Interferon-gamma release assay levels and risk of progression to active tuberculosis: a systematic review and dose-response meta-regression analysis

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Abstract

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Objective: To summarize and quantify the dose-response relationship between interferon-gamma release assay (IGRA) levels and the risk of progression to active tuberculosis (TB)

Design: Systematic review and Bayesian dose-response meta-regression

Data sources: PubMed and Embase from 2001 to 10 May 2020, and references from relevant systematic reviews.

Eligibility criteria and data analysis: Retrospective or prospective cohort studies and clinical trials that followed individuals over time to assess the relationship between IGRA levels and risk of developing TB were included. Study results related to incident TB were extracted and two authors independently assessed the quality of included studies using the Newcastle-Ottawa scale (NOS). Data were pooled using a novel Bayesian meta-regression method to generate a dose-response risk curve.

Results: 34 of 1,074 identified studies met the criteria for inclusion in the analysis. Higher levels of interferon-gamma were associated with increased risk of progression to active tuberculosis. In the dose-response curve, the risk increased sharply between interferon-gamma levels 0 and 5 IU/ml, after which the risk continued to increase moderately but at a slower pace until reaching about 15 IU/ml where the risk levels off. Compared to 0 IU/ml, the relative risk of progression to active TB among those with interferon-gamma levels of 0.35, 1, 5, 10, 15, and 20 IU/ml were: 1.67 (1.30 – 2.13), 2.91 (2.12 – 3.96), 10.13 (5.57 – 14.57), 16.42 (11.07 – 23.44), 19.11 (13.01 –

27.82), and 19.65 (13.52 – 28.82), respectively. The dose-response relationship remains consistent when limiting the analysis to studies that scored high in the NOS.

Conclusions: The current practice of dichotomizing IGRA test results simplifies the TB infection disease continuum. Evaluating the IGRA test results over a continuous scale could enable the identification of individuals at greatest risk of progression to active TB.

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1. Introduction

Tuberculosis (TB) is the leading cause of mortality from a single infectious agent, with more than 1 million deaths per year.[1] Mycobacterium tuberculosis (Mtb) is the causative agent of TB, though a person with Mtb infection can remain asymptomatic in a state known as latent TB infection (LTBI). While individuals with LTBI are asymptomatic, they are an important reservoir for future TB cases. Approximately one quarter of the world's population is estimated to have LTBI[2], of which 5 to 15 percent will develop active TB at some point in their lives. Identifying individuals with LTBI and placing those at risk of developing active TB on preventive treatment is thus critical for eliminating the disease.[3]

The tuberculin skin test (TST) has traditionally been used to test for latent TB infection, but has known limitations. Most notably, its specificity is adversely affected by BCG vaccination or infection with nontuberculous mycobacteria. Additionally, TST requires multiple health care visits over 48-72 hours to place the test and read the result, which may be prone to inter-reader variability.[4] Alternatives to the TST are T-cell-based interferon-gamma release assays (IGRAs). Two forms of IGRAs are currently available for commercial use: QuantiFERON TB Gold in tube (QFT-GIT) and T-SPOT.TB. IGRAs have several advantages over TST such as higher specificity for Mtb and lack of cross reaction with BCG vaccination. IGRAs have become the primary diagnostic tool for LTBI in low to intermediate TB burden countries.[5] The use of IGRAs is expected to further expand in high TB burden countries, as the WHO has recently endorsed the use of QFT-GIT for the Stop TB strategy.[6]

Given the likely increased use of QFT-GIT in high TB burden settings, it is critical to review the utility of QFT-GIT to predict progression to active TB. A recent meta-analysis of cohort studies indicated that TB contacts with a positive IGRA result have a 10.8-fold higher rate of progression to active TB.[7] In addition, recent individual studies have suggested a need to further examine the entire distribution of IGRA values for risk analyses of subsequent active TB.[8–10] These studies have shown a marked increase in the risk of incident active TB disease with higher IGRA values. Some researchers have called for a need to report a borderline zone, an intermediate area between a negative and positive IGRA test, to improve the diagnostic accuracy of potential development of active TB.[11–13] Together the literature suggests that there is potentially a loss of

information for identification of individuals at high risk of active TB when IGRA results are dichotomized by the traditional 0.35 IU/ml threshold.

Previously published systematic reviews and meta-analyses of IGRA performance have yet to take into account the full spectrum of the infection by considering IGRA values at a continuous scale. A consideration of the entire distribution of IGRA levels rather than a binary cut-off may help inform treatment considerations for those at the highest risk of progressing to active TB. We aimed to conduct a systematic review and meta-analysis to quantify the dose-response relationship between IGRA levels and risk of progression to active TB using all available global data sources.

2. Methods

2.1. Literature Search

In this systematic review and meta-analysis we followed reporting guidelines established by PRISMA and MOOSE. We searched PubMed and Embase from 1 January 2001 to 10 May 2020 for studies that reported the risk of progression from latent to active TB based on baseline IGRA values. The full search strategy is available in the supplementary material. We restricted to papers published in 2001 and afterwards as IGRAs were approved by the U.S. Food and Drug Administration in 2001.[14] In addition, we made no restrictions in study language. The reference lists of eligible full texts and identified systematic reviews were reviewed for additional studies.

2.2. Study Selection

Retrospective or prospective cohort studies and clinical trials that assessed QFT-GIT results as the exposure variable and progression to active tuberculosis as an outcome were eligible for inclusion. The study participants were adults or children who were free of active TB disease at baseline. We excluded studies that contained a sample with a confounding disease (e.g. lung cancer, rheumatic diseases, inflammatory bowel diseases) or participants undergoing immunosuppression therapies, did not test all individuals with QFT-GIT, and did not follow-up all individuals for progression to active TB disease. We further excluded studies that only focused on QFT-GIT conversion or had participants with previous positive QFT-GIT tests.

2.3. Data Extraction

Data were extracted by JL using a standardized data extraction form developed a priori. A random sample of 26% of the included studies were re-extracted by JM, with discrepancies resolved by consensus. The following variables were extracted from each study: study design, location, follow-up duration, sample attrition rate, baseline age-sex distribution, TB preventive treatment use, sample size by baseline QFT-GIT results (IU/ml categories), number of cases progressing to active TB by IU/ml categories, and method for diagnosing active TB. Information on participant characteristics (e.g. general population, TB contacts, healthcare workers, etc.) was also extracted. For person-year information, we used the study mean or median as follow-up time if follow-up time was not disaggregated for every QFT-GIT category.

2.4. Assessment of Quality of Included Studies

The quality of included studies was examined independently by JRL and JM using the Newcastle-Ottawa quality assessment scale (NOS).[15] Two authors, JRL and HHK, developed the evaluation criteria. Potential scores range from 0 to 9 points, with higher scores representing higher quality studies. Study scores were based on the following criteria: selection of the study population, comparability between exposed and non-exposed groups, and assessment of the outcome. Any disagreements during quality assessment review were resolved by discussion or by involving a third author (HHK).

2.5. Data Analysis

We used a novel Bayesian meta-regression method[16] to analyze data from included studies and generate a continuous risk curve for the association between IGRA values and risk of progression to active TB. This method allowed us to incorporate random-effects across studies and include heterogeneous data with various IGRA categories. Detailed methods and equations can be found in the appendix. We separately analyzed studies where the study population were people living with HIV (PLHIV).

