Science Center (Fort Worth)* Thaddeus Miller.

Correspondence to: Dr Christine S Ho, US Embassy, Shantipath, New Delhi, India, gtb9@cdc.gov.

Contributors

CSH, DJK, JES, and MN conceived the study. MC provided statistical supported and performed the analysis. MN, JES, LP, RR, and RG provided input to the conception and design of the study. All authors were involved in interpretation of the data and writing or editing of the manuscript. CSH and DJK wrote the first and final drafts. P-JIF and DJK had access to the database and verified its accuracy. All authors reviewed and approved the final draft. All study collaborators had full access to all data in the study; the corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

A deidentified and restricted dataset, with accompanying data dictionary, can be provided by approved request after completion of a data use agreement, by emailing tbinfo@cdc.gov with the subject line Attention: TBESC.

See **Online** for appendix

Richard Garfein,
Division of Global Public Health, School of Medicine, University of California, San Diego, CA, USA

Randall Reves,
Denver Health and Hospital Authority, Denver, CO, USA

Dolly J Katz,
Division of Tuberculosis Elimination, US Centers for Disease Control and Prevention, Atlanta, GA, USA

Tuberculosis Epidemiologic Studies Consortium*

Summary

Background—Treatment of latent tuberculosis infection is an important strategy to prevent tuberculosis disease. In the USA, three tests are used to identify latent tuberculosis infection: the tuberculin skin test (TST) and two IFN-γ release assays (T-SPOT.*TB* and QuantiFERON). To our knowledge, few large studies have compared all three tests among people at high risk of latent tuberculosis infection or progression to tuberculosis disease. We aimed to assess test agreement between IFN-γ release assays and TST to provide guidance on their use in important risk groups.

Methods—In this observational cohort study, we enrolled participants at high risk of latent tuberculosis infection or progression to tuberculosis disease at ten US sites with 18 affiliated clinics, including close contacts of infectious tuberculosis cases, people born in countries whose populations in the USA have high (≥100 cases per 100 000 people) or moderate (10–99 cases per 100 000 people) tuberculosis incidence, and people with HIV. Participants were interviewed about demographics and medical risk factors, and all three tests were administered to each participant. The primary endpoints for this study were the proportions of positive test results by test type stratified by risk group and test concordance by risk group for participants with valid results for all three test types. The study is registered at ClinicalTrials.gov, NCT01622140.

Findings—Between July 12, 2012, and May 5, 2017, 26 292 people were approached and 22 131 (84·2%) were enrolled in the study. Data from 21 846 (98·7%) participants were available for analysis, including 3790 (17·3%) born in the USA and 18 023 (82·5%) born outside the USA. Among non-US-born participants overall, the RR comparing the proportions of TST-positive results (7476 [43·2%] of 17 306 participants) to QuantiFERON-positive results (4732 [26·5%] of 17 882 participants) was 1·6 (95% CI 1·6–1·7). The risk ratio (RR) for the comparison with the proportion of T-SPOT.*TB*-positive results (3693 [21·6%] of 17 118 participants) was 2·0 (95% CI 1·9–2·1). US-born participants had less variation in the proportions of positive results across all tests. The RRs for the proportion of TST-positive results (391 [10·9%] of 3575 participants) compared with the proportion of QuantiFERON-positive results (445 [12·0%] of 3693 participants) and T-SPOT.*TB*-positive results (295 [8·1%] of 3638 participants) were 0·9 (95% CI 0·8–1·0) and 1·3 (1·2–1·6), respectively. 20 149 (91·0%) of 21 846 participants had results for all three tests, including 16 712 (76%) non-US-born participants. Discordance between TST and IFN-γ release assay results varied by age among non-US-born participants and was greatest among the 848 non-US-born children younger than 5 years. 204 (87·2%) of 234 non-US-born children younger than 5 years with at least one positive test were TST-positive and IFN-γ release assay-negative. The proportion of non-US-born participants who were TST-negative

but IFN-γ release assay-positive ranged from one (0·5%) of 199 children younger than 2 years to 86 (14·5%) of 594 participants aged 65 years and older (p_{trend}<0·0001). Test agreement was higher between the two IFN-γ release assays than between TST and either IFN-γ release assay, regardless of birthplace. κ agreement was particularly low between TST and IFN-γ release assays in non-US-born children younger than 5 years.

Interpretation—Our findings support the preferential use of IFN-γ release assays for the diagnosis of latent tuberculosis in high-risk populations, especially in very young and older people born outside the USA.

Funding—US Centers for Disease Control and Prevention.

Introduction

Treatment of latent tuberculosis infection is an important strategy to prevent tuberculosis disease. People with latent tuberculosis infection are asymptomatic and non-infectious, but harbour *Mycobacterium tuberculosis* bacteria, and some risk progression to tuberculosis disease unless they are diagnosed and treated. Based on the molecular epidemiology of *M tuberculosis* strains, more than 80% of tuberculosis cases in the USA arise not from recent exposure to people with tuberculosis, but from reactivation of longstanding untreated latent tuberculosis infection. Progress towards tuberculosis elimination in the USA—defined as less than one case per million people—will depend largely on treating people with latent tuberculosis infection.[1]

Effective targeting of latent tuberculosis infection treatment requires sensitive, specific tests for infection. The US Food and Drug Administration (FDA) has approved three diagnostic tests: the tuberculin skin test (TST) and two IFN-γ release assays—T-SPOT.*TB* (Oxford Immunotec; Oxford, UK) and QuantiFERON (Qiagen Diagnostics; Hamburg, Germany). These are all indirect tests that measure the immunological response to previous infection with *M tuberculosis*.[2] Thus, there is no reference standard or gold-standard test for latent tuberculosis infection. The tests have different performance characteristics and operational advantages and disadvantages.

TST is inexpensive and well characterised, but requires two visits, one for placement and another to assess the response. Measurement of the response—the size of a skin induration—is subject to misclassification.[3] TST can cross-react with non-tuberculous mycobacteria and with the BCG anti-tuberculosis vaccine, routinely given to neonates in many countries outside the USA, and sometimes to older children as a booster shot.[4]

IFN-γ release assays use blood samples collected at a single visit that a laboratory must process within a required timeframe. Although more expensive than TST, IFN-γ release assays might be more cost-effective, particularly in specific high-risk groups.[5] IFN-γ release assays have greater specificity in BCG-vaccinated populations because they do not cross-react with BCG antigens. This makes IFN-γ release assays attractive alternatives to TST for non-US-born people, who have an estimated latent tuberculosis prevalence of 20%, compared with 1·5% for US-born residents.[4,6] However, IFN-γ release assays have their own limitations in reproducibility and variability.[7]

Clinical practice guidelines for latent tuberculosis infection testing were jointly published in 2017 by the US Centers for Disease Control and Prevention (CDC), American Thoracic Society, and Infectious Diseases Society of America. The guidelines recommend IFN-γ release assays over TST in people aged 5 years and older who are likely to be infected with *M tuberculosis*, have low to intermediate risk for progression to tuberculosis, and have a history of BCG vaccination or are unlikely to return for a TST reading. The guidelines suggest that TST should be used in healthy children younger than 5 years. However, most of these recommendations are conditional, based on very low to moderate quality evidence.[8] Few large US-based studies have compared all three tests in high-risk populations, and questions remain about their advantages and disadvantages in specific populations.[4,9]

The Tuberculosis Epidemiologic Studies Consortium (TBESC) is a CDC-funded collaboration with academic and public health partners across the USA.[10] TBESC conducts studies to improve the diagnosis and treatment of latent tuberculosis infection. Beginning in July, 2012, TBESC enrolled a prospective cohort of people at high risk for latent tuberculosis infection or progression to tuberculosis disease, tested them with all three latent tuberculosis infection tests, and followed them up for development of tuberculosis disease. We aimed to evaluate the agreement between the TST and the two commercially available IFN-γ release assays and determine the ability of each test to predict progression to tuberculosis disease, overall and in important subgroups. We aimed to assess concordance and discordance between IFN-γ release assays and TST to provide guidance to clinicians on appropriate use of these tests in important risk groups.

