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PII: S0012-3692(25)00144-8

DOI: https://doi.org/10.1016/j.chest.2025.01.031

Reference: CHEST 6711

To appear in: *CHEST*

Received Date: 11 July 2024

Revised Date: 18 January 2025

Accepted Date: 22 January 2025

Please cite this article as: Chen C, Xue H, Horsburgh CR, Amour M, Hatherill M, Tameris M, von Reyn CF, Rees C, Shen Y, McShane H, García-Basteiro AL, Liu D, Wang Y, Nathavitharana RR, Graviss EA, Shao Y, Liu Q, Lu W, Zhu L, Martinez L, Trajectories of interferon-gamma release assay results over two years in independent cohorts from China, South Africa, Tanzania, and the United States *CHEST* (2025), doi: https://doi.org/10.1016/j.chest.2025.01.031.

Trajectories of interferon-gamma release assay results over two years in independent cohorts from China, South Africa, Tanzania, and the United States

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LM and CC conceived the study. All authors contributed to data acquisition. LM received and checked the data from the multiple cohorts and had full access to all materials and results. LM accessed and verified the underlying data. CC and LM did all analyses and wrote the first draft of the manuscript. CC and LM edited subsequent versions of the manuscript until dissemination to the broader author group. All authors read and edited the drafted manuscript for important intellectual content and assisted in data interpretation. All authors approved the final version of the manuscript. All authors had final responsibility for the decision to submit for publication.

Declaration

All authors declared no conflict of interest.

Acknowledgments and Funding Information

CRH was supported by the Providence/Boston Center for AIDS Research (P30AI042853), the Boston University/Rutgers Tuberculosis Research Unit (U19AI111276) and the Indo-U.S. Vaccine Action Program (VAP) Initiative on Tuberculosis (CRDF Global/ National Institute of Allergy and Infectious Diseases). RRN was supported by a National Institutes of Health Director's New Innovator Award (NIAIDDP2-AI176896). We acknowledge and thank the participants and investigators in each of these studies.

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Manuscript Word Count: 3416 words

Abstract Word Count: 279 words

Tables: 2

Figures: 3

References: 33

Key Words: interferon gamma release assay, tuberculosis clearance, *Mycobacterium tuberculosis*, transmission.

Abstract

Background: There is an ongoing debate about whether clearance of *Mycobacterium tuberculosis* infection occurs and at what magnitude. Recent studies quantifying 'uncertainty zones' of interferon-gamma release assays (IGRA) provide a more stringent estimate of reversion, potentially indicating clearance.

Research Question: When accounting for 'uncertainty zones' through stringent cutoffs, what are the trajectories of interferon-gamma release assays in cases of *Mycobacterium* tuberculosis infection?

Study Design and Methods: We followed five cohorts from South Africa, China, Tanzania, and the United States tested with an IGRA test three or more times for stringent conversion and reversion. The annual risk of IGRA reversion was assessed after an IGRA conversion and among those with baseline positivity.

Results: 26,596 IGRA measurements were taken over 13,593 years of follow-up ($N_{participants}$=7,683). Stringent reversion at year 2 after stringent conversion at year 1 varied between cohorts, occurring in 48% (43/90) for WANTAI, 37% (22/59) for QuantiFERON, and 17% (2/12) for T-SPOT.TB, respectively. In the U.S. cohorts, stringent reversion at year 1 after stringent conversion at 6 months was 58% (15/26) for QuantiFERON and 18% (12/60) for T-SPOT.TB. Stringent reversion at 1 year after baseline positivity occurred in 12% (47/404) for WANTAI, 21% (10/48) for QuantiFERON and 44% for T-SPOT.TB (45/102). In one cohort from (N=399; age range, 59 years [IQR, 48–67]), IGRA reversion was more common in younger participants (Adjusted Odds Ratio [aOR], 0.95; 95% CI, 0.93–0.97) and those without recent close tuberculosis exposure (aOR, 0.35; 95%CI, 0.11–1.03 in South Africa; 0.10; 95%CI, 0.01–0.61 in China).

Interpretation: These results suggest high annual rates of IGRA reversion, even with the use of 'uncertainty zones'; reversion rates decreased with time from exposure and at older ages.

Although tuberculosis is preventable, over 10 million people developed the disease in 2022, with the burden heavily skewed towards low- and middle-income countries.[1] Historically, global tuberculosis control has focused on increasing population-level tuberculosis diagnoses through passive detection[2,3] without the need for widescale interventions based on prevention; however, this strategy has yielded disappointing results.[4] There is now a broad consensus that tuberculosis prevention is a critical component of disease control and is necessary for tuberculosis elimination.[5,6] A common approach for targeted preventive interventions is by testing individuals for *Mycobacterium tuberculosis* （*M tuberculosis*） infection through current diagnostic tests, interferon-gamma assays (IGRA) or tuberculin skin tests.[7,8] However, a positive IGRA or tuberculin skin test using standard cutoffs has poor predictive value for incident active disease. After exposure to *M tuberculosis*, only a small proportion of individuals (<5%) ever develop tuberculosis suggesting that at least a portion of these individuals may clear *M tuberculosis*.[6,9,10]