2.6. Sensitivity Analyses and Subgroup Analyses

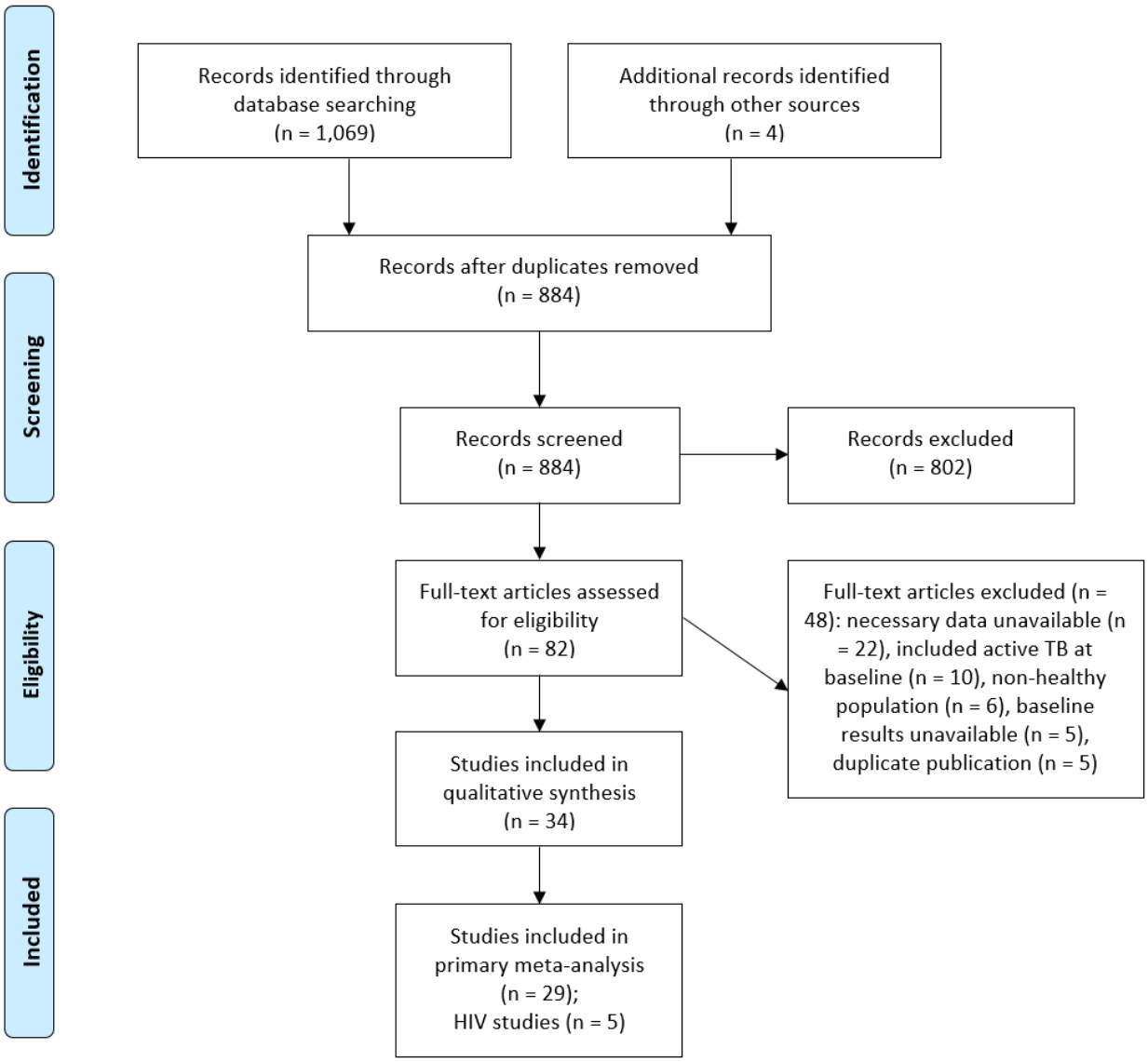
We assessed the robustness of the dose-response risk curve by conducting a sensitivity analysis stratifying results by their NOS score. We assessed for the potential of effect modification by study-level population. The population subgroup analyses included: TB case contacts, healthcare workers, migrants, PLHIV, adults (>18 years), and children (<18 years). We conducted additional subgroup analyses by stratifying results by whether studies provided any TB preventive treatment (TPT). Across the subgroup analyses, all model parameters for the Bayesian meta-regression remained consistent with the primary analysis. To investigate differences in the dose-response curves between subgroups we generated 1,000 estimates from the posterior distributions to generate a ratio of the relative risks with uncertainty.

3. Results

3.1. Study Characteristics

Our literature search identified a total of 1,074 citations (Figure 1). After removal of duplicate citations, 884 remained for title and abstract review of which 82 were included for full-text assessment. We included 34 studies in our dose-response meta-analysis, 18 of which were conducted in Europe, 8 in Asia, 2 in North America, 2 in the Middle East, 2 in Sub-Saharan Africa, 1 in Latin America, and 1 in Australasia. The 34 studies provided a combined cohort size of 581,956 person-years with a total of 788 incident cases of TB. The median study duration was 2.5 years (IQR 1.75 – 4.30).

Figure 1: Flow chart of study selection

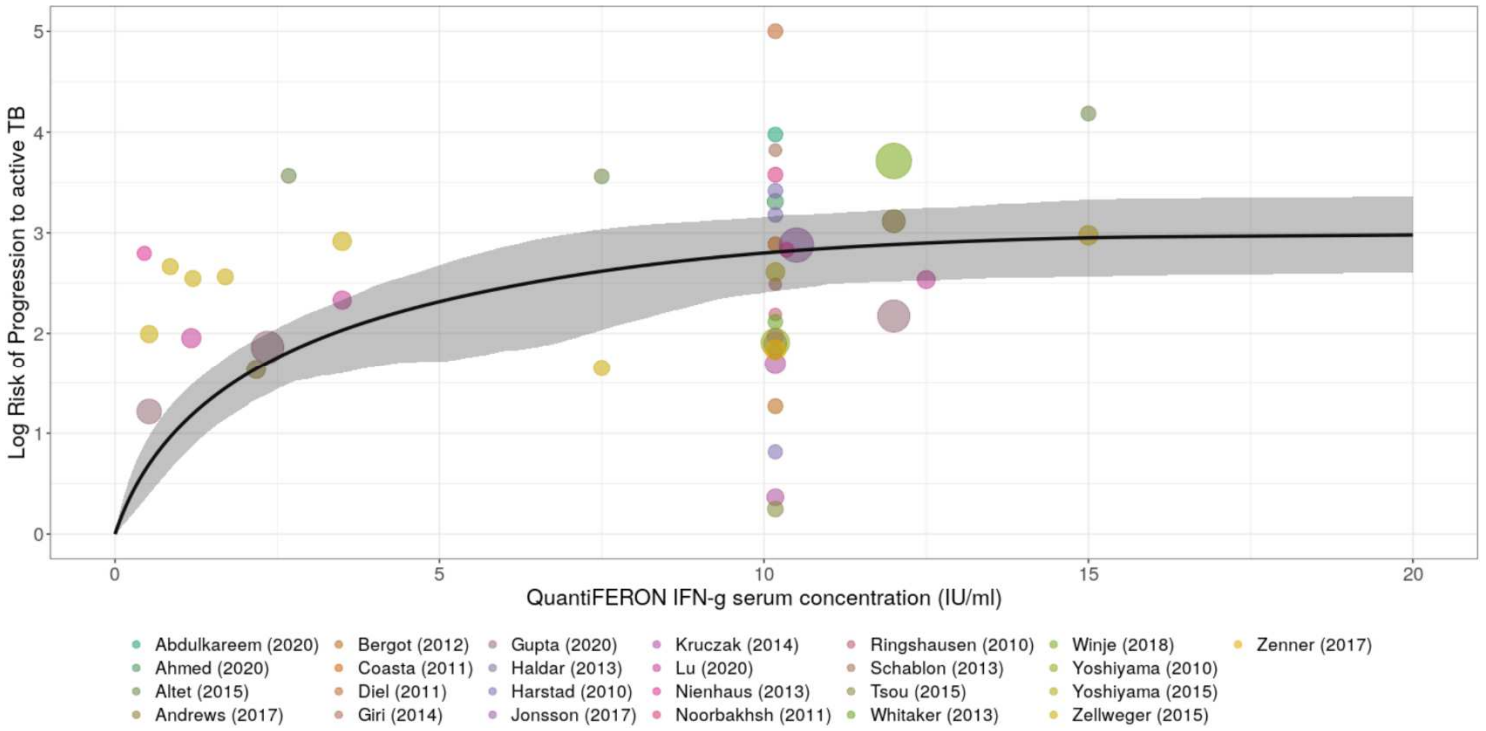


Most study cohorts included participants at elevated risk for TB (Table S1). Of the included studies, 15 cohorts included TB case contacts, 8 cohorts of healthcare workers, and 5 cohorts included migrants or asylum seekers. In addition, 2 studies were population-based and another study included individuals without known exposure to TB. 17 studies provided TPT to participants ranging from 1 to 19 percent of the study sample, while 7 studies did not provide TPT.

3.2. Dose-Response Relationship

Overall, higher levels of IFN-gamma were associated with increased risk of progression to active tuberculosis (figure 2). We find that the risk increased sharply between IFN-gamma levels 0 and 5 IU/ml, after which the risk continued to increase moderately but at a slower pace until reaching about 15 IU/ml where the risk levels off until 20 IU/ml. Table 1a provides quantitative measurements of the dose-response risk curve for the primary analysis. Specifically, the relative risk of progression to active TB compared to 0 IU/ml for those with IFN-gamma levels of 0.20, 0.35, 0.70, 1, 5, 10, 15, and 20 IU/ml were: 1.38 (1.16 – 1.66), 1.67 (1.30 – 2.13), 2.33 (1.70 – 3.14), 2.91 (2.12 – 3.96), 10.13 (5.57 – 14.57), 16.42 (11.07 – 23.44), 19.11 (13.01 – 27.82), and 19.65 (13.52 – 28.82), respectively.

Figure 2: Dose-response curve for the association between interferon gamma levels and risk of developing active tuberculosis



The continuous dose-response curve illustrating the risk of developing active tuberculosis in the logarithmic scale as a function of QFT-GIT IFN-gamma levels (IU/ml) with input data informing this analysis. Circle size represents the inverse of the variance of the data. Extreme values not shown.