Methods

Study design and population

We did an observational cohort study of people at high risk for latent tuberculosis infection or progression to tuberculosis disease who were tested for latent tuberculosis infection at study entry and followed up for development of tuberculosis disease for 2 years after enrolment and by state registry matches through to the end of the observation period in Nov 15, 2020. Participants were enrolled at 18 TBESC-affiliated clinics from ten sites across the USA that served people at high risk for latent tuberculosis infection or progression to tuberculosis disease, which included tuberculosis clinics, student health clinics, refugee programmes, clinics for homeless or HIV-infected people, and clinics with large proportions of non-US-born patients (appendix p 1). People eligible for enrolment were close contacts of people with infectious tuberculosis, people from countries whose populations in the USA have high (≥100 cases per 100 000 people) tuberculosis incidence (appendix p 2),[11] recent arrivals (≤5 years) from countries whose populations in the USA have moderate (10–99 cases per 100 000 people) tuberculosis incidence (appendix p 3),[11] visitors (≥30 days) in the previous 5 years to countries whose populations in the USA have high tuberculosis incidence, people living with HIV, or members of local populations with documented latent tuberculosis infection prevalence of 25% or greater (homeless people [two sites] or people born in countries with moderate rates of tuberculosis who had arrived in the USA >5 years previously [from Mexico at two sites, and from Mexico and El Salvador at one site]). Exclusion criteria were history of anaphylactic reaction to tuberculin, current treatment for

tuberculosis disease or latent tuberculosis infection, foster children, or plans to leave the USA in less than 2 years. Records were excluded from this analysis if participants were diagnosed with tuberculosis during enrolment, were contacts of cases with negative *M tuberculosis* test results, or had no analysable test results. Each site was required to provide a detailed implementation plan that included descriptions of how potential participants would be identified. This plan varied from site to site, and depended partly on the clinic layout and partly on the type of clinic. For example, if recruitment was in a refugee clinic, almost every person at the clinic would be eligible to be approached.

The study protocol and amendments were approved by the CDC institutional review board (IRB), which oversaw the overall ethical conduct of the study. IRBs at each site either approved the protocol and amendments or signed authorisation agreements to rely on the CDC IRB. All participants provided written informed consent, assent, or (for people aged <18 years) had written parental or guardian permission.

Procedures

Interviewers used a standardised questionnaire to collect demographic, epidemiological, and medical risk factor information, and latent tuberculosis infection and tuberculosis treatment history. Each participant had blood drawn simultaneously for the two IFN-γ release assays according to the manufacturers' handling and processing procedures, followed by TST placement on the same day with a result read 44–76 h later. Previous TST results were accepted for people referred to the clinics for evaluation of positive TSTs if the TST was administered and read by trained staff at a qualified facility no more than 14 days before the date of consent. Previous IFN-γ release assay results were not accepted. All test results were shared with providers and participants.

All but one site sent T-SPOT.*TB* samples to the Oxford Immunotec central processing facility in Memphis (TN, USA). The Hawaii Department of Health, which could not ship samples within the required time limits (within 32 h of blood draw), processed them onsite beginning on Oct 16, 2013, after training and quality assurance testing from Oxford Immunotec. Almost all missing T-SPOT.*TB* results are from the Hawaii site during the first 15 months of enrolment.

Test results were interpreted according to national and manufacturers' published guidelines. For TST measurements, an induration of at least 5 mm was considered positive for recent contacts of people with infectious tuberculosis disease, people with fibrotic changes on chest radiographs, people with HIV, and people with other immunosuppressive conditions. An induration of at least 10 mm was considered positive for all other participants.[8] For QuantiFERON test results, the manufacturer's indicated cutoff of more than 0·35 IU/mL was considered positive.

A positive T-SPOT.*TB* test result is defined differently in the USA and internationally. The FDA-approved definition is at least eight spots; five, six, and seven spots are borderline, with retesting recommended. The international definition is at least six spots, with no borderline range. For the main analysis, we used the US definition, and classified borderline results

as negative. We did a sensitivity analysis using the international cutoff. We did not retest borderline results because the study protocol predated FDA guidelines on the subject.

Participants would not have three usable results if they did not return for TST readings, blood samples were not processed within the time limits (within 16 h of blood draw for QuantiFERON and within 32 h of blood draw for T-SPOT.*TB*), results were invalid, or they were enrolled early by the Hawaii Department of Health.

Outcomes

For this study, the outcome was a positive or negative result on one or more latent tuberculosis infection tests at the time of study enrolment. We compared the proportions of US-born and non-US-born participants who were positive by TST, QuantiFERON, and T-SPOT.*TB* individually and in combination, and stratified by age group (<5 years, 5–9 years, 10–14 years, 15–24 years, 25–44 years, 45–64 years, and ≥65 years). We also assessed positivity proportions by other risk groups, as follows: close contacts, homeless people, and people with HIV. The primary endpoints for this study were the proportion of positive test results by test type stratified by risk group and test concordance by risk group, for participants with valid results for all three test types. At the time of writing, data were not finalised on number of incident cases of tuberculosis stratified by test type; these data will be reported separately.

Statistical analysis

Power calculations were based on site projections of the numbers of participants they could enrol. The power calculations estimated the number of cases of tuberculosis disease needed to detect differences in progression rates between participants with positive TST results versus those with positive IFN-γ release assay results; results for this calculation will be reported separately. The power calculations included estimates of the proportions of the study participants who would have a positive result by any diagnostic test (23·4%) and, among those positive results, the proportions who would have positive TST and positive IFN-γ release assay results (43·3%), positive TST and negative IFN-γ release assay results (40·1%), and negative TST and positive IFN-γ release assay results (16·6%).[12]

Statistics on demographic and risk characteristics were calculated for all participants. The proportion who were positive for each test was defined as the number of participants with a positive test result divided by the total number of participants with a result for that test. Positive TST results from referrals were excluded from the calculation of the proportion of positive TST results. We calculated risk ratios (RRs) and 95% CIs for comparisons of proportions. We used the Cochran-Armitage trend test to examine the association of age categories with test results. Test agreement was evaluated with percentage concordance between TST, QuantiFERON, and T-SPOT. *TB* pairs, and with Cohen's κ. We also compared TST with combined IFN-γ release assay results when the result was considered positive if either or both IFN-γ release assays were positive, and negative if both were negative. Only participants who had results for all three tests were included in test combination analyses.

All analyses were done using SAS version 9.4. The study is registered at ClinicalTrials.gov, NCT01622140.

Role of the funding source

Decisions about study design and data collection, analysis, and interpretation were made by consortium members, including CDC principal investigators and epidemiologists. CDC scientific directors reviewed the final report before submission.

Results

Between July 12, 2012, and May 5, 2017, 26 292 people were approached and 22 131 (84·2%) were enrolled in the study. Data from 21 846 (98·7%) participants were available for analysis. 20 149 (91·0%) participants had results for all three tests (figure 1).