The meaning of tuberculin or QuantiFERON reversion and conversion is debated. This is especially true for reversion which has been largely neglected in the field. Few studies have followed participants after a tuberculin or QuantiFERON reversion. A prospective study, the US Public Health Service trial of household contacts, found a decrease in progression to tuberculosis among participants who reverted their tuberculin skin test at 12 months compared to those who remained positive (0.8% versus 2%)[11]. This suggests tuberculin reversion may lower the risk of subsequent tuberculosis. However, overall, the evidence is lacking. Reversion of tuberculin skin tests has shown high variability in the literature ranging from 1% annual risk of reversion in Malawi to 22% in Ontario.[12] Prior studies showing reversion have been limited in several ways. First, they used limited follow-up or only two testing timepoints, likely representing only short-term changes in *M. tuberculosis* infection status. Second, they use standard manufacturer-derived cutoffs which have been shown to either over or underestimate changes in IGRA or TST status.[12] Studies quantifying 'uncertainty zones' of IGRAs provide a more stringent estimate of reversion.[13-15] Lastly, most studies have been performed in low-burden settings.[16] Large, population-based, prospective, cohort studies with serial follow-up IGRA testing from a variety of settings are needed to further understand IGRA trajectories over time.

We aimed to evaluate stringent IGRA conversion and reversion in five independent cohorts tested annually over two years using 'uncertainty zones' to account for test variability. We also evaluated whether risk factors such as age, sex, and recent close tuberculosis exposure were associated with changes in IGRA status.

Study Design and Methods

We included and collated five independent cohorts of participants followed for IGRA conversion and reversion from China, South Africa, Tanzania, and the United States (U.S.), as reported previously.[17-21] For inclusion, each cohort had to contain at least three IGRA tests over follow-up. In cohorts from China, South Africa, and Tanzania, participants with conversion were managed per local guidelines which, at the time of the study, did not recommend preventive treatment for *M tuberculosis* infection; to the best of our knowledge, no participants from these cohorts received preventive treatment during the study. In U.S. cohorts, some participants were given preventive therapy; these participants were excluded from this analysis. Participants with IGRA conversion in each cohort were referred for further tuberculosis evaluation. Briefly, we describe each cohort below.

Cohort 1, South Africa

The MVA85A 020 trial was a double-blinded, randomized, placebo-controlled clinical trial undertaken near Cape Town, South Africa, between July 2009 and Oct 2012.[19,20] Parents of recently born infants were approached at local immunization clinics or at home about study participation. Healthy young children (aged 4–6 months) were enrolled if they were HIV-negative, BCG vaccinated and had no known household or other close exposure to a tuberculosis patient. QuantiFERON-TB Gold In-Tube (QFT) testing was done and participants were excluded if testing positive at baseline.

QFT testing was done at baseline and repeated at day 336 and at the end of the study (e-Figure 1). QFT testing was done at baseline and follow-up visits using the same procedures at every study visit. QFT was done according to manufacturer's instructions (Qiagen, Venlo, The Netherlands) and was used to detect in-vitro *M tuberculosis*-specific immune responses by measuring interferon-γ concentration in plasma harvested from whole blood incubated with *M tuberculosis*-specific antigens minus interferon-γ detected in unstimulated control (nil). Young children were actively followed every 3 months to identify signs or symptoms of disease, or history of exposure to tuberculosis.

Cohort 2, China

This was a community-based, cohort study of serial interferon-gamma assay testing in eight villages in rural Dongtai, a rural county in Jiangsu Province, China.[18] Participants were randomly recruited and cluster sampling was conducted. Eligible participants were identified by a door-to-door survey. Individuals with tuberculosis or pregnancy at baseline were excluded.

The Wantai tuberculosis-specific whole-blood interferon gamma release assay (TB-IGRA, Beijing Wantai Biological Pharmacy Enterprise) was used for all study visits (baseline, 1 year, 2 years, e-Figure 2). TB-IGRA has demonstrated comparable clinical performance with both QFT and tuberculin skin tests.[22] Four ml of venous whole blood anticoagulated by heparin was collected from all participants at all study visits, following manufacturer instructions. Whole blood was then suspended into 'N', 'T' and 'P' culture tubes after incubation at 37 C for 22 hours (±2 hours). Tubes were centrifuged at 3,000g for 10 minutes to collect plasma. The continuous concentration of interferon gamma values was then detected by an enzyme-linked immunosorbent assay.

Cohort 3, Tanzania

This was a randomized, double-blind, placebo-controlled study of healthy adolescents (aged 13–15 years) from 16 secondary schools in Dar es Salaam, Tanzania recruited in 2016.[17] Follow-up using serial T-SPOT.TB tests was performed over several years. Eligibility requirements included a BCG immunization, a baseline negative T-SPOT.TB (Oxford Immunotec, Oxford, UK), a normal complete blood count, normal vital signs, and no prior tuberculosis history or chronic illness.