Table 1a. Risk of progression to active TB across IFN-gamma levels (IU/ml) by model

IFN-gamma levels (IU/ml)	Relative Risk (95% Uncertainty interval)					
	Primary Analysis	High Quality Studies*	Received TPT	No TPT	Adults	Children
0.00	REF	REF	REF	REF	REF	REF
0.10	1.19 (1.07 to 1.33)	1.27 (1.11 to 1.44)	1.18 (1.02 to 1.38)	1.22 (1.08 to 1.38)	1.23 (1.09 to 1.38)	1.13 (1.00 to 1.41)
0.20	1.38 (1.16 to 1.66)	1.52 (1.23 to 1.88)	1.36 (1.05 to 1.75)	1.44 (1.17 to 1.74)	1.46 (1.18 to 1.74)	1.26 (1.00 to 1.81)
0.30	1.57 (1.25 to 1.98)	1.78 (1.34 to 2.30)	1.53 (1.08 to 2.12)	1.64 (1.26 to 2.10)	1.68 (1.28 to 2.10)	1.37 (1.01 to 2.19)
0.35	1.67 (1.30 to 2.13)	1.90 (1.41 to 2.51)	1.62 (1.10 to 2.31)	1.75 (1.31 to 2.27)	1.79 (1.33 to 2.27)	1.43 (1.01 to 2.38)
0.40	1.76 (1.35 to 2.28)	2.02 (1.47 to 2.71)	1.70 (1.12 to 2.49)	1.85 (1.36 to 2.44)	1.89 (1.38 to 2.44)	1.49 (1.01 to 2.57)
0.50	1.95 (1.46 to 2.57)	2.27 (1.60 to 3.11)	1.87 (1.15 to 2.85)	2.05 (1.45 to 2.77)	2.10 (1.48 to 2.78)	1.60 (1.01 to 2.95)
0.70	2.33 (1.70 to 3.14)	2.74 (1.85 to 3.88)	2.19 (1.25 to 3.52)	2.44 (1.66 to 3.40)	2.50 (1.69 to 3.41)	1.81 (1.02 to 3.67)
1.00	2.91 (2.12 to 3.96)	3.42 (2.23 to 4.95)	2.66 (1.43 to 4.45)	3.01 (1.99 to 4.27)	3.07 (2.01 to 4.29)	2.13 (1.03 to 4.73)
2.00	4.84 (3.53 to 6.54)	5.40 (3.57 to 7.90)	4.08 (2.09 to 7.03)	4.68 (3.11 to 6.78)	4.65 (3.06 to 6.66)	3.10 (1.06 to 7.67)
3.00	6.72 (4.68 to 9.05)	6.99 (4.48 to 10.59)	5.31 (2.49 to 9.13)	6.05 (4.02 to 8.57)	5.80 (3.76 to 8.31)	3.95 (1.15 to 11.06)
4.00	8.49 (5.27 to 11.86)	8.22 (4.88 to 13.83)	6.34 (2.68 to 10.73)	7.15 (4.38 to 10.30)	6.61 (4.07 to 9.41)	4.72 (1.28 to 14.53)
5.00	10.13 (5.57 to 14.57)	9.19 (5.04 to 16.96)	7.26 (2.91 to 12.47)	8.03 (4.61 to 12.03)	7.17 (4.24 to 10.58)	5.48 (1.45 to 18.14)

6.00	11.64 (6.20 to 17.48)	10.01 (5.16 to 20.20)	8.14 (3.47 to 13.79)	8.79 (4.84 to 13.83)	7.59 (4.43 to 11.53)	6.30 (1.72 to 21.91)
7.00	13.05 (6.93 to 19.83)	10.80 (5.40 to 22.70)	9.08 (4.37 to 15.21)	9.54 (5.41 to 15.38)	7.99 (4.90 to 12.54)	7.23 (2.03 to 25.37)
8.00	14.33 (8.33 to 21.51)	11.61 (5.91 to 25.13)	10.06 (5.57 to 16.38)	10.30 (6.24 to 16.71)	8.43 (5.38 to 13.30)	8.25 (2.46 to 27.55)
10.00	16.42 (11.07 to 23.44)	13.13 (6.51 to 28.92)	11.91 (7.61 to 17.99)	11.72 (7.41 to 18.17)	9.30 (6.21 to 14.22)	10.24 (2.96 to 33.94)
12.00	17.86 (12.38 to 25.29)	14.35 (6.86 to 33.04)	13.39 (8.45 to 20.84)	12.86 (8.10 to 20.18)	10.06 (6.47 to 15.72)	11.90 (3.47 to 39.68)
15.00	19.11 (13.01 to 27.89)	15.48 (7.17 to 36.29)	14.79 (9.03 to 24.85)	14.01 (8.59 to 23.25)	10.93 (6.85 to 17.76)	13.44 (4.03 to 45.99)
20.00	19.65 (13.52 to 28.83)	16.02 (7.64 to 36.82)	15.32 (9.44 to 25.67)	14.51 (8.99 to 23.87)	11.40 (7.27 to 18.22)	14.04 (4.33 to 46.61)

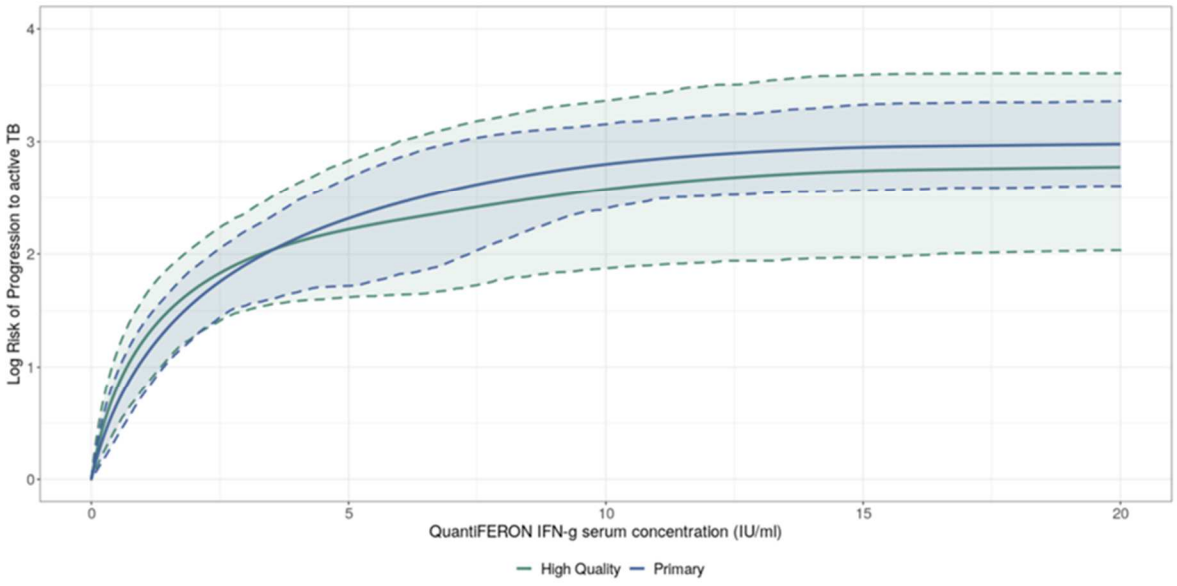
*Sensitivity analysis excluding studies with NOS score <5

NOTE: TPT (TB preventive treatment)

3.3. Sensitivity Analyses

The quality assessment scores for each study are in Table S1. According to the quality assessment, the quality of the including studies ranged between 6, indicating moderate quality, and 2, indicating lower quality. Particularly, 11 (32%) studies scored between 5 and 6, 12 (35%) studies scored a 4, and the remaining 11 (32%) studies scored between 2 and 3. Sensitivity analyses that excluded studies with an NOS score lower than 5 exhibit similar results to models utilizing the complete dataset (Figure 3; Table 1a). While the curve including high-quality studies was steeper at the lower end and lower at the higher end compared to the primary analysis, the differences were not statistically significant.

Figure 3: Sensitivity analysis results (excluding studies with NOS quality score <5)