The 21 846 participants included 3790 (17·3%) born in the USA and 18 023 (82·5%) born outside the USA (table 1). 33 (0·2%) participants did not have information on birthplace and 170 (0·8%) were missing age data. 10 639 (48·7%) of 21 846 participants were female, of whom 361 (3·4%) were pregnant. The median participant age was 31 years (IQR 19–45; range 7 weeks to 101 years), with 962 (4·4%) participants younger than 5 years, 234 (1·1%) younger than 2 years, and 754 (3·5%) aged 65 years or older. 887 (92·2%) of 962 children younger than 5 years were born outside the USA. The top ten countries of birth were as follows: the USA (3790 [17·3%] participants), Myanmar (2651 [14·7%]), Philippines (2306 [12·8%]), Bhutan (1183 [6·6%]), Iraq (1080 [6·0%]), Mexico (1031 [5·7%]), Nepal (883 [4·9%]), Somalia (652 [3·6%]), Honduras (523 [2·9%]), and El Salvador (475 [2·6%]). Racial or ethnic identifications included 2081 (9·5%) White or Caucasian participants, 6527 (29·9%) Asian participants, 4545 (20·8%) Black or African American participants, and 2596 (11·9%) Hispanic or Latino participants. 2091 (9·6%) of 21 846 participants were close contacts of infectious tuberculosis cases, including 302 (94·7%) of the 319 US-born children younger than 15 years. US-born participants were more likely than non-US-born participants to be close contacts of infectious tuberculosis cases, have HIV infection, or report histories of homelessness, incarceration, or residence in long-term care or drug treatment facilities. The proportion of participants enrolled by clinic ranged from 3458 (15·8%) of 21 846 participants in DeKalb County, GA, to 61 (0·3%) in Miami-Dade County, FL, and 60 (0·3%) in Montgomery County, MD (appendix p 1).

The proportions of single test positive results varied by birthplace, age, and risk group (tables 2, 3). Non-US-born participants had substantially higher proportions of positive results than did US-born participants for any test, overall and by risk groups (table 2). Among non-US-born participants overall, the RR comparing the proportions of TST-positive results (7476 [43·2%] of 17 306 participants) to QuantiFERON-positive results (4732 [26·5%] of 17 882) was 1·6 (95% CI 1·6–1·7). The RR for the comparison with the proportion of T-SPOT.*TB*-positive results (3693 [21·6%] of 17 118 participants) was 2·0 (95% CI 1·9–2·1). US-born participants had less variation in the proportions of positive results across all tests. The RRs for the proportion of TST-positive results (391 [10·9%] of 3575 participants) compared with the proportion of QuantiFERON-positive results (445 [12·0%] of 3693) and T-SPOT.*TB*-positive results (295 [8·1%] of 3638) were 0·9 (95%

CI 0·8–1·0) and 1·3 (1·2–1·6), respectively. The RR for the comparison of QuantiFERON-positive results with T-SPOT.*TB*-positive results was 1·5 (1·3–1·7; table 2).

Among participants overall, increases in age were associated with increases in positive test results for both types of IFN-γ release assay (p_{trend}<0·0001; table 3). However, when stratified by birthplace, this association remained only for non-US-born participants (p_{trend}<0·0001), with no apparent trend for US-born participants (QuantiFERON p_{trend}=0·91; T-SPOT.*TB* p_{trend}=0·90). Among non-US-born participants, TST-positive results showed two age peaks, in those younger than 2 years (67 [32·5%] of 206 participants) and 25–44 years (3486 [50·3%] of 6934) age groups (table 3). For all participants, the ratio of positive TST results to positive IFN-γ release assay results was inversely associated with age, with the highest ratio among children younger than 2 years (TST *vs* QuantiFERON RR 22·5, 95% CI 7·2–70·6; TST *vs* T-SPOT. *TB* 67·3, 9·4–480·6) and the lowest ratio among participants aged 65 years and older (TST *vs* QuantiFERON 1·0, 0·9–1·1; TST *vs* T-SPOT.*TB* 1·2, 1·0–1·4; table 3). The proportions of positive tests in young children varied by birthplace. Although US-born children younger than 5 years had similar proportions of positive TST, QuantiFERON, and T-SPOT.*TB* results (TST *vs* QuantiFERON RR 0·7, 95% CI 0·3–1·8; TST *vs* T-SPOT.*TB* 1·3, 0·4–3·5; QuantiFERON *vs* T-SPOT.*TB* 1·7, 0·6–4·4), non-US-born children in that age group had substantially higher proportions of positive TST results than positive QuantiFERON (7·3, 5·1–10·5) and T-SPOT. *TB* (17·2, 9·9–29·8; table 3). In the oldest age group (≥65 years), results were relatively consistent across tests among non-US-born participants (table 3; TST *vs* QuantiFERON RR 1·0, 95% CI 0·8–1·1; TST *vs* T-SPOT.*TB* 1·1, 1·0–1·3; QuantiFERON *vs* T-SPOT.*TB* 1·2, 1·0–1·4). Among US-born participants aged 65 years and older, the proportions positive by TST, QuantiFERON, and T-SPOT.*TB* were similar (TST vs QuantiFERON RR 1·1, 0·6–2·1; TST *vs* T-SPOT.*TB* 1·8, 0·9–3·5; QuantiFERON *vs* T-SPOT.*TB* 1·5, 0·8–3·1; table 3).

Among close contacts of infectious tuberculosis cases, test results for US-born participants showed no linear age trend (TST p=0·05, QuantiFERON p=0·12, T-SPOT.*TB* p=0·37; data not shown). 73 (97·3%) of 75 US-born participants younger than 5 years were enrolled as close contacts of infectious tuberculosis cases. These children were the only risk group whose proportions of positive IFN-γ release assay results were higher in US-born participants than in non-US-born participants (QuantiFERON-positive ten [13·9%] of 72 US-born participants *vs* 31 [3·6%] of 871 non-US-born participants, RR 3·9, 95% CI 2·0–7·7; T-SPOT.*TB*-positive six [8·2%] of 73 US-born participants *vs* 13 [1·5%] of 866 non-US-born participants, RR 5·5, 95% CI 2·1–14·0; table 2).

US-born participants who were enrolled because they had reported HIV infection had relatively low proportions of positive tests: 84 (5·4%) of 1561, 115 (7·3%) of 1577, and 40 (2·6%) of 1556 for those with valid tests for TST, QuantiFERON, and TSPOT.*TB*, respectively (TST *vs* QuantiFERON RR 0·74, 95% CI 0·56–0·97; TST *vs* T-SPOT.*TB* 2·1, 1·4–3·0; QuantiFERON *vs* T-SPOT.*TB* 2·8, 2·0–4·0; table 2). For both US-born and non-US-born homeless people, the proportions of positive tests for TST (158 [11·1%] of 1424 US-born; 96 [39·2%] of 245 non-US-born), QuantiFERON (195 [13·1%] of 1490 US-born; 86 [30·3%] of 284 non-US-born), and T-SPOT.*TB* (143 [9·8%] of 1460 US-born; 62

[23·0%] of 269 non-US-born) were similar to those of the overall US-born and non-US-born populations (table 2).

11 317 (56·2%) of 20 149 participants with three test results were negative for all three (triple negative), including 2852 (83·4%) of 3418 US-born participants and 8450 (50·6%) of 16 712 non-US-born participants. 3094 (15·4%) of 20 149 participants were positive on all tests (triple positive), including 167 (4·9%) of 3418 US-born participants and 2926 (17·5%) of 16 712 non-US-born participants (RR 3·6, 95% CI 3·1–4·2). 3662 (18·2%) of 20 149 participants were positive only by TST, of whom 3510 (95·8%) were born outside the USA (table 4).

Among non-US-born participants, discordance between TST and IFN-γ release assay results varied by age (figure 2). Discordance was greatest among the 848 non-US-born children younger than 5 years. 204 (87·2%) of 234 non-US-born children younger than 5 years with at least one positive test were TST-positive and IFN-γ release assay-negative (appendix p 4). The TST-positive but IFN-γ release assay-negative discordance persisted in the 45–64 age group. Older age was associated with a decrease in the proportion of isolated TST positives, and an increase in the proportion of TST-positive plus IFN-γ release assay-positive and TST-negative plus IFN-γ release assay-positive results. The proportion of non-US-born participants who were TST-negative but IFN-γ release assay-positive ranged from one (0·5%) of 199 children younger than 2 years to 86 (14·5%) of 594 participants aged 65 years and older (p_{trend}<0·0001; appendix pp 4, 7).