T-SPOT.TB assays were performed according to manufacturer's instructions.[23] The T-SPOT.TB was performed at the baseline screening, month 2, and at follow-up visits at 1, 2, and 3 years. For this analysis, we only included baseline, year 1, and 2. Spot counts were enumerated by a blinded study technician based on manual reading of wells in the 96-well microtiter plate using a hand lens and categorized as negative, positive, borderline, or invalid for the per protocol study endpoints. The manual count limit was 20 spot forming counts (SFCs). Study plates were subsequently shipped to Oxford Immunotec (Oxford, UK) to allow quantitative blinded reading (automated, with manual confirmation), including responses with >20 SFCs.

Cohort 4 and 5, United States

Cohorts 4 and 5 are from a prospective cohort of healthcare workers undergoing occupational tuberculosis screening at four healthcare institutions enrolled across the U.S.[21] A healthcare worker was defined as anyone working in a healthcare setting, regardless of direct patient contact. Adult participants (18 or older) were enrolled between 2008–2011. After baseline testing, follow-up visits occurred at 6, 12, and 18 months in which a structured interview and phlebotomy for IGRAs. Two separate cohorts were used: (i) those with four QFT tests over the study duration (Cohort 4, e-Figure 3) and (ii) participants with four T-SPOT.TB tests over the study duration (Cohort 5).

Definitions

For each IGRA test, we defined a positive, negative, and 'uncertainty zone' (e-Table 1). We excluded indeterminate results, which were rare. 'Uncertainty zones' for QFT and T-SPOT.TB tests were defined based on prior analyses.[13,14,23] For QFTs, we defined a stringent positive as >0.7 IU/ml with an uncertainty zone between 0.2–0.7 IU/ml. A stringent negative test was defined as <0.2 IU/ml. For Wantai tests, we defined a stringent positive as >=20 pg/ml with an uncertainty zone between 10–19 pg/ml. A stringent negative test was defined as <10 pg/ml. For T-SPOT.TB results, we defined a stringent positive test at baseline as >8 spots with an uncertainty zone between 6–8 spots. A stringent negative test was defined as <6 spots.

Stringent conversion for each test was defined as a stringent negative test followed by a stringent positive test. Similarly, a stringent reversion was defined as a stringent positive test followed by a stringent negative test.

In this study, recent close tuberculosis exposure was defined as persons staying in the same room as the index who had ⩾8 hours of exposure per week with the tuberculosis index at any time in the 3 months prior to diagnosis.

Statistical Analysis

We analyzed each cohort independently. South African and Tanzanian cohorts included only participants that were IGRA negative at baseline. The Chinese and U.S. cohorts included participants that were either IGRA negative or positive at baseline. Interquartile ranges and standard 2×2 contingency tables were used to summarize continuous and categorical variables.

We evaluated the annual risk of stringent IGRA conversion and reversion after 1 and 2 years of follow-up. Our primary analysis used the stringent conversion and reversion definitions described above which consider an 'uncertainty zone'. As a secondary analysis, we used standard cutoffs for each test. We considered annual rates of IGRA conversion among participants testing negative at baseline as well as the annual rate of conversion at the 2nd year visit among persons with a stringent reversion. We considered annual rates of

IGRA reversion among participants testing positive at baseline as well as the annual rate of reversion at the 2nd year visit among persons with a stringent conversion.

We conducted several multivariable binary logit regression models assessing variables associated with stringent conversion or reversion at year 1 and 2. We also conducted models assessing stringent reversion after conversion and vice versa.

Ethical Approval

Ethics Committees approved the study of each cohort separately as previously reported (Appendix, page 1).[17-21] All participants from each cohort gave written informed consent.

Results

Demographic characteristics from each cohort

In total, 7,683 individuals were included in the final analysis from the five longitudinal cohorts (Table 1). The median age of participants in cohorts from South Africa, China, Tanzania, and the two US cohorts were 1 (IQR, 0.9–1.1), 59 (48–67), 14 (13–14), 37 (28–48), and 37 (28–49). For inclusion, BCG vaccination was mandatory in the South African and Tanzanian cohorts; 14%, 10%, and 9% of participants were vaccinated in the Chinese and two US cohorts, respectively. The number of participants varied from 545 from Cohort 3 (1,635 IGRA measurements) to 2,046 from Cohort 1 (6,138 IGRA measurements). (Table 1).

Annual risks of stringent IGRA conversion and reversion over 2 years

First, we examined annual risks of stringent conversion throughout follow-up. From baseline to year 1 testing, the annual risk of stringent conversion was 2.9% (95% CI, 2.2–3.7), 7.9% (95% CI, 6.5–9.6), 2.2% (95% CI, 1.3–3.8), 0.06% (0.0–0.3), and 3.6% (95% CI, 2.8–4.7) in South Africa, China, Tanzania, the United States cohort 1 (QuantiFERON), and the United States cohort 2 (T-SPOT.TB) (Figure 1). These were substantially lower than when using standard IGRA cutoffs. In year 2, stringent conversion rates were similar for South African (3.2%; 95% CI, 2.7–3.8) and Chinese cohorts (4.3%; 95% CI, 3.6–5.2) compared to the first year but similar for the Tanzanian cohort (2.2%; 95% CI, 1.4–3.3). The annual rate of conversion after a stringent reversion were 29.2% (95% CI, 12.6–51.1) in China.