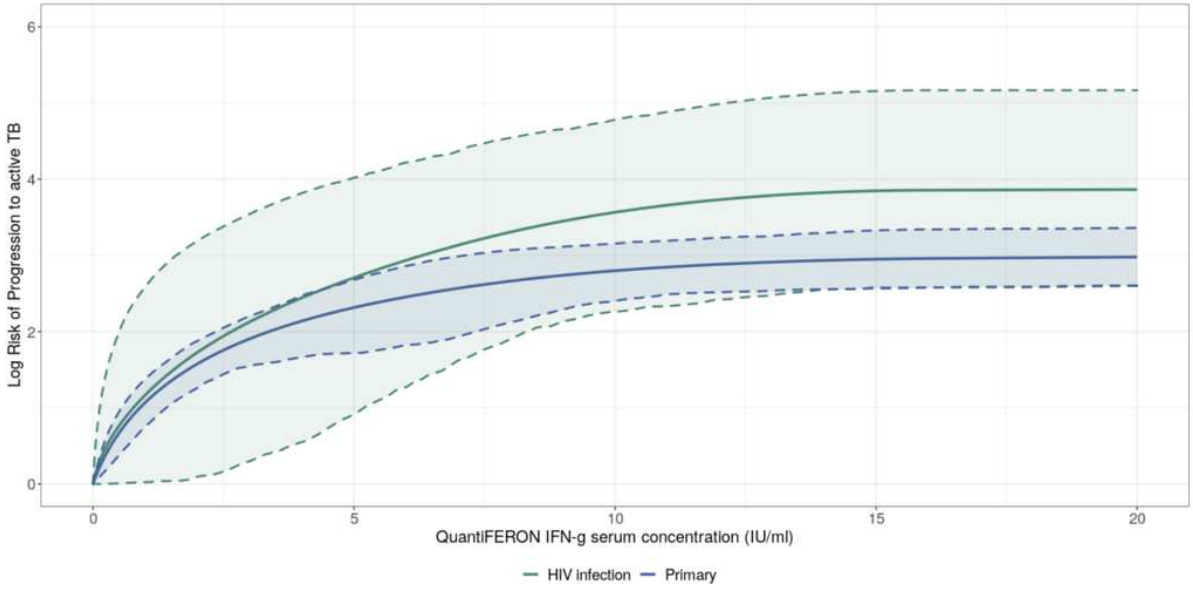


IFN-gamma levels (IU/ml)	Ratio of Relative Risks (95% UI)
0.00	1.00 (1.00 to 1.00)
0.10	1.07 (0.91 to 1.26)
0.20	1.11 (0.84 to 1.46)
0.30	1.15 (0.80 to 1.60)
0.35	1.16 (0.79 to 1.66)
0.40	1.17 (0.78 to 1.70)
0.50	1.19 (0.76 to 1.78)
0.70	1.21 (0.74 to 1.87)
1.00	1.21 (0.73 to 1.91)
2.00	1.15 (0.68 to 1.79)
3.00	1.08 (0.59 to 1.78)
4.00	1.02 (0.51 to 1.89)
5.00	0.98 (0.43 to 2.01)
6.00	0.94 (0.38 to 2.00)
7.00	0.92 (0.36 to 1.94)
8.00	0.90 (0.36 to 1.89)
10.00	0.89 (0.35 to 1.88)
12.00	0.90 (0.33 to 2.00)
15.00	0.91 (0.33 to 2.13)
20.00	0.92 (0.34 to 2.11)

3.4. Subgroup Analyses

In subgroup analyses, there was some heterogeneity in risk across IFN-gamma levels for at risk populations. The risk of TB among PLHIV was higher compared to the rate found in the primary analysis. Across all levels of IFN-gamma, the dose-response risk curve for PLHIV was substantially higher compared to the primary analysis (Figure 4a; Table 1b). Among TB case contacts (Figure 4b; Table 1b) and migrants (Figure 4c; Table 1b) the risk was steeper at the lower end of IFN-gamma levels (<2.5 IU/ml) but the risk was lower in the remaining IFN-gamma levels compared to the primary analysis. For healthcare workers (Figure 4d; Table 1b), the dose-response risk curve yielded similar results to the primary analysis. Similarly, we found no difference in the risk of progression to active TB when stratifying results by whether studies provided TPT. (Figure 4e; Table 1a). Finally, we found that the dose-response risk curve was steeper at the lower end (<7.5 IU/ml) for adults compared to children but the risks converged afterwards (Figure 4f; Table 1a).

Figure 4a: Subgroup analysis results (comparing PLHIV with HIV-negative individuals)

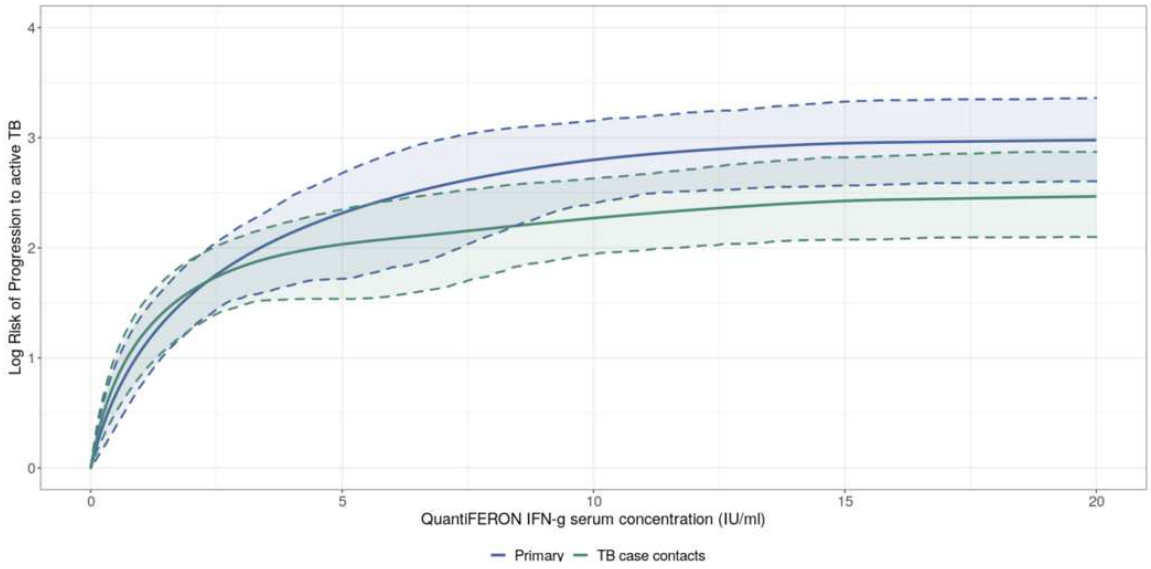


IFN-gamma levels (IU/ml)	Ratio of Relative Risks (95% UI)
0.00	1.00 (1.00 to 1.00)
0.10	1.11 (0.78 to 1.94)
0.20	1.19 (0.65 to 2.60)
0.30	1.25 (0.56 to 3.08)
0.35	1.28 (0.53 to 3.28)
0.40	1.30 (0.50 to 3.46)
0.50	1.35 (0.46 to 3.76)
0.70	1.42 (0.40 to 4.15)
1.00	1.49 (0.34 to 4.52)
2.00	1.61 (0.23 to 5.22)
3.00	1.71 (0.20 to 5.36)
4.00	1.83 (0.20 to 5.41)
5.00	1.96 (0.25 to 5.68)
6.00	2.09 (0.29 to 6.06)
7.00	2.23 (0.37 to 6.49)
8.00	2.37 (0.46 to 6.87)
10.00	2.65 (0.55 to 7.73)
12.00	2.92 (0.58 to 8.74)
15.00	3.12 (0.64 to 9.62)
20.00	3.08 (0.64 to 9.48)

Table 1b. Risk of progression to active TB across IFN-gamma levels (IU/ml) by risk group