Among the 1511 HIV-positive US-born participants with three test results, 23 (1·5%) were triple-positive, 1356 (89·7%) were triple-negative, 108 (7·1%) were positive on one test, and 24 (1·6%) were positive on two tests (appendix p 4). Ten (0·7%) of 1511 participants with HIV reported previous contact with a person who had tuberculosis disease.

Proportions of invalid (T-SPOT.*TB*) or indeterminate (QuantiFERON) results in the overall study population were 119 (0·6%) of 20 778 participants and 91 (0·4%) of 21 603, respectively. 777 (3·7%) of 20 788 valid T-SPOT. *TB* results were borderline on the basis of the US definition and were analysed as negative. The sensitivity analysis that reclassified borderlines as negative (five spots) or positive (six or seven spots) on the basis of the international definition showed small effects on results. For example, the number of participants with triple-negative results changed from 11 317 (56·2%) of 20 149 with the US definition to 11 226 (55·7%) of 20 149 with the international definition. Similarly, the number of triple-positive and isolated TST positive changed from 3094 (15·4%) of 20 149 participants to 3296 (16·4%) of 20 149 participants and from 3662 (18·2%) of 20 149 participants to 3534 (17·5%) of 20 149 participants, respectively (appendix p 4).

Agreement between the TST and each IFN-γ release assay was higher in US-born participants than in non-US-born participants (appendix p 5). The lower agreement in non-US-born participants primarily reflected a greater number of TST-positive but IFN-γ release assay-negative results. Agreement was higher between the two IFN-γ release assays than between TST and either IFN-γ release assay, regardless of birthplace (appendix p 5). The same pattern evident in the overall population was also seen in the oldest and youngest

groups, regardless of birthplace. κ values were particularly low for the comparisons of TST with IFN-γ release assays in non-US-born children younger than 5 years (appendix p 5).

Discussion

In this study, we report findings from the largest US study, to our knowledge, comparing TST with both QuantiFERON and T-SPOT.*TB* IFN-γ release assays. Our participants represent those at high risk of tuberculosis infection or progression to tuberculosis disease, whom the CDC recommends be tested for latent tuberculosis infection. Our cohort had good representation across all age groups, including almost 1000 children younger than 5 years. A third of our cohort was of non-US-born Asian or Native Hawaiian or Pacific Islander race or ethnicity. In the USA, tuberculosis incidence is highest among non-US-born Asian people (25·4 cases per 100 000 people) and Native Hawaiian or Pacific Islanders (25·0 cases per 100 000 people), compared with 0·4 cases per 100 000 people among all US-born people.[13] Previous studies have not had good representation of these populations.[14] Thus, the results from this study can inform latent tuberculosis infection screening for people in the USA who could most benefit from treatment.

In our study, isolated positive TST results occurred almost exclusively among non-US-born participants and decreased with age. This pattern of TST-positive but IFN-γ release assay-negative discordance has been reported in other studies.[12,15] Among children younger than 5 years, most discordant results were TST-positive and IFN-γ release assay-negative. Younger age at arrival to the USA translated into less opportunity for exposure and a lower prevalence of latent tuberculosis infection for such children. Therefore, the discordant results probably represent false-positive TST results—most likely due to BCG vaccination—rather than true infection. TST within 2 years of BCG vaccination has been shown to result in false-positive results that revert to negative.[16] Our findings are reflected in the American Academy of Pediatrics Redbook recommendations that lowered the age limit for IFN-γ release assays to 2 years.[17] However, IFN-γ release assay-negative discordance, although highest in children, persists in age groups up to 64 years, suggesting that even in non-US-born adults, substantial numbers of TST-positive results are false positives. These results are consistent with the UK PREDICT TB study, which showed a higher proportion of positive TST results (at the 10 mm cutoff) than for either IFN-γ release assay in an adult population with high (estimated >80%) prevalence of BCG vaccination.[18]

The association between age and proportion of positive tests among non-US-born participants is consistent with the scientific premise that, in the absence of known tuberculosis exposure, latent tuberculosis infection prevalence should increase with length of time for opportunity for exposure—and therefore with age—in countries with high prevalence of tuberculosis. In countries with low prevalence of TB, one would expect the association of the proportion of positive tests to be with exposure and not age. This is reflected in the fairly equal prevalence among US-born close contacts of infectious tuberculosis cases over all ages.

For participants aged 65 years and older, the three tests showed high agreement, regardless of birthplace. This was caused largely by the higher proportion of TST-negative and IFN-γ

release assay-positive results in older non-US-born participants, who accounted for almost 90% of participants in this age group. A study of health-care workers in Germany also showed a higher prevalence of positive IFN-γ release assay results among those in the oldest age group, possibly related to cumulative tuberculosis exposure.[19] The pattern of discordance between TSTs and IFN-γ release assays was previously observed among the low-risk population-based sample for the National Health and Nutrition Examination Survey (NHANES).[20] Previous research attributed this to age-related decline in cell-mediated immunity.[20,21] These results suggest that IFN-γ release assays might be more sensitive tests compared with TST among older adults and might be preferred to identify those who require treatment in high-risk settings, such as contact investigations.

Test results for US-born participants with HIV were mostly negative or only positive on a single test. The interpretation of a single positive test in a population at high risk for tuberculosis progression but without tuberculosis exposure is challenging. Site clinicians were free to decide how to manage these patients, and follow-up of untreated patients could give us more information. The estimated prevalence of latent tuberculosis infection in this population was close to the estimated false-positive proportion.[6,22] This issue of sensitivity and specificity, although a potential source of bias for all patients, is particularly acute for people with HIV, whose immune systems are compromised, adding to uncertainty about interpretation of results. Therefore, it is unclear how best to approach latent tuberculosis infection testing in US-born people with HIV who do not have a history of contact with tuberculosis cases.[8] Although the risk of progression to tuberculosis is heightened in people with HIV, test performance might also differ because of the reliance of diagnostic tests on the immunological response. In a separate publication,[23] we used latent class analysis to explore the differences in sensitivity and specificity in people with various conditions, such as young age or HIV infection, that could affect test performance.

The proportions of positive tests in US-born and non-US-born homeless participants in our study did not differ from the proportions in US-born and non-US-born study participants overall. This finding reflects the circumstances that in a country with low tuberculosis prevalence, it might not be homelessness per se that increases the risk for tuberculosis, but rather associated factors, such as ongoing tuberculosis transmission in the local homeless community or residence in homeless shelters. This finding has implications for public health practices to reduce the burden of tuberculosis in these populations. Future studies should explore risk factors for tuberculosis in homeless populations.

Our findings of discordance between TST and IFN-γ release assays are in line with previously published studies.[24] Studies that used a higher TST cutoff of 15 mm (or 10 mm for close contacts) or had a high proportion of participants from regions with high tuberculosis incidence (eg, Africa or India) more often had equal or higher proportions of positive results by IFN-γ release assay than by TST.[3,25] Studies that used a 5 mm or 10 mm TST cutoff, had fewer immigrants from regions with high tuberculosis incidence, or did not include chest radiograph signs of previous tuberculosis (eg, fibrosis) were more likely to have a higher proportion of positive results by TST.[13,26]

The proportions of positive tests reported in this study are higher than those reported in the most recent NHANES, but in line with previously published estimates of the global burden of latent tuberculosis infection.[27] The 2011–12 NHANES estimates for latent tuberculosis infection among non-US-born people ranged from 15·9% for QuantiFERON results to 20·5% for TST, compared with 26·8% and 43·9%, respectively, for our study participants. Since our study focused on groups at the highest risk for latent tuberculosis infection or progression to tuberculosis, the differences in latent tuberculosis infection prevalence compared with the general population sample in NHANES are unsurprising.