Next, we examined annual risks of reversion during follow-up. Among participants testing positive at baseline in the China cohort, the annual risk of stringent reversion in the first year of testing was 6.8% (95% CI, 4.4–9.9). This was much lower than when using standard IGRA cutoffs for reversion. Over two years of follow-up, the annual rate of stringent reversion remained similar in this cohort (7.7%; 95% CI, 5.8–10.0). In the U.S. cohorts, the annual rate of stringent reversion was much higher, especially at the first six-month visit (between 21% and 39%; Figure 2).

Annual rates of stringent reversion after a stringent conversion were much higher than after baseline positive tests (Figure 3). These rates were highest in the U.S. cohorts (74% and 77% for QFT and T-SPOT.TB) but also above 40% for China and South African cohorts.

Risk factor for IGRA conversion

IGRA conversion was related to distinct results in the four cohorts. In the United States, only male sex was associated with QuantiFERON conversion at 6 months (age-adjusted odds ratio, 2.10, 95% CI, 1.25–3.54) and 12 months (1.57, 95% CI, 1.02–2.40). Older age was associated with IGRA conversion at 24 months (1.01; 95% CI, 1.00–1.02), but not at 12 months. In South Africa, only household tuberculosis exposure was associated with conversion at both 12 (2.27; 95% CI, 1.79–2.88) and 24 months (5.87; 95% CI, 4.70–7.34).

Risk factors for IGRA reversion

We were able to assess risk factors for reversion in South African and Chinese cohorts (Table 2). In the South African cohort, participants were less likely to have a stringent IGRA reversion after a stringent conversion if they were recently closely exposed to a person with tuberculosis (36.5% versus 16.7%; risk difference 20.0%; 95% CI, 1.3–38.6). In China, stringent reversion after a stringent conversion was less likely as age increased (Adjusted Odds Ratio [aOR], 0.92; 95% CI, 0.88–0.97) and among males (aOR, 0.17; 95% CI, 0.04–0.76). When assessing stringent reversion after a baseline IGRA positive test, persons were less likely to revert if they were recently closely exposed to tuberculosis (aOR, 0.13; 95% CI, 0.02–0.98).

Consistency after a result in the 'uncertainty Zone' or a second consecutive stringent negative IGRA result

The majority of results in the 'uncertainty zone' (after a baseline stringently negative test) reverted to stringently negative on subsequent tests (e-Table 2). In the South African, Tanzania, China, and U.S. cohorts, the rate of reversion in year 2 among participants in the 'uncertainty zone' in Year 1 was 95% (91 of 96), 100%, 64%, 70%, and 86% (48 of 56), respectively.

Among participants with two consecutive stringent IGRA negative results, between 90% and 96% of participants across all five cohorts had a third consecutive stringent negative test in year 2 (e-Table 2).

Quantitative IGRA conversion values (at visit 1 after baseline) and risk of reversion (visit 2)

We found distinct reversion risks based on quantitative conversion values (e-Table 3). In cohort 1, a strong relationship was seen between the quantitative IU/mL values at year 1 and risk of reversion at year 2. Among all (94%) infants with 0.35–0.70 IU/ml values at year 1, reverted at year 2 (32 of 34). Only 16% of infants with >4.00 IU/ml values at year 1, reverted at year 2 (5/31). In cohort 4, almost participants with 0.35–0.70 IU/ml values at 6 months, 58% reverted at year 1 (21/36). A similar proportion of participants reverted at year 1 if they had 0.71–2.00 IU/ml values at 6 months (53%). For WANTAI, high levels of reversion at year 2 were seen (between 42–69%) regardless of the pg/mL value seen at year 1.

Discussion

In five independent cohorts encompassing over 7,000 individuals serially tested with IGRAs over 2 years, a large proportion (ranging from 17–60%) of stringent IGRA conversions at year 1 had reverted by year 2. Higher levels of stringent IGRA reversion were related to younger age (from a cohort in China) and recent tuberculosis exposure (from cohorts in China and South Africa). Participants in the 'uncertainty zone' at year 1 were much more likely to revert to negative at year 2 (range, 56–94% in the five cohorts). These results highlight the need to use sustained conversion endpoints for future clinical trials that focus on *M. tuberculosis* infection as an outcome. Furthermore, these results suggest high annual rates of IGRA reversion, higher than some prior study estimates.

We found high, but heterogenous, rates of stringent reversion after a stringent conversion. These high stringent reversion rates were observed despite the fact that we used 'uncertainty zones', which account for test variability and IGRA results close to traditionally used diagnostic cutoffs.[13-15] Stringent reversion after stringent conversion was highest from the cohort in the US (58%), with slightly lower findings in China (55%) and South Africa (36%). The annual risk of stringent reversion after stringent conversion was lowest, approximately 17%, from the Tanzanian cohort however the sample size of stringent converters was low (N=12) and may have explained the low observed proportion. Potential reasons for variability, other than sample size, include the use of distinct IGRA tests.[16] Although all three used IGRA tests are currently recommended for *M tuberculosis* infection testing by the World Health Organization[24] and have shown relatively similar diagnostic value when measured head-to-head,[21] there is likely to be test and measurement variability between them. 'Uncertainty zones' may not overlap precisely between tests.[16]