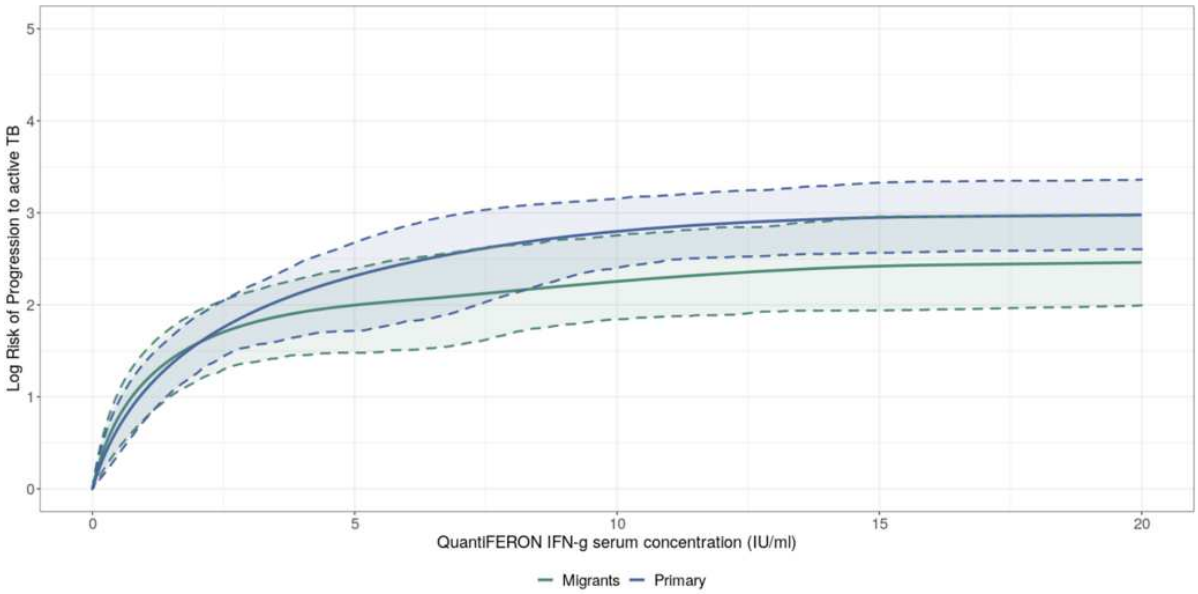
IFN-gamma levels (IU/ml)	Relative Risk (95% Uncertainty interval)			
	People living with HIV	TB Case Contacts	Healthcare workers	Migrants
0.00	REF	REF	REF	REF
0.10	1.28 (1.00 to 2.33)	1.26 (1.13 to 1.38)	1.20 (1.00 to 1.75)	1.25 (1.11 to 1.39)
0.20	1.51 (1.00 to 3.62)	1.51 (1.26 to 1.75)	1.38 (1.00 to 2.48)	1.49 (1.22 to 1.78)
0.30	1.73 (1.00 to 4.88)	1.75 (1.40 to 2.11)	1.54 (1.00 to 3.19)	1.73 (1.33 to 2.15)
0.35	1.83 (1.00 to 5.50)	1.87 (1.46 to 2.29)	1.62 (1.00 to 3.54)	1.84 (1.39 to 2.34)
0.40	1.94 (1.01 to 6.11)	1.99 (1.53 to 2.46)	1.70 (1.00 to 3.89)	1.96 (1.45 to 2.52)
0.50	2.14 (1.01 to 7.36)	2.22 (1.66 to 2.80)	1.85 (1.00 to 4.57)	2.18 (1.56 to 2.87)
0.70	2.56 (1.01 to 9.85)	2.67 (1.93 to 3.45)	2.16 (1.01 to 5.91)	2.61 (1.79 to 3.55)
1.00	3.21 (1.02 to 13.27)	3.29 (2.32 to 4.35)	2.61 (1.02 to 7.91)	3.21 (2.15 to 4.45)
2.00	5.62 (1.10 to 24.32)	5.00 (3.54 to 6.65)	4.15 (1.04 to 14.67)	4.86 (3.22 to 6.92)
3.00	8.39 (1.35 to 34.57)	6.23 (4.38 to 8.20)	5.70 (1.13 to 20.44)	6.04 (3.95 to 8.52)
4.00	11.50 (1.73 to 45.48)	7.07 (4.63 to 9.41)	7.28 (1.32 to 25.47)	6.84 (4.28 to 9.89)
5.00	14.99 (2.49 to 55.66)	7.63 (4.65 to 10.45)	8.97 (1.71 to 32.51)	7.37 (4.39 to 10.99)
6.00	18.83 (3.56 to 67.91)	8.03 (4.78 to 11.36)	10.80 (2.25 to 37.49)	7.77 (4.53 to 12.22)
7.00	23.00 (5.07 to 78.98)	8.41 (5.14 to 12.16)	12.80 (2.91 to 42.91)	8.16 (4.79 to 13.22)
8.00	27.30 (6.68 to 94.05)	8.83 (5.83 to 12.85)	14.89 (3.61 to 48.48)	8.60 (5.44 to 14.14)
10.00	35.34 (9.59 to 119.43)	9.68 (6.97 to 13.88)	18.78 (5.13 to 60.87)	9.54 (6.32 to 15.74)
12.00	41.74 (11.25 to 146.63)	10.44 (7.48 to 15.09)	21.82 (5.99 to 72.87)	10.37 (6.63 to 17.17)
15.00	46.86 (13.17 to 173.69)	11.31 (7.96 to 16.81)	24.37 (6.81 to 87.58)	11.26 (6.95 to 19.29)
20.00	47.70 (13.46 to 175.51)	11.79 (8.15 to 17.67)	25.03 (7.22 to 90.24)	11.72 (7.35 to 19.49)

Figure 4b: Subgroup analysis results (comparing TB case contacts with primary analysis)



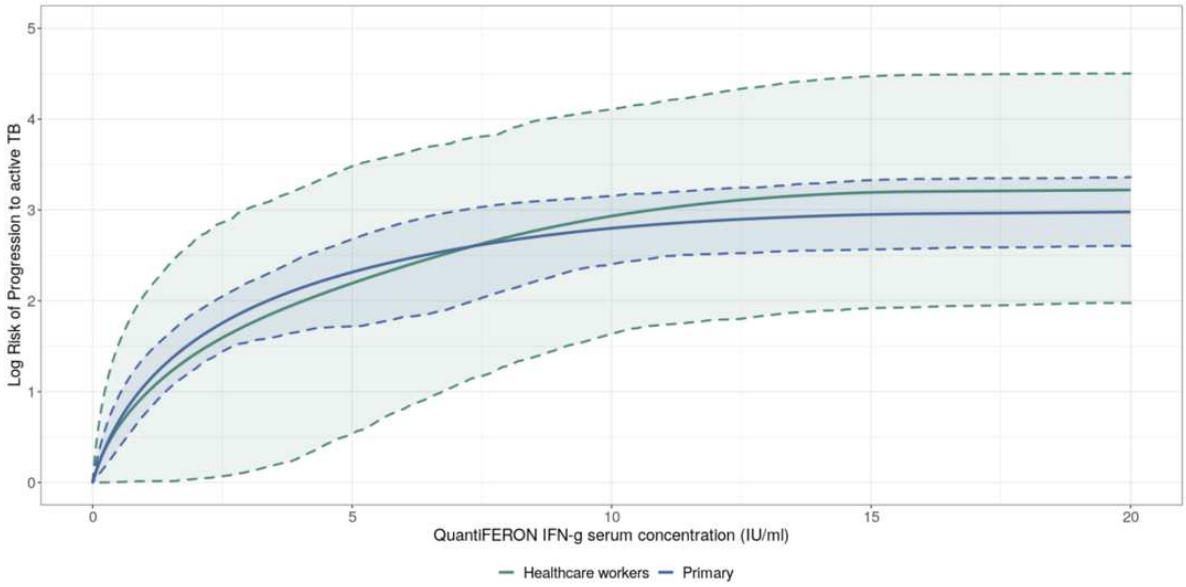
IFN-gamma levels (IU/ml)	Ratio of Relative Risks (95% UI)
0.00	1.00 (1.00 to 1.00)
0.10	1.06 (0.91 to 1.21)
0.20	1.10 (0.85 to 1.37)
0.30	1.13 (0.81 to 1.49)
0.35	1.14 (0.80 to 1.54)
0.40	1.15 (0.79 to 1.59)
0.50	1.16 (0.77 to 1.66)
0.70	1.17 (0.74 to 1.71)
1.00	1.16 (0.72 to 1.74)
2.00	1.06 (0.65 to 1.56)
3.00	0.95 (0.57 to 1.45)
4.00	0.86 (0.48 to 1.47)
5.00	0.79 (0.40 to 1.45)
6.00	0.73 (0.35 to 1.44)
7.00	0.68 (0.34 to 1.30)
8.00	0.65 (0.34 to 1.14)
10.00	0.61 (0.36 to 0.95)
12.00	0.60 (0.36 to 0.97)
15.00	0.62 (0.35 to 1.02)
20.00	0.62 (0.35 to 1.04)

Figure 4c: Subgroup analysis results (comparing migrants with primary analysis)



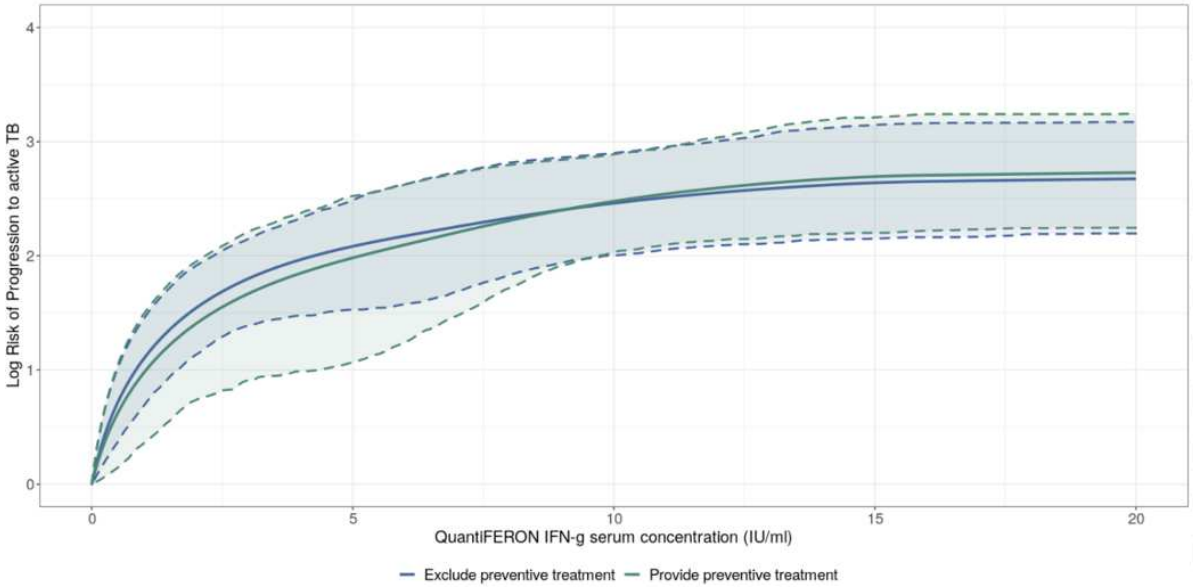
IFN-gamma levels (IU/ml)	Ratio of Relative Risks (95% UI)
0.00	1.00 (1.00 to 1.00)
0.10	1.05 (0.91 to 1.22)
0.20	1.09 (0.85 to 1.39)
0.30	1.11 (0.80 to 1.51)
0.35	1.12 (0.79 to 1.56)
0.40	1.13 (0.77 to 1.61)
0.50	1.14 (0.75 to 1.68)
0.70	1.15 (0.71 to 1.75)
1.00	1.14 (0.67 to 1.78)
2.00	1.04 (0.60 to 1.62)
3.00	0.93 (0.52 to 1.50)
4.00	0.84 (0.45 to 1.52)
5.00	0.77 (0.37 to 1.50)
6.00	0.71 (0.34 to 1.45)
7.00	0.67 (0.32 to 1.34)
8.00	0.64 (0.32 to 1.23)
10.00	0.61 (0.33 to 1.06)
12.00	0.61 (0.33 to 1.09)
15.00	0.62 (0.33 to 1.16)
20.00	0.63 (0.33 to 1.15)