Our findings support smaller prospective studies that assessed the predictive abilities of IFN-γ release assay and TST. For example, published studies of progression to tuberculosis disease in close contacts of infectious cases have reported much lower tuberculosis incidence among IFN-γ release assay-negative contacts—0·1% and 0·3% compared with 3·3% and 2·7% for those with negative and positive QuantiFERON and T-SPOT.*TB* results, respectively, and a five times higher likelihood of progressing to tuberculosis disease with a positive QuantiFERON result.[28,29] Given the increased specificity of IFN-γ release assays, their use could translate into fewer radiographic studies and clinical evaluations and less latent tuberculosis infection treatment. Cost-effectiveness studies and models that consider these downstream effects generally favour screening strategies that use IFN-γ release assays alone or as a follow-up to positive TST results.[14,27,29–32] Substantial numbers of health departments have already shifted latent tuberculosis infection testing from TST to IFN-γ release assays, despite their increased cost and the need for phlebotomy, because of these perceived programmatic advantages.[33] Our results show relatively high agreement among IFN-γ release assays. The decision over which test to use probably will depend on other factors, such as cost and convenience. When indicated, TST is acceptable, especially in non-BCG-vaccinated children or adults.[8] Because all current tests for tuberculosis infection are based on immunological responses to past or current infection rather than to identification of the organism, the tests might have lower sensitivity in those with impaired immune responses. People who fall into these categories, such as those with HIV or on immunosuppressive medication such as TNF inhibitors, are also at the highest risk for progression from tuberculosis infection to tuberculosis disease. Clinicians use various strategies to address this potential decrease in test sensitivity, including multiple testing methods and empirical treatment in high-risk patients. As always, test results are subject to interpretation and must be used in context with patient history and likelihood of exposure. In our cohort, the proportion of people who would fall under this category was low, so this type of bias in our estimates of latent tuberculosis infection prevalence would be negligible.

Limitations of this study relate primarily to the way tests were interpreted or done. We did not retest borderline T-SPOT.*TB* results, and we treated borderline results as negative. However, our sensitivity analysis showed that treating borderline results as positive would not significantly affect our study conclusions. T-SPOT.*TB* tests from the Hawaii site were processed in a different laboratory to all other sites. QuantiFERON processing procedures differed among sites, although all followed the manufacturer's instructions. Some sites batched their samples, froze them after incubation and centrifugation, and ran them once a week. Other sites ran samples daily and did not freeze them. The lack of three analysable results from all participants (see methods) limited the sample size for some analyses.

BCG vaccination histories and comorbidities, including HIV infection and diabetes, were self-reported. Finally, enrolment numbers for people with chronic kidney failure or other immunosuppressive conditions were too small for separate analyses.

This report is a sub-analysis of a prospective study to compare the predictive abilities of IFN-γ release assays and TST. Each participant was actively followed up for 2 years and continued to be followed up through state tuberculosis registry matches until Nov 15, 2020, or development of tuberculosis. We will assess tuberculosis incidence in the cohort overall and by important subgroups at high risk of progression to tuberculosis disease. Among other questions addressed, the study will build on knowledge of the risk of progression to tuberculosis among people who are TST-positive and IFN-γ release assay-negative. Analysis of tuberculosis incidence will also refine estimates, by test, of the number needed to treat to prevent a case of tuberculosis. We anticipate that the number needed to treat will be much lower for IFN-γ release assays than for TST.[27]

This large study of US residents at the highest risk of latent tuberculosis infection or progression to tuberculosis disease supports some longstanding guidance, such as the recommendation to test people from countries with a high tuberculosis prevalence. The high rates of TST and IFN-γ release assay discordance that persist among non-US-born people beyond the youngest age groups support the recommendations for preferential use of IFN-γ release assays for diagnosis in this population. Our findings suggest the need to revisit or refine other guidance.

In conclusion, those who would most benefit from latent tuberculosis infection diagnosis and treatment, such as close contacts of cases of infectious tuberculosis, people with immunosuppressive conditions due to disease or medication, and others with a high local prevalence of latent tuberculosis infection, should be tested. Non-institutionalised US-born people without additional risk factors for latent tuberculosis infection or progression to tuberculosis disease should not be tested, because of low yield and the increased probability of false-positive results. Future studies should assess the benefits of testing institutionalised US-born people.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The US Centers for Disease Control and Prevention (CDC) funded the study through 10-year contracts with each of the Tuberculosis Epidemiologic Studies Consortium (TBESC) sites. The contracts covered all TBESC research studies. The findings and conclusions in this report are those of the authors and do not necessarily represent official CDC positions. We are grateful for the assistance of the CDC headquarters TBESC team: Gabrielle Fanning-Dowdell, Rose Punnoose, Matthew Whipple, and Yanjue Wu. We also acknowledge the contributions of the previous TBESC project officer, Denise Garrett, and branch chief, Tom Navin. We acknowledge the assistance of the TBESC site project coordinators: Katya Salcedo, Laura Romo, Christine Kozik, Carlos Vera, Juanita Lovato, Laura Farrow, Colleen Traverse Kristian Atchley, Fernanda Maruri, Kursten Lyon, Debra Turner, Nubia Flores, Jane Tapia, Livia Sura, Joanne C Li, Marie McMillan, Stephanie Reynolds-Bigby, Angela Largen, Thara Venkatappa, Aurimar Ayala, Elizabeth Munk, Gina Maltas, Yoseph Sorri, Kenji Matsumoto, Amy Board, and James Akkidas.

References

1. Menzies NA, Cohen T, Hill AN, et al. Prospects for tuberculosis elimination in the United States: results of a transmission dynamic model. Am J Epidemiol 2018; 187: 2011–20. [PubMed: 29762657]
2. O'Garra A, Redford PS, McNab FW, Bloom CI, Wilkinson RJ, Berry MPR. The immune response in tuberculosis. Annu Rev Immunol 2013; 31: 475–527. [PubMed: 23516984]
3. Pottumarthy S, Morris AJ, Harrison AC, Wells VC. Evaluation of the tuberculin gamma interferon assay: potential to replace the Mantoux skin test. J Clin Microbiol 1999; 37: 3229–32. [PubMed: 10488182]
4. Pai M, Denkinger CM, Kik SV, et al. Gamma interferon release assays for detection of *Mycobacterium tuberculosis* infection. Clin Microbiol Rev 2014; 27: 3–20. [PubMed: 24396134]
5. Linas BP, Wong AY, Freedberg KA, Horsburgh CR Jr. Priorities for screening and treatment of latent tuberculosis infection in the United States. Am J Respir Crit Care Med 2011; 184: 590–601. [PubMed: 21562129]
6. Miramontes R, Hill AN, Yelk Woodruff RS, et al. Tuberculosis infection in the United States: prevalence estimates from the National Health and Nutrition Examination Survey, 2011–2012. PLoS One 2015; 10: e0140881. [PubMed: 26536035]
7. Banaei N, Gaur RL, Pai M. Interferon gamma release assays for latent tuberculosis: what are the sources of variability? J Clin Microbiol 2016; 54: 845–50. [PubMed: 26763969]
8. Lewinsohn DM, Leonard MK, LoBue PA, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention clinical practice guidelines: diagnosis of tuberculosis in adults and children. Clin Infect Dis 2017; 64: 111–15. [PubMed: 28052967]
9. Chee CBE, Reves R, Zhang Y, Belknap R. Latent tuberculosis infection: opportunities and challenges. Respirology 2018; 23: 893–900. [PubMed: 29901251]
10. US Centers for Disease Control and Prevention. Tuberculosis Epidemiologic Studies Consortium. TBESC-II: striving to prevent, control, and eliminate tuberculosis. https://www.cdc.gov/tb/topic/research/tbesc/default.htm (accessed May 31, 2020).
11. Cain KP, Benoit SR, Winston CA, Mac Kenzie WR. Tuberculosis among foreign-born persons in the United States. JAMA 2008; 300: 405–12. [PubMed: 18647983]
12. Weinfurter P, Blumberg HM, Goldbaum G, et al. Predictors of discordant tuberculin skin test and QuantiFERON®-TB Gold In-Tube results in various high-risk groups. Int J Tuberc Lung Dis 2011; 15: 1056–61. [PubMed: 21740668]
13. US Centers for Disease Control and Prevention. Reported tuberculosis in the United States 2016. Atlanta: US Centers for Disease Control and Prevention, 2017.
14. Campbell JR, Chen W, Johnston J, et al. Latent tuberculosis infection screening in immigrants to low-incidence countries: a meta-analysis. Mol Diag Ther 2015; 19: 107–17.
15. Erkens CG, Dinmohamed AG, Kamphorst M, et al. Added value of interferon-gamma release assays in screening for tuberculous infection in the Netherlands. Int J Tuberc Lung Dis 2014; 18: 413–20. [PubMed: 24670695]
16. Burl S, Adetifa UJ, Cox M, et al. The tuberculin skin test (TST) is affected by recent BCG vaccination but not by exposure to non-tuberculosis mycobacteria (NTM) during early life. PLoS One 2010; 5: e12287. [PubMed: 20808814]
17. American Academy of Pediatrics. Tuberculosis. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2018 Report of the Committee on Infectious Diseases, 31st edn. Itasca, IL: American Academy of Pediatrics, 2018: 829–53.
18. Abubakar I, Drobniewski F, Southern J, et al. Prognostic value of interferon-γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. Lancet Infect Dis 2018; 18: 1077–87. [PubMed: 30174209]
19. Schablon A, Beckmann G, Harling M, Diel R, Nienhaus A. Prevalence of latent tuberculosis infection among health care workers in a hospital for pulmonary diseases. J Occup Med Toxicol 2009; 4: 1. [PubMed: 19134168]