We found multiple factors that were correlated to stringent reversion. Importantly, persons who had recent close tuberculosis exposure were 90% less likely to experience stringent reversion after stringent conversion. On the other hand, those with standard conversion may proceed to a high reversion rate irrespective of tuberculosis exposure. And stringent converters without tuberculosis exposure may have a high reversion than those with tuberculosis exposure. If tuberculosis exposure is correlated with recent *M tuberculosis* infection, our findings suggest that reversion may be most common soon after *M tuberculosis* infection and then declines over time (similar to trends around progression from infection to disease).[12,25] Alternatively, this finding may be explained by ongoing exposure to tuberculosis and recurrent subclinical infection. Stringent reversion after stringent conversion was less common as participants aged in the cohort from China. Young children are commonly used as a marker for background community *M. tuberculosis* transmission rates.[26] If *M tuberculosis* clearance is more (or less) likely in younger populations, there may be ramifications in interpreting tuberculin or IGRA surveys that are measured at one timepoint.[27] There has been debate about the magnitude of the annual risk of *M tuberculosis* infection in high-burden settings and these results suggest we may be underestimating true risk.[28,29] Male sex was associated with reversion after conversion in the China cohort but not related with other definitions such as reversion after baseline positivity.

There has been an ongoing discussion about the use of IGRA testing, as both an eligibility criterion and as an endpoint, in TB vaccine clinical trials.[30-32] Our findings indicate that 20–50% of individuals with recent IGRA conversion turn negative within a year with no secondary intervention. In addition, among participants testing IGRA positive at baseline, we found that ~15% reverted to negative using standard cutoffs (as used in the trials). Combined, these results suggest that including a second confirmatory IGRA test, especially for the first conversion IGRA values among the "Uncertainty zones" in our study may be prudent when assigning trial endpoints for the prevention of *M. tuberculosis* infection (i.e., sustained IGRA conversion as an outcome).[33]

There are limitations to this study. First, we cannot distinguish whether distinct results between cohorts are due to between-test variability or other cohort differences such as sample size, cohort age, or background tuberculosis burden. We were unable to assess whether certain co-morbidities (e.g., HIV infection) as well as other health factors, impacted IGRA changes over time. The impact of these potential modifiers should be assessed in future studies. However, results from two cohorts with longitudinal QFT and T-SPOT.TB results showed broadly consistent results; our analysis suggested that similar risk factors were related to stringent reversion across cohorts. Second, the age distribution in South African and Tanzanian cohorts was narrow due to the clinical trial design,[17,19,20] limiting our ability to evaluate age as a predictor of reversion in these cohorts. Third, although 'uncertainty zones' have been studied for QFT and T-SPOT.TB assays,[13,14,23] they are less well studied for the WANTAI diagnostic. Fourth, some of our analysis (e.g., for reversion after conversion) had low numbers of events limiting statistical power. Lastly, we did not follow-up these cohorts for incident tuberculosis which would have given corroborative evidence that IGRA reversion in these studies is related to *M. tuberculosis* clearance. However, other cohorts have previously been followed cohorts for incident tuberculosis when deriving 'uncertainty zones'.[13]

Interpretation

In five cohorts with diverse populations, settings, and background tuberculosis risk, the annual risk of stringent IGRA reversion after a stringent conversion was high, ranging from 20–50%, even after accounting for 'uncertainty zones'. Stringent reversion after a stringent conversion was less common with time from exposure from two cohorts and in older age from one cohort. These results highlight the need to use sustained IGRA endpoints for future clinical trials focusing on prevention of *M. tuberculosis* infection and progression from *M tuberculosis* infection to disease. Furthermore, they suggest high annual rates of *M. tuberculosis* infection clearance that decline over time.

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Tables and Figures.

Table 1. Demographic characteristics of participants in 3 included cohorts from China, South Africa, and Tanzania.

Table 2. Predictors for clearance of *Mycobacterium tuberculosis* infection in multiple cohorts.

Figure 1. Trajectories of interferon-gamma release assay results among recent converters from five longitudinal cohorts in China, South Africa, Tanzania, and the United States.

Figure 2. Annual rates of (i) stringent conversion and (ii) stringent reversion in five cohorts of serially IGRA tested participants.

Figure 3. Annual rates of (i) stringent reversion after conversion and (ii) stringent conversion after reversion in five cohorts of serially IGRA tested participants.

Take Home Message

Study Question: When accounting for 'uncertainty zones' through stringent cutoffs, what are the trajectories of interferon-gamma release assays in cases of *Mycobacterium* tuberculosis infection?

Results: Stringent interferon-gamma release assays reversion over two years was common (between 20-60%) even after accounting for 'uncertainty zones'.

Interpretations: High annual rates of *Mycobacterium* tuberculosis infection clearance occurred which was greater than previously estimated.

Table 1. Demographic characteristics of participants in 5 included cohorts from China, South Africa, Tanzania, and the United States.