Figure 4d: Subgroup analysis results (comparing healthcare workers with primary analysis)



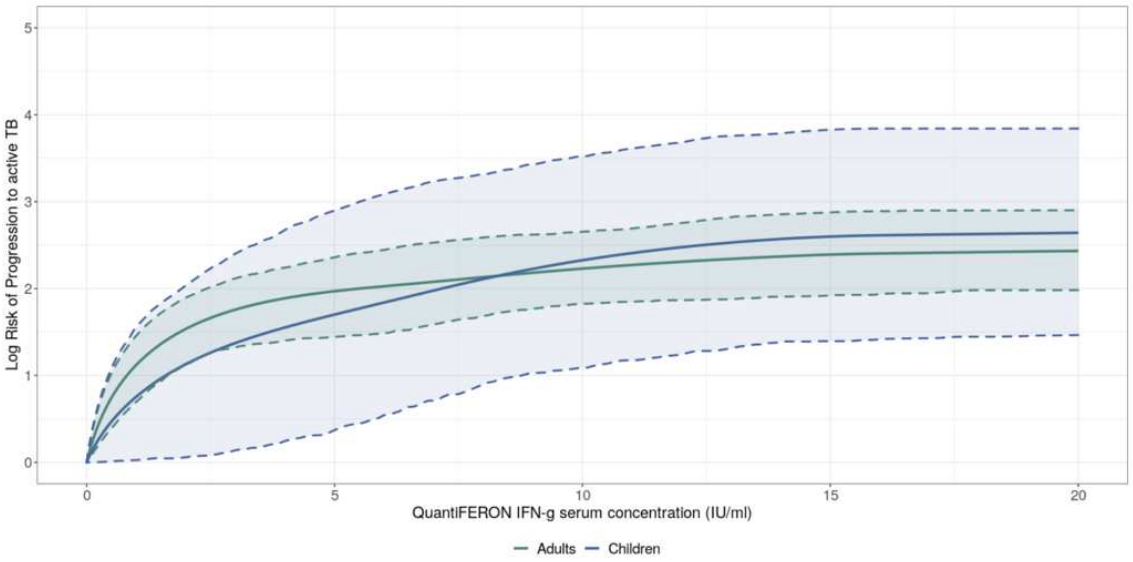
IFN-gamma levels (IU/ml)	Ratio of Relative Risks (95% UI)
0.00	1.00 (1.00 to 1.00)
0.10	1.02 (0.78 to 1.51)
0.20	1.04 (0.64 to 1.89)
0.30	1.06 (0.56 to 2.17)
0.35	1.06 (0.53 to 2.29)
0.40	1.07 (0.50 to 2.40)
0.50	1.08 (0.45 to 2.58)
0.70	1.09 (0.39 to 2.80)
1.00	1.10 (0.32 to 2.96)
2.00	1.11 (0.21 to 3.04)
3.00	1.12 (0.16 to 3.14)
4.00	1.15 (0.15 to 3.31)
5.00	1.19 (0.16 to 3.49)
6.00	1.24 (0.17 to 3.54)
7.00	1.29 (0.20 to 3.80)
8.00	1.33 (0.23 to 3.85)
10.00	1.44 (0.28 to 3.96)
12.00	1.54 (0.31 to 4.26)
15.00	1.62 (0.33 to 4.77)
20.00	1.61 (0.35 to 4.68)

Figure 4e: Subgroup analysis results (comparing studies providing preventive treatment with studies not providing preventive treatment)



IFN-gamma levels (IU/ml)	Ratio of Relative Risks (95% UI)
0.00	1.00 (1.00 to 1.00)
0.10	1.04 (0.84 to 1.25)
0.20	1.07 (0.76 to 1.46)
0.30	1.10 (0.71 to 1.64)
0.35	1.11 (0.69 to 1.72)
0.40	1.12 (0.67 to 1.79)
0.50	1.14 (0.64 to 1.93)
0.70	1.18 (0.61 to 2.12)
1.00	1.21 (0.59 to 2.30)
2.00	1.23 (0.58 to 2.45)
3.00	1.24 (0.58 to 2.54)
4.00	1.24 (0.55 to 2.91)
5.00	1.24 (0.51 to 3.05)
6.00	1.21 (0.48 to 3.01)
7.00	1.16 (0.50 to 2.64)
8.00	1.11 (0.51 to 2.26)
10.00	1.04 (0.54 to 1.89)
12.00	1.01 (0.51 to 1.80)
15.00	1.01 (0.48 to 1.87)
20.00	1.01 (0.48 to 1.87)

Figure 4f: Subgroup analysis results (comparing adults with children)



IFN-gamma levels (IU/ml)	Ratio of Relative Risks (95% UI)
0.00	1.00 (1.00 to 1.00)
0.10	1.10 (0.87 to 1.31)
0.20	1.18 (0.79 to 1.61)
0.30	1.26 (0.74 to 1.88)
0.35	1.30 (0.72 to 2.01)
0.40	1.33 (0.70 to 2.13)
0.50	1.39 (0.68 to 2.36)
0.70	1.49 (0.64 to 2.73)
1.00	1.59 (0.60 to 3.32)
2.00	1.75 (0.53 to 4.63)
3.00	1.79 (0.48 to 5.41)
4.00	1.77 (0.41 to 5.67)
5.00	1.68 (0.37 to 5.46)
6.00	1.55 (0.33 to 4.87)
7.00	1.40 (0.30 to 4.25)
8.00	1.28 (0.27 to 4.10)
10.00	1.14 (0.25 to 3.42)
12.00	1.07 (0.23 to 3.25)
15.00	1.04 (0.22 to 3.21)
20.00	1.02 (0.22 to 3.04)

4. Discussion

To our knowledge, this is the first meta-analysis to summarize and quantify the dose-response relationship between QFT-GIT IFN-gamma levels and the risk of progression to active TB using all available global data sources. Using data from 34 studies, we found that the risk of TB development increased with higher IFN-gamma levels. Our continuous dose-response curve indicates that the risk of incident TB sharply increases between IFN-gamma levels of 0 and 5 IU/ml after which the risk continued to increase moderately but at a slower pace until reaching 15 IU/ml where the risk levels off. Sensitivity analyses revealed that our findings are robust to the quality of the studies as the results did not differ significantly by the quality of studies.

We found that the risk of TB is higher with larger IFN-gamma levels. Our findings show that the risk for incident TB is 2.91-fold higher at 1 IU/ml, 10.13-fold higher at 5 IU/ml, 16.42-fold higher at 10 IU/ml, 19.11-fold higher at 15 IU/ml, and 19.65-fold higher at 20 IU/ml. These findings underscore a limitation of the current practice of dichotomizing IGRA results where the interpretation is that risk is constant for all positive IGRA test. However, our findings show that the risk of active TB development is not the same for everyone with a positive IGRA when considering full spectrum of positive IGRA reactions. In addition, the results indicate that very

high IFN-gamma levels from a QFT-GIT test, beyond the traditional threshold, are powerful indicators of progression to active TB from latent infection. Some authors have suggested that these very high levels of IFN-gamma levels are markers for subclinical active TB disease or early incipient disease.[10,17]

The dose-response relationship found in this meta-analysis can be used to help guide clinical decisions to perform additional tests and treat latent tuberculosis infection within the context of TB programs and local epidemiology. Guidance in clinical decisions would particularly be useful in high TB burden areas where preventive treatment for latent TB is under-utilized.[18,19] The results from this meta-analysis can help make clinical decisions more efficient when results are in the intermediate area between a negative and positive IGRA test called the borderline zone. A recent large cohort study found that half of the patients with an INF-gamma level in the borderline zone (0.20 – 1.00 IU/ml) were IGRA negative in a follow-up test.[12] Results in this borderline zone can provide justification for secondary IGRA tests to prevent unnecessary treatment in resource-constrained settings. Furthermore, our results show that the risk of incident TB is markedly high in large IFN-gamma levels. Current WHO recommendations are to provide preventive treatment to a subset of risk groups such as PLHIV and TB case contacts.[6] The findings from this study suggest an opportunity to consider the potential benefit of extending TB preventive treatment to those with high IFN-gamma levels while taking into account risk factors for disease progression.