20. Ghassemieh BJ, Attia EF, Koelle DM, Mancuso JD, Narita M, Horne DJ. Latent tuberculosis infection test agreement in the National Health and Nutrition Examination Survey. Am J Respir Crit Care Med 2016; 194: 493–500. [PubMed: 26890477]
21. Van den Brande P, Demedts M. Four-stage tuberculin testing in elderly subjects induces age-dependent progressive boosting. Chest 1992; 101: 447–50. [PubMed: 1735271]
22. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for latent tuberculosis infection in adults: US Preventive Services Task Force recommendation statement. JAMA 2016; 316: 962–69. [PubMed: 27599331]
23. Stout JE, Wu Y, Ho CS, et al. Evaluating latent tuberculosis infection diagnostics using latent class analysis. Thorax 2018; 73: 1062–70. [PubMed: 29982223]
24. Pai M, Denkinger CM, Kik SV, et al. Gamma interferon release assays for detection of *Mycobacterium tuberculosis* infection. Clin Microbiol Rev 2014; 27: 3–20. [PubMed: 24396134]
25. Adetifa IM, Lugos MD, Hammond A, et al. Comparison of two interferon gamma release assays in the diagnosis of Mycobacterium tuberculosis infection and disease in The Gambia. BMC Infect Dis 2007; 7: 122. [PubMed: 17961228]
26. Painter JA, Graviss EA, Hai HH, et al. Tuberculosis screening by tuberculosis skin test or QuantiFERON-TB Gold In-Tube Assay among an immigrant population with a high prevalence of tuberculosis and BCG vaccination. PLoS One 2013; 8: e82727. [PubMed: 24367546]
27. Lange C, Mandalakas AM, Kalsdorf B, Denkinger CM, Sester M. Clinical application of interferon-γ release assays for the prevention of tuberculosis in countries with low incidence. Pathog Immun 2016; 1: 308–29. [PubMed: 28217762]
28. Zellweger JP, Sotgiu G, Block M, et al. Risk assessment of tuberculosis in contacts by IFN-γ release assays. A Tuberculosis Network European Trials Group study. Am J Respir Crit Care Med 2015; 191: 1176–84. [PubMed: 25763458]
29. Altet N, Dominguez J, Souza-Galvão ML, et al. Predicting the development of tuberculosis with the tuberculin skin test and QuantiFERON testing. Ann Am Thorac Soc 2015; 12: 680–88. [PubMed: 25699406]
30. Nienhaus A, Schablon A, Costa JT, Diel R. Systematic review of cost and cost-effectiveness of different TB-screening strategies. BMC Health Serv Res 2011; 11: 247. [PubMed: 21961888]
31. Abubakar I, Lalvani A, Southern J, et al. Two interferon gamma release assays for predicting active tuberculosis: the UK PREDICT TB prognostic test study. Health Technol Assess 2018; 22: 1–96.
32. Tasillo A, Salomon JA, Trikalinos TA, Horsburgh CR Jr, Marks SM, Linas BP. Cost-effectiveness of testing and treatment for latent tuberulosis infection in residents born outside the United States with and without medical comorbidities in a simulation model. JAMA Intern Med 2017; 177: 1755–64. [PubMed: 29049814]
33. Schluger NW, Burzynski J. Recent advances in testing for latent TB. Chest 2010; 138: 1456–63. [PubMed: 21138881]

Research in context

Evidence before this study

In October, 2009, the US Centers for Disease Control and Prevention (CDC) steering committee for the Tuberculosis Epidemiologic Studies Consortium (TBESC) convened an expert panel of tuberculosis researchers and public health officials from the CDC, WHO, Health Canada, the International Union Against TB and Lung Diseases, and other academic and public health institutions to review research gaps and identify the focus for the 2012–21 research consortium. The consensus of the Strategic Planning Working Group was that an assessment of IFN-γ release assays versus the tuberculin skin test (TST) was critically needed: "…we currently lack the large scale studies needed to establish (1) the appropriate parameters of the test, (2) the meaning of specific quantitative results, (3) the correct cutpoints for different populations, (4) the characteristics of the tests in paediatric populations, and (5) the tests' ability to predict progression to tuberculosis disease. The TBESC could provide the infrastructure for these large-scale tests." The consortium began its work in 2012. Since then, to our knowledge, no similar large studies have been conducted in the USA that involved recruitment of individuals documented to be free of tuberculosis disease at enrolment, who were given all three US Food and Drug Administration-approved tests for tuberculosis infection, actively followed up for 2 years to identify incident cases, and followed up by registry match for 4–9 years thereafter to determine which test best predicted development of tuberculosis disease. Even in 2017, new guidelines acknowledged that the quality of evidence in favour of one test or another was low. To our knowledge, the only similar study done to date is the UK PREDICT study, initiated at around the same time as ours. Having two large studies available to assess test performance in two different populations is an important opportunity to validate and compare study methods and outcomes.

Added value of this study

The focus of this study was to describe the prevalence of latent tuberculosis infection by single and combination test results and examine the concordance among the tests in a diverse group of high-risk people living in the USA. In the absence of a gold standard, concordance studies can help establish the validity of distinct diagnostic techniques, such as IFN-γ release assays, and show equivalence of different techniques. In this study, the largest to our knowledge in the USA to assess concordance of tests for latent tuberculosis infection, we found higher concordance between the two IFN-γ release assays than between either IFN-γ release assay and the TST in people not born in the USA, particularly very young people (<5 years). Isolated positive TSTs occurred almost exclusively in people born outside the USA. Proportions of positive IFN-γ release assay results increased with age—as would be expected in people from countries with high rates of tuberculosis—but proportions of positive TST results did not. Low proportions of invalid TSPOT.*TB* results (0·6%) and indeterminate QuantiFERON results (0·4%) suggested relatively few patients would require retesting.

Implications of all the available evidence

As intensified tuberculosis prevention efforts get underway to meet the WHO End TB Strategy goals, the logistical difficulties of treating millions of people with positive tests underscore the importance of tests with higher specificity. Use of IFN-γ release assays will reduce overdiagnosis and allow public health programmes to effectively focus their scarce resources. Our conclusions for immigrants from countries with moderate to high incidence of tuberculosis with BCG vaccination would be relevant for other low-risk countries with similar tuberculosis burden and epidemiology. Future studies should compare the cost-effectiveness of each IFN-γ release assay in people born outside the USA.