Characteristics	**Cohort 1 N (%)**	**Cohort 2 N (%)**	**Cohort 3 N (%)**	**Cohort 4 N (%)**	**Cohort 5 N (%)**
Country	South Africa	China	Tanzania	United States	United States
IGRA test used	QFT	WANTAI	T-SPOT.TB	QFT	T-SPOT.TB
'Uncertainty zone' used	0.2 to 0.7 IU/ml	10 to 19 pg/mL	6 to 8 spots	0.2 to 0.7 IU/ml	6 to 8 spots
N_{total}	2,046	1,618	545	1,992	1,599
$N_{baseline\ stringent\ positive}$	0	353	0	48	121
$N_{baseline\ 'uncertainty\ zone'}$	0	124	0	88	62
$N_{baseline\ stringent\ negative}$	2,046	1,141	545	1,786	1,416
Timepoints for follow-up testing, days	336, 730	365, 730	365, 730	180, 365, 540	180, 365, 540
Total IGRA measurements	6,138	4,635	1,635	7,792	6,396
Total follow-up time, years	4,092	3,090	1,090	2,922	2,399
Median age, year (IQR)	1 (1–1)	59 (48–67)	14 (13–14)	37 (28–48)	37 (28–49)
Male sex	1,040 (51)	598 (39)	248 (46)	483 (25)	407 (26)
BCG vaccination	2,046 (100)	222 (14)	545 (100)	188 (10)	149 (9)
HIV status	0 (0)	0 (0)	N/A	10 (<1)	7 (<1)
Prior tuberculosis	0 (0)	21 (1)	0 (0)	0 (0)	0 (0)
Tuberculosis exposure at baseline	0 (0)	90 (6)	0 (0)	753 (39)	618 (39)

N/A, not available. Data with this value represents data that was not collected as part of the primary study.

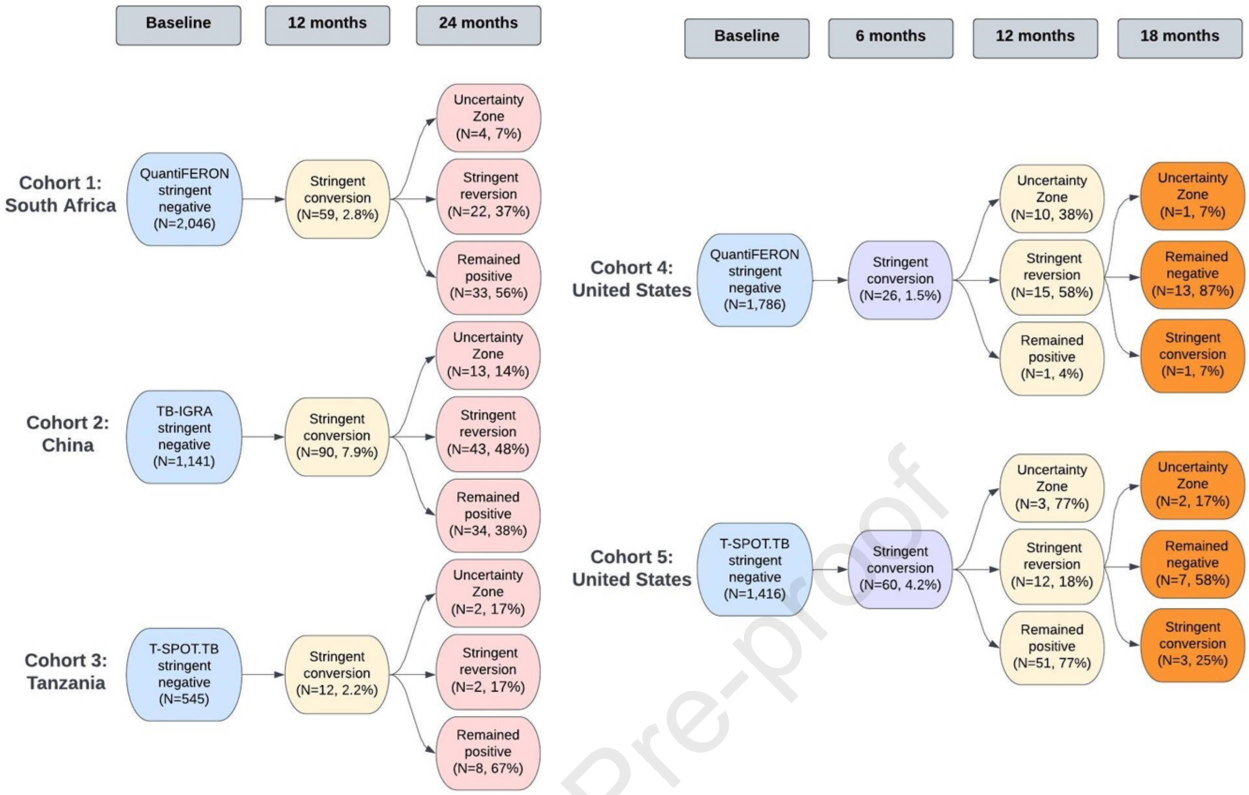
Table 2. Predictors for different definitions of stringent IGRA reversion in multiple cohorts.