We found some variation in the dose-response relationship by population. Compared to our primary curve, excluding studies where the entire study population is HIV positive, the dose-response relationship was substantially greater for HIV positive individuals. Though some studies have found that IGRA's have modest predictive power for incident TB among HIV positive individuals[20,21], our results are consistent with studies indicating that IGRAs are sensitive tools for predicting TB progression.[22–24]

In addition, we found some differences in the dose-response relationship when stratifying analyses by adults and children. The relative risk of incident TB was lower for children compared to adults at the lower end of the curve before converging at 7.5 IU/ml. The lower risk is likely due to mixed findings on the utility of IGRA's among very young children. Several studies have found

that there is insufficient reaction to *M. tuberculosis* antigen among young children that adversely impacts IGRA results.[25–27] More investigations are needed to assess the efficacy of IGRAs to predict progression to active TB to confirm the performance of IGRA at lower levels of IFN-gamma levels.

Contrary to expectations, we found no evidence of effect modification when stratifying models by whether studies provided preventive treatment for TB. The lack of difference in the curves can be due to not all participants accepting treatment in studies where treatment is provided. In addition, only a small fraction of those accepting treatment completed the regimen in these studies.

Finally, the findings from this study bring into question the predictive value for progression to active TB of IGRAs. Various systematic reviews have concluded that IGRAs have poor accuracy for the prediction of incident TB.[20,28] These results may change by taking into account the full dynamic nature of latent infection instead of dichotomizing IGRA results with conventional thresholds. In studies where IFN-gamma levels were evaluated at larger cutoffs beside the threshold of 0.35 IU/ml, the predictive value of subsequent TB improved.[8,10,29,30]

4.1. Strengths and Limitations

Our study has several key strengths. In our meta-regression we were able to include data with different IFN-gamma categories into a singular analysis while incorporating between study heterogeneity in our uncertainty estimation. Our study is the first meta-analysis to examine TB risk over the entire distribution of IFN-gamma levels, allowing for improved identification of individuals who may be at highest risk for progressing to active TB. Finally, we were able to stratify results by important at risk populations to evaluate for potential confounding and effect modification.

However, our findings should be interpreted in terms of key limitations. First, we could not assess for effect modification by known risk factors for progression to active TB including tobacco smoke, alcohol consumption, diabetes, malnutrition, and indoor air pollution, as these data were not routinely included in studies. Second, several studies included in our systematic review used passive-follow-up for detection of active TB through national TB registries. These surveillance

systems are often prone to under-reporting which may have caused lower rates of observed TB cases in the studies. Third, our quality assessment indicated that almost all studies have some source of bias as all studies were considered to be of low to moderate quality. We conducted sensitivity analyses to evaluate the impact of study quality on the results and we found that the results did not differ significantly.

Fourth, most studies were conducted in low to intermediate TB burden countries potentially limiting the generalizability of our findings. Fifth, time since infection may impact results as recent infection is associated with higher risk for active TB. However, this information was unavailable in most studies. Finally, we may have missed articles as we restricted our search to two databases. We believe this had a small impact on our findings because PubMed and Embase yield high coverage[30] and we manually searched the reference list of relevant articles.

Our study has implications for future studies. We found that the risk of incident TB is not the same for everyone with a positive IGRA reaction. Future cohort studies should therefore collect granular data on IGRA levels and the associated risk of progression to active tuberculosis. For example, out of the 34 included studies in our systematic review, only 9 reported more IGRA values besides the traditional cutoff of 0.35 IU/ml. Reporting more granular IGRA values and corresponding risks for progression to active TB will also help reassess the predictive value of IGRAs given the dose-response nature of the data. Future studies may also incorporate additional risk factors for progression to active tuberculosis such as alcohol, smoking, malnutrition, and diabetes to identify individuals at greatest risk of subsequent TB.

4.2. Conclusion

We developed a dose-response risk curve for the progression to active TB as a function of a continuous measure of IGRA values. Our findings show that the current practice of dichotomizing IGRA test results simplifies the TB infection disease continuum. The findings of this study showed that the risk of active TB development is not the same for everyone with a positive IGRA with higher IGRA values being strongly associated with disease progression. With IGRAs starting to scale up in high TB burden areas, the findings from this study can help clinicians make an informed decisions by providing different relative risks of progression to active TB for a

range of IGRA values within the borderline zone and very high IGRA reactions. More investigations using detailed quantification of IGRA values will help to find more accurate estimates of the dose-response relationship and allow for a reexamination of the predictive power of IGRA tests.

5. References

1. Roth, G. A. et al. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392, 1736–1788 (2018).
2. Houben, R. M. G. J. & Dodd, P. J. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. PLoS Med. 13, e1002152 (2016).
3. Rangaka, M. X. et al. Controlling the seedbeds of tuberculosis: diagnosis and treatment of tuberculosis infection. Lancet 386, 2344–2353 (2015).
4. Gualano, G. et al. Tuberculin skin test – Outdated or still useful for Latent TB infection screening? Int. J. Infect. Dis. 80, S20–S22 (2019).
5. Trajman, A., Steffen, R. E. & Menzies, D. Interferon-Gamma Release Assays versus Tuberculin Skin Testing for the Diagnosis of Latent Tuberculosis Infection: An Overview of the Evidence. Pulm. Med. 2013, 1–11 (2013).
6. World Health Organization. Global tuberculosis report 2019.
7. Campbell, J. R., Winters, N. & Menzies, D. Absolute risk of tuberculosis among untreated populations with a positive tuberculin skin test or interferon-gamma release assay result: systematic review and meta-analysis. BMJ m549 (2020). doi:10.1136/bmj.m549
8. Winje, B. A. et al. Stratification by interferon-γ release assay level predicts risk of incident TB. Thorax 73, 652–661 (2018).
9. Zellweger, J.-P. 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. 191, 1176–1184 (2015).
10. Andrews, J. R. et al. Serial QuantiFERON testing and tuberculosis disease risk among young children: an observational cohort study. Lancet Respir. Med. 5, 282–290 (2017).
11. Hermansen, T. S., Lillebaek, T., Langholz Kristensen, K., Andersen, P. H. & Ravn, P. Prognostic value of interferon-γ release assays, a population-based study from a TB low-incidence country. Thorax 71, 652–658 (2016).
12. Jonsson, J. et al. A borderline range for Quantiferon Gold In-Tube results. PLoS One 12, e0187313 (2017).

13. Nienhaus, A. & Costa, J. T. Screening for tuberculosis and the use of a borderline zone for the interpretation of the interferon-γ release assay (IGRA) in Portuguese healthcare workers. J. Occup. Med. Toxicol. 8, 1 (2013).
14. Mazurek, G. H. et al. Updated Guidelines for Using Interferon Gamma Release Assays to Detect Mycobacterium Tuberculosis Infection - United States, 2010. Morb. Mortal. Wkly. Rep. Recomm. reports 59, 1–25 (2010).
15. Wells, G. et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. (2011).
16. Zheng, P., Aravkin, A. Y., Barber, R., Sorensen, R. J. D. & Murray, C. J. L. Trimmed Constrained Mixed Effects Models: Formulations and Algorithms. (2019).
17. Drain, P. K. et al. Incipient and Subclinical Tuberculosis: a Clinical Review of Early Stages and Progression of Infection. Clin. Microbiol. Rev. 31, (2018).
18. Churchyard, G. J. & Swindells, S. Controlling latent TB tuberculosis infection in high-burden countries: A neglected strategy to end TB. PLoS Med. 16, e1002787 (2019).
19. Sharma, S. K., Mohanan, S. & Sharma, A. Relevance of Latent TB Infection in Areas of High TB Prevalence. Chest 142, 761–773 (2012).
20. Cattamanchi, A. et al. Interferon-Gamma Release Assays for the Diagnosis of Latent Tuberculosis Infection in HIV-Infected Individuals: A Systematic Review and Meta-Analysis. JAIDS J. Acquir. Immune Defic. Syndr. 56, 230–238 (2011).
21. Sester, M. et al. Risk Assessment of Tuberculosis in Immunocompromised Patients. A TBNET Study. Am. J. Respir. Crit. Care Med. 190, 1168–1176 (2014).
22. Aichelburg, M. C. et al. Detection and Prediction of Active Tuberculosis Disease by a Whole□Blood Interferon□γ Release Assay in HIV□1–Infected Individuals. Clin. Infect. Dis. 48, 954–962 (2009).
23. Doyle, J. S. et al. Latent Tuberculosis Screening Using Interferon-Gamma Release Assays in an Australian HIV-Infected Cohort. JAIDS J. Acquir. Immune Defic. Syndr. 66, 48–54 (2014).
24. Lee, S., Lee, J. E., Kang, J. S., Lee, S. O. & Lee, S. H. Long-term performance of the IGRA to predict and prevent active tuberculosis development in HIV-infected patients. Int. J. Tuberc. Lung Dis. 23, 422–427 (2019).