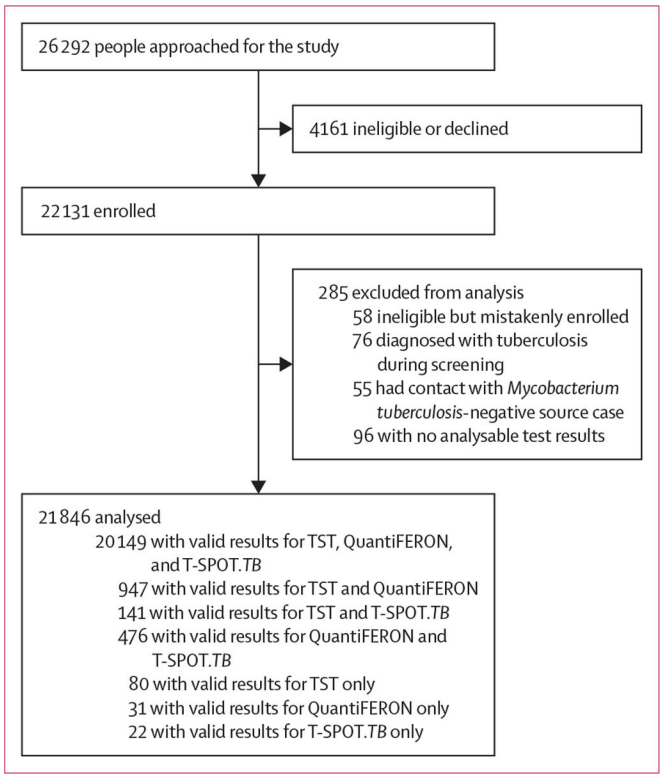

Figure 1: Recruitment results and number included in analysis
TST=tuberculin skin test.

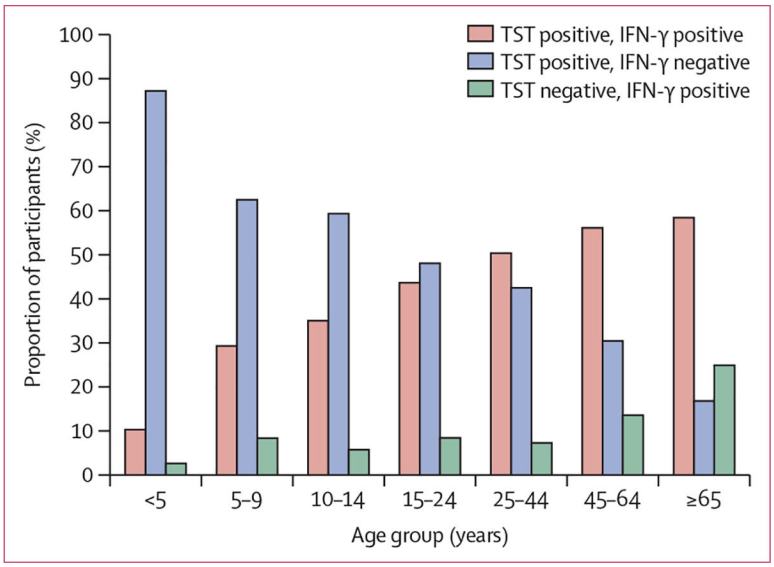

Figure 2: Test combinations for non-US-born participants with at least one positive test

IFN-γ denotes either IFN-γ release assay. TST=tuberculin skin test.

Table 1:

Demographic, medical, and social risk characteristics of study participants

	All participants* (n=21 846)	US-born participants (n=3790)	Non-US-born participants (n=18 023)
Gender			
Male	11 184 (51·2%)	2393 (63·1%)	8769 (48·7%)
Female	10 639 (48·7%)	1380 (36·4%)	9248 (51·3%)
Transgender male to female	23 (0·1%)	17 (0·4%)	6 (<0·1%)
Pregnant women	361/10 639 (3·4%)	28/1380 (2·0%)	333/9248 (3·6%)
Age, years†			
<2	234 (1·1%)	24 (0·6%)	210 (1·2%)
2–4	728 (3·3%)	51 (1·3%)	677 (3·8%)
5–9	1364 (6·2%)	122 (3·2%)	1242 (6·9%)
10–14	1516 (6·9%)	122 (3·2%)	1394 (7·7%)
15–24	3792 (17·4%)	307 (8·1%)	3482 (19·3%)
25–44	8429 (38·6%)	1184 (31·2%)	7239 (40·2%)
45–64	4859 (22·2%)	1872 (49·4%)	2979 (16·5%)
≥65	754 (3·5%)	97 (2·6%)	656 (3·6%)
Race or ethnicity‡			
American Indian or Alaska Native	127 (0·6%)	120 (3·2%)	7 (<0·1%)
Asian	6527 (29·9%)	139 (3·7%)	6388 (35·4%)
Black or African American	4545 (20·8%)	1959 (51·7%)	2578 (14·3%)
White or Caucasian	2081 (9·5%)	1143 (30·2%)	932 (5·2%)
Native Hawaiian or Pacific Islander	463 (2·1%)	45 (1·2%)	418 (2·3%)
Hispanic or Latino	2596 (11·9%)	445 (11·7%)	2148 (11·9%)
Other	4603 (21·1%)	104 (2·7%)	4498 (25·0%)
Do not know or did not answer	1232 (5·6%)	39 (1·0%)	1192 (6·6%)
Reason for enrolment‡			
Close contact of an infectious tuberculosis case	2091 (9·6%)	797 (21·0%)	1285 (7·1%)
Born outside the USA			
In country whose US residents have high tuberculosis risk	13 426 (61·5%)	··	13 426 (74·5%)
In country whose US residents have medium tuberculosis risk	4407 (20·2%)	··	4407 (24·5%)
Refugee	9811 (44·9%)	··	9811 (54·4%)
Homeless§	1304 (6·0%)	1286 (33·9%)	0
Spent at least 30 days in a country with high TB rates	5213 (23·9%)	147 (3·9%)	5066 (28·1%)
HIV-positive	1873 (8·6%)	1595 (42·1%)	273 (1·5%)
Self-reported medical histories and risk factors			
BCG vaccination	11 819 (54·1%)	189 (5·0%)	11 629 (64·5%)
HIV-positive	1881 (8·6%)	1600 (42·2%)	280 (1·6%)
Liver disease	793 (3·6%)	619 (16·3%)	174 (1·0%)

	All participants* (n=21 846)	US-born participants (n=3790)	Non-US-born participants (n=18 023)
Chronic kidney failure	131 (0·6%)	74 (2·0%)	57 (0·3%)
Diabetes	1116 (5·1%)	372 (9·8%)	742 (4·1%)
Immunosuppressive therapy	324 (1·5%)	180 (4·7%)	144 (0·8%)
Self-reported social or behavioural risk factors			
Ever lived or worked in a prison or jail¶	1951 (8·9%)	1429 (37·7%)	515 (2·9%)
Ever lived or worked in a homeless shelter	1851 (8·5%)	1548 (40·8%)	289 (1·6%)
Ever lived or worked in another residential facility‖	1958 (9·0%)	1326 (35·0%)	630 (3·5%)
Ever smoked (>100 cigarettes in lifetime)**	5566 (25·5%)	2336 (61·6%)	3218 (17·9%)
Regular alcohol use (>4 drinks per week)**	366 (1·7%)	203 (5·4%)	163 (0·9%)
Ever used recreational drugs‖	2597 (11·9%)	2138 (56·4%)	454 (2·5%)

*33 participants with missing data on birth location.

†170 participants with missing age data.

‡Not mutually exclusive.

§Member of a local population with latent tuberculosis infection prevalence ≥25%.

¶For participants who were >11 years old.

‖Drug treatment and long-term care facilities.