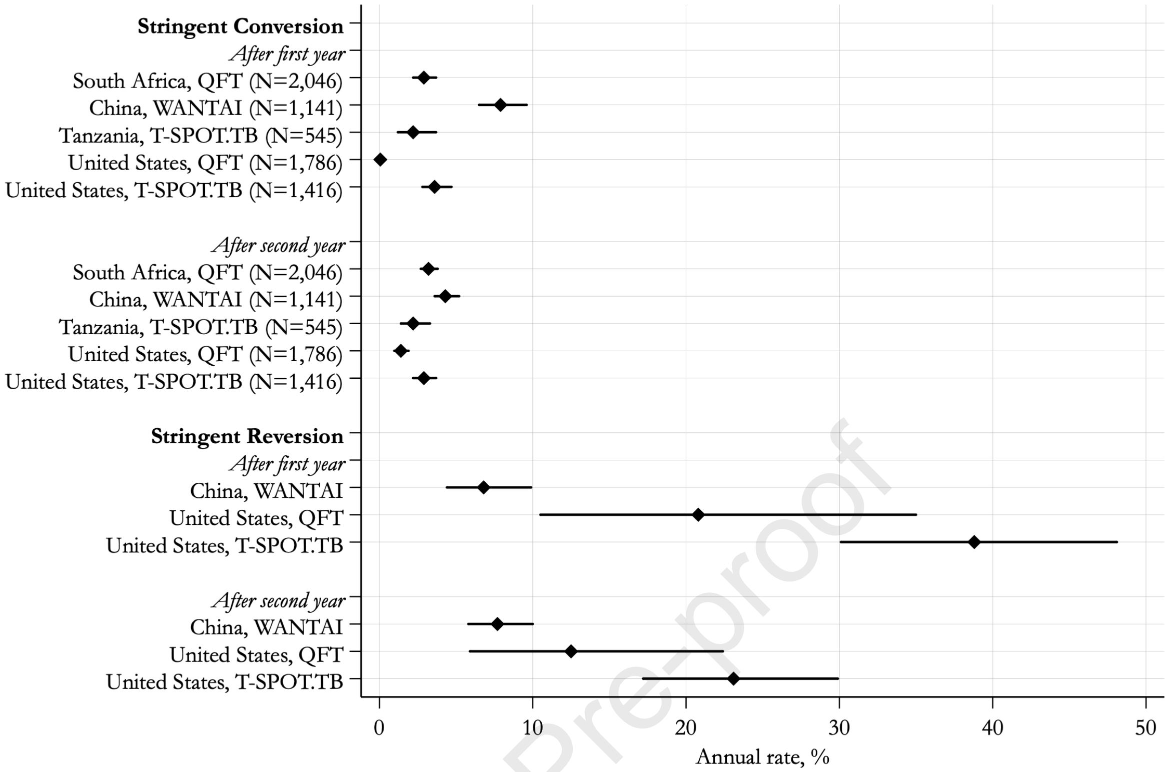
	Adjusted Odds Ratio	95% CI	P value
Cohort 1: South Africa			
‘Stringent’ cutoff			
Reversion after conversion (N_{events}=24; N_{total}=82)			
Age, years‡	0.99	0.96–1.03	0.653
Male sex	1.36	0.51–3.60	0.540
Recent close tuberculosis exposure	0.35	0.11–1.06	0.063
Cohort 2: China			
‘Stringent’ cutoff			
Reversion after conversion (N_{events}=27; N_{total}=53)			
Age, years‡	0.92	0.88–0.97	0.002
Male sex	0.17	0.04–0.76	0.020
Recent close tuberculosis exposure	N/A	N/A	N/A
Reversion after baseline positivity (N_{events}=48; N_{total}=346)			
Age, years‡	0.97	0.95–0.99	0.048
Male sex	0.93	0.50–1.71	0.807
Recent close tuberculosis exposure	0.13	0.02–0.98	0.047
Combined reversion (N_{events}=75; N_{total}=399)			
Age, years‡	0.95	0.93–0.97	<0.001
Male sex	0.77	0.45–1.32	0.345
Recent close tuberculosis exposure	0.10	0.01–0.61	0.014

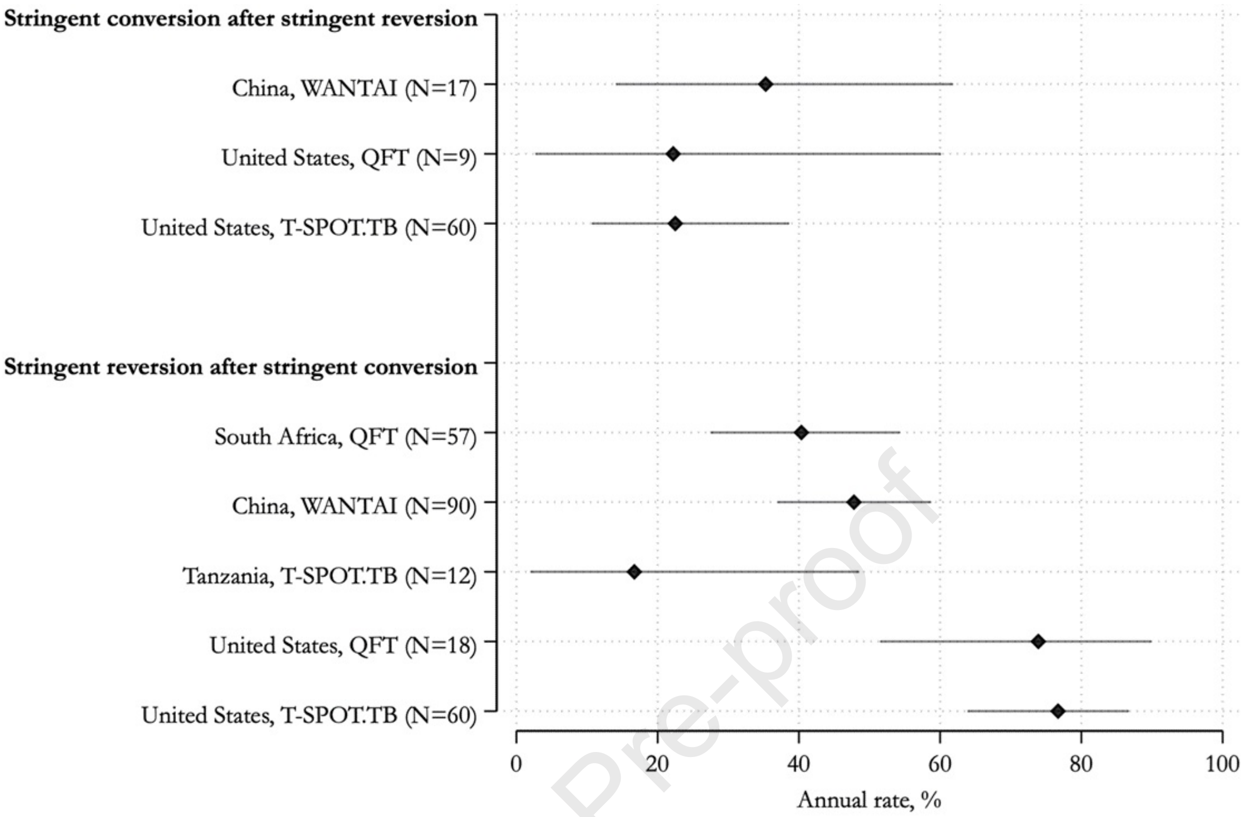
‡ Age was treated as a continuous variable.

N/A in the table signifies there was insufficient power in the regression model.

We were not able to assess risk factors for reversion in other cohorts due to low sample size or lack of corresponding variables during data collection.


Baseline
12 months
24 months
Baseline
6 months
12 months
18 months
Cohort 1: South Africa
QuantiFERON stringent negative (N=2,046)
Stringent conversion (N=59, 2.8%)
Uncertainty Zone (N=4, 7%)
Stringent reversion (N=22, 37%)
Remained positive (N=33, 56%)
Cohort 2: China
TB-IGRA stringent negative (N=1,141)
Stringent conversion (N=90, 7.9%)
Uncertainty Zone (N=13, 14%)
Stringent reversion (N=43, 48%)
Remained positive (N=34, 38%)
Cohort 3: Tanzania
T-SPOT.TB stringent negative (N=545)
Stringent conversion (N=12, 2.2%)
Uncertainty Zone (N=2, 17%)
Stringent reversion (N=2, 17%)
Remained positive (N=8, 67%)
Cohort 4: United States
QuantiFERON stringent negative (N=1,786)
Stringent conversion (N=26, 1.5%)
Uncertainty Zone (N=10, 38%)
Stringent reversion (N=15, 58%)
Remained positive (N=1, 4%)
Uncertainty Zone (N=1, 7%)
Remained negative (N=13, 87%)
Stringent conversion (N=1, 7%)
Cohort 5: United States
T-SPOT.TB stringent negative (N=1,416)
Stringent conversion (N=60, 4.2%)
Uncertainty Zone (N=3, 77%)
Stringent reversion (N=12, 18%)
Remained positive (N=51, 77%)
Uncertainty Zone (N=2, 17%)
Remained negative (N=7, 58%)
Stringent conversion (N=3, 25%)


Stringent Conversion
After first year
South Africa, QFT (N=2,046)
China, WANTAI (N=1,141)
Tanzania, T-SPOT.TB (N=545)
United States, QFT (N=1,786)
United States, T-SPOT.TB (N=1,416)
After second year
South Africa, QFT (N=2,046)
China, WANTAI (N=1,141)
Tanzania, T-SPOT.TB (N=545)
United States, QFT (N=1,786)
United States, T-SPOT.TB (N=1,416)
Stringent Reversion
After first year
China, WANTAI
United States, QFT
United States, T-SPOT.TB
After second year
China, WANTAI
United States, QFT
United States, T-SPOT.TB
0
10
20
30
40
50
Annual rate, %


Stringent conversion after stringent reversion
China, WANTAI (N=17)
United States, QFT (N=9)
United States, T-SPOT.TB (N=60)
Stringent reversion after stringent conversion
South Africa, QFT (N=57)
China, WANTAI (N=90)
Tanzania, T-SPOT.TB (N=12)
United States, QFT (N=18)
United States, T-SPOT.TB (N=60)
0
20
40
60
80
100
Annual rate, %