**For participants who were aged ≥15 years.

Table 2:

Single test positivity for all participants

	Tuberculin skin test		QuantiFERON		T-SPOT.*TB*	
	Tested	**Positive**	**Tested**	**Positive**	**Tested**	**Positive**
Birthplace						
All participants (n=21 846)	20 900	7870 (37·7%)	21 603	5184 (24·0%)	20 788	3995 (19·2%)
US-born participants	3575	391 (10·9%)	3693	445 (12·0%)	3638	295 (8·1%)
Non-US-born participants	17 306	7476 (43·2%)	17 882	4732 (26·5%)	17 118	3693 (21·6%)
RR (95% CI)	··	3·9 (3·6–4·3)	··	2·2 (2·0–2·4)	··	2·7 (2·4–3·0)
HIV positive						
All participants (n=1881)	1834	155 (8·5%)	1853	190 (10·3%)	1826	77 (4·2%)
US-born participants	1561	84 (5·4%)	1577	115 (7·3%)	1556	40 (2·6%)
Non-US-born participants	272	71 (26·1%)	275	75 (27·3%)	269	37 (13·8%)
RR (95% CI)	··	4·9 (3·6–6·5)	··	3·7 (2·9–4·9)	··	5·4 (3·5–8·2)
<5 years old						
All participants (n=962)	936	231 (24·7%)	946	41 (4·3%)	939	19 (2·0%)
US-born participants	68	7 (10·3%)	72	10 (13·9%)	73	6 (8·2%)
Non-US-born participants	868	224 (25·8%)	874	31 (3·5%)	866	13 (1·5%)
RR (95% CI)	··	2·5 (1·2–5·1)	··	0·3 (0·1–0·5)	··	0·2 (0·1–0·5)
≥65 years old						
All participants (n=754)	720	287 (39·9%)	751	309 (41·1%)	707	239 (33·8%)
US-born participants	92	19 (20·7%)	95	17 (17·9%)	94	11 (11·7%)
Non-US-born participants	627	268 (42·7%)	655	292 (44·6%)	612	228 (37·3%)
RR (95% CI)	··	2·1 (1·4–3·1)	··	2·5 (1·6–3·9)	··	3·2 (1·8–5·6)
Close contacts of infectious tuberculosis cases						
All participants (n=2091)	1993	818 (41·0%)	2069	554 (26·8%)	2052	411 (20·0%)
US-born participants	759	153 (20·2%)	784	152 (19·4%)	788	104 (13·2%)
Non-US-born participants	1231	665 (54·0%)	1277	401 (31·4%)	1255	306 (24·4%)
RR (95% CI)	··	2·7 (2·3–3·1)	··	1·6 (1·4–1·9)	··	1·8 (1·5–2·3)
Homeless						
All participants (n=1851)	1680	256 (15·2%)	1786	284 (15·9%)	1742	209 (12·0%)

	Tuberculin skin test		QuantiFERON		T-SPOT.*TB*	
	Tested	**Positive**	**Tested**	**Positive**	**Tested**	**Positive**
US-born participants	1424	158 (11·1%)	1490	195 (13·1%)	1460	143 (9·8%)
Non-US-born participants	245	96 (39·2%)	284	86 (30·3%)	269	62 (23·0%)
RR (95% CI)	··	3·5 (2·9–4·4)	··	2·3 (1·9–2·9)	··	2·3 (1·8–3·1)

RR=risk ratio. The sum of US-born and non-US-born for people tested and positive does not equal the total tested and positive because of missing values for age and birthplace. Non-US-born participants were used as the reference group.

Table 3:

Single test positivity by age group

	Tuberculin skin test		QuantiFERON		T-SPOT.*TB*	
	Tested	**Positive**	**Tested**	**Positive**	**Tested**	**Positive**
All participants						
<5 years	936	231 (24·7%)	946	41 (4·3%)	939	19 (2·0%)
<2 years	227	67 (29·5%)	229	3 (1·3%)	228	1 (0·4%)
2–4 years	709	164 (23·1%)	717	38 (5·3%)	711	18 (2·5%)
5–9 years	1326	263 (19·8%)	1349	124 (9·2%)	1342	89 (6·6%)
10–14 years	1459	446 (30·6%)	1510	216 (14·3%)	1468	163 (11·1%)
15–24 years	3608	1210 (33·5%)	3763	740 (19·7%)	3572	546 (15·3%)
25–44 years	8037	3574 (44·5%)	8335	2220 (26·6%)	8039	1797 (22·4%)
45–64 years	4670	1808 (38·7%)	4789	1499 (31·3%)	4554	1107 (24·3%)
≥65 years	720	287 (39·9%)	751	309 (41·1%)	707	239 (33·8%)
Total	20 756	7819 (37·7%)	21 443	5149 (24·0%)	20 621	3960 (19·2%)
Non-US-born participants						
<5 years	868	224 (25·8%)	874	31 (3·5%)	866	13 (1·5%)
<2 years	206	67 (32·5%)	207	2 (1·0%)	205	1 (0·5%)
2–4 years	662	157 (23·7%)	667	29 (4·3%)	661	12 (1·8%)
5–9 years	1206	239 (19·8%)	1228	103 (8·4%)	1220	74 (6·1%)
10–14 years	1341	422 (31·5%)	1389	195 (14·0%)	1346	150 (11·1%)
15–24 years	3321	1179 (35·5%)	3458	706 (20·4%)	3272	523 (16·0%)
25–44 years	6934	3486 (50·3%)	7182	2126 (29·6%)	6899	1734 (25·1%)
45–64 years	2877	1608 (55·9%)	2958	1250 (42·3%)	2761	941 (34·1%)
≥65 years	627	268 (42·7%)	655	292 (44·6%)	612	228 (37·3%)
Total	17 174	7426 (43·2%)	17 744	4703 (26·5%)	16 976	3663 (21·6%)
US-born participants						
<5 years	68	7 (10·3%)	72	10 (13·9%)	73	6 (8·2%)
<2 years	21	0	22	1 (4·5%)	23	0
2–4 years	47	7 (14·9%)	50	9 (18·0%)	50	6 (12·0%)
5–9 years	120	24 (20·0%)	121	21 (17·4%)	122	15 (12·3%)
10–14 years	118	24 (20·3%)	121	21 (17·4%)	122	13 (10·7%)
15–24 years	284	31 (10·9%)	302	34 (11·3%)	297	23 (7·7%)
25–44 years	1099	88 (8·0%)	1148	93 (8·1%)	1134	61 (5·4%)
45–64 years	1785	197 (11·0%)	1824	246 (13·5%)	1786	165 (9·2%)
≥65 years	92	19 (20·7%)	95	17 (17·9%)	94	11 (11·7%)
Total	3566	390 (10·9%)	3683	442 (12·0%)	3628	294 (8·1%)

Table 4:

Test result combinations

	All participants (n=20 149)	US-born participants (n=3418)	Non-US-born participants (n=16 712)
Triple positive (+++)	3094 (15·4%)	167 (4·9%)	2926 (17·5%)
Triple negative (−−−)	11 317 (56·2%)	2852 (83·4%)	8450 (50·6%)
Isolated TST+ (+−−)	3662 (18·2%)	152 (4·4%)	3510 (21·0%)
Isolated QuantiFERON+ (−+−)	492 (2·4%)	110 (3·2%)	382 (2·3%)
Isolated T-SPOT.*TB*+ (−−+)	141 (0·7%)	23 (0·7%)	118 (0·7%)
TST+ and QuantiFERON+ (++−)	827 (4·1%)	50 (1·5%)	775 (4·6%)
QuantiFERON+ and T-SPOT.*TB*+ (−++)	326 (1·6%)	54 (1·6%)	271 (1·6%)
TST+ and T-SPOT.*TB*+ (+−+)	290 (1·4%)	10 (0·3%)	280 (1·7%)

TST=tuberculin skin test. Results are listed in brackets in the following order for each combination: TST, QuantiFERON, and T-SPOT.*TB*. Sum of US-born and non-US-born test results will not equal the total because of missing values for birthplace.