25. Lewinsohn, D. A., Lobato, M. N. & Jereb, J. A. Interferon-γ release assays: new diagnostic tests for Mycobacterium tuberculosis infection, and their use in children. Curr. Opin. Pediatr. 22, 71–76 (2010).
26. Haustein, T. et al. The Likelihood of an Indeterminate Test Result from a Whole-Blood Interferon-γ Release Assay for the Diagnosis of Mycobacterium tuberculosis Infection in Children Correlates With Age and Immune Status. Pediatr. Infect. Dis. J. 28, 669–673 (2009).
27. Lighter, J., Rigaud, M., Eduardo, R., Peng, C.-H. & Pollack, H. Latent Tuberculosis Diagnosis in Children by Using the QuantiFERON-TB Gold In-Tube Test. Pediatrics 123, 30–37 (2009).
28. Rangaka, M. X. et al. Predictive value of interferon-γ release assays for incident active tuberculosis: a systematic review and meta-analysis. Lancet Infect. Dis. 12, 45–55 (2012).
29. Altet, N. et al. Predicting the Development of Tuberculosis with the Tuberculin Skin Test and QuantiFERON Testing. Ann. Am. Thorac. Soc. 12, 680–688 (2015).
30. Gupta, R. K. et al. Quantitative IFN-γ Release Assay and Tuberculin Skin Test Results to Predict Incident Tuberculosis. A Prospective Cohort Study. Am. J. Respir. Crit. Care Med. 201, 984–991 (2020).
31. Bramer, W. M., Giustini, D. & Kramer, B. M. R. Comparing the coverage, recall, and precision of searches for 120 systematic reviews in Embase, MEDLINE, and Google Scholar: a prospective study. Syst. Rev. 5, 39 (2016).

6. Appendix

Table S1. Characteristics of the studies included in the meta-analysis

Study	Study Type	Population	Country	Time period	Age	Sample size	Follow-up time	TB Preventive Treatment	TB diagnosis	NOS Quality Score
Abdulkareem (2020)[1]	Prospective cohort	Tuberculosis case contacts	Iraq	2018 – 2018	Adults and children 1 to 100 years	401	6 months	Unknown	Bacteriologically, radiologically	4
Ahmed (2020)[2]	Prospective cohort	High risk population: case contacts, recent migrants	United States of America	2012 – 2018	Children 0 to 15 years	3593	Median: 4.3 Years	Yes unknown %	Bacteriologically	5
Aichelburg (2009)[3]	Prospective cohort	HIV-infected patients	Austria	2006 – 2008	Adults and children 0 to 100 years	775	Median: 1.6 Years	No 0 %	Clinically	6
Altet (2015)[4]	Prospective cohort	Tuberculosis case contacts	Spain	2007 – 2013	Adults and children 0 to 100 years	937	4 Years	No 0 %	Clinically confirmed through TB Control Program databases	5
Andrews (2017)[5]	Double blinded, randomized clinical trial	Young healthy children	South Africa	2009 – 2012	Children 4 to 6 months	2374	2 Years	Yes unknown %	Bacteriologically	4

Bergot (2012)[6]	Prospective cohort	Tuberculosis case contacts	France	2007 – 2009	Adults and children 0 to 100 years	674	Mean: 2.8 Years	Yes 14 %	Clinically, radiologically, bacteriologically, histology	5
Costa (2011)[7]	Prospective cohort	Healthcare workers	Portugal	2007 – 2010	Adults 18 to 100 years	2865	Mean: 1.6 Years	Unknown	Radiologically	3
Diel (2011)[8]	Prospective cohort	Tuberculosis case contacts	Germany	2005 – 2010	Adults and children 0 to 100 years	954	Mean: 2.5 Years	Yes unknown %	Bacteriologically, radiologically, clinically	3
Doyle (2014)[9]	Retrospective cohort	HIV-infected patients	Australia	2003 – 2011	Adults 18 to 88 years	913	Median: 2.2 Years	Yes unknown %	Bacteriologically	4
Giri (2014)[10]	Retrospective cohort	Healthcare workers	United Kingdom	2009 – 2013	Adults and children 0 to 100 years	1258	1 Year	Yes 3 %	Bacteriologically, clinically	4
Gupta (2020)[11]	Prospective cohort	High risk population: case contacts, migrants	United Kingdom	2010 – 2017	Adults 16 to 100 years	8440	Median: 4.7 Years	No 0 %	Clinically confirmed through national TB surveillance program	5
Haldar (2013)[12]	Prospective cohort	Tuberculosis case contacts	United Kingdom	2007 – 2009	Adults 16 to 100 years	811	Median: 2.5 Years	Yes 12 %	Bacteriologically, clinically	4

Harstad (2010)[13]	Prospective cohort	Asylum seekers	Norway	2005 – 2008	Adults 18 to 100 years	823	23 to 32 months	Yes 1 %	Clinically confirmed through National TB registry	2
Jonsson (2017)[14]	Retrospective cohort	All residents meeting Swedish guidelines for LTBI testing	Sweden	2009 – 2016	Adults and children 0 to 100 years	38785	Median: 4.3 Years	Yes unknown %	Clinically confirmed through national TB register	3
Joshi (2011)[15]	Prospective cohort	Healthcare workers	India	2004 – 2010	Adults 18 to 100 years	726	6 Years	Yes unknown %	Bacteriologically, clinically	4
Kruczak (2014)[16]	Prospective cohort	High risk population: homeless, case contacts, elderly, (healthy) control group	Poland	2007 – 2012	Adults and children 0 to 100 years	785	4 to 5 Years	No 0 %	Clinically confirmed through local pulmonary clinic	5
Lee (2019)[17]	Retrospective cohort	HIV-infected patients	Republic of Korea	2006 – 2016	Adults 15 to 100 years	416	Median: 4 Years	Yes unknown %	Bacteriologically, radiologically	5
Lu (2020)[18]	Prospective cohort	Population based	China	2013 – 2019	Adults and children 5 to 100 years	5,405	6 Years	Unknown	Bacteriologically, clinically	5

Mahomed (2011)[19]	Prospective cohort	Children	South Africa	2005 – 2009	Children 12 to 18 years	5244	Median: 2.4 Years	No 0 %	Bacteriologically	5
Nienhaus (2013)[20]	Prospective cohort	Healthcare workers	Portugal	2007 – 2010	Adults and children 0 to 100 years	2815	Mean: 1.1 Years	Unknown	Clinically, radiologically, symptoms	3
Noorbakhsh (2011)[21]	Prospective cohort	Tuberculosis case contacts	Iran	2006 – 2008	Children 0 to 19 years	49	1 Year	Unknown	Clinically	4
Ringshausen (2010)[22]	Prospective cohort	Healthcare workers	Germany	2005 – 2010	Adults 18 to 100 years	180	Median: 2.7 years	Unknown	Radiologically	3
Rose (2014)[23]	Retrospective cohort	HIV-infected patients	Canada	2010 – 2011	Children 0 to 18 years	80	2 year	Yes 3 %	Bacteriologically, clinically	3
Santin (2011)[24]	Prospective cohort	HIV-infected patients	Spain	2007 – 2009	Adults 18 to 100 years	135	Median: 1.6 Years	No 0 %	Clinically confirmed through national TB surveillance program	4
Schablon (2013)[25]	Prospective cohort	Healthcare workers	Germany	2008 – 2012	Adults 17 to 53 years	194	3 years	Unknown	Clinically, radiologically	4

Sharma (2017)[26]	Prospective cohort	Tuberculosis case contacts	India	2008 – 2014	Adults and children 1 to 65 years	1498	2 Years	Unknown	Bacteriologically, clinically	4
Tsou (2015)[27]	Prospective cohort	Elderly nursing home residents	Taiwan (Province of China)	2004 – 2009	Adults 65 to 100 years	139	5 years	Unknown	Clinically	5
Verhagen (2014)[28]	Prospective cohort	Tuberculosis case contacts	Venezuela (Bolivarian Republic of)	2010 – 2012	Children 0 to 15 years	140	1 Year	No 0 %	Clinically confirmed through national TB surveillance program	5
Whitaker (2013)[29]	Prospective cohort	Healthcare workers	Georgia	2009 – 2011	Adults 18 to 100 years	319	2.2 Years	Unknown	Clinically confirmed through TB Control Program databases	3
Winje (2018)[30]	Prospective cohort	Population based	Norway	2009 – 2014	Adults and children 0 to 100 years	44006	2 to 8.5 years	Yes unknown %	Clinically confirmed through national TB surveillance program	4
Yoshiyama (2010)[31]	Retrospective cohort	Tuberculosis case contacts	Japan	2003 – 2007	Adults and children 10 to 100 years	3102	Mean: 1.6 Years	Yes 15 %	Bacteriologically confirmed through public health centers	3
Yoshiyama (2015)[32]	Retrospective cohort	Tuberculosis case contacts	Japan	2010 – 2013	Adults and children 0 to 100 years	625	Mean: 1.7 Years	Yes 17 %	Bacteriologically, clinically	3

Zellweger (2015)[33]	Prospective cohort	Tuberculosis case contacts	Europe	2009 – 2013	Adults and children 0 to 100 years	3425	Median: 2.5	Yes 19 %	Clinically confirmed through national TB surveillance program	3
Zenner (2017)[34]	Retrospective cohort	Migrants	United Kingdom	2009 – 2014	Adults and children 0 to 35 years	1320	Median: 2.2	Yes 18 %	Clinically confirmed through national TB register	4

Table S2. Search strategies

Study type	Search Terms
Retrospective or prospective cohort studies	PubMed search terms: (“Interferon-gamma Release Tests”[MeSH] OR “IGRA”[tiab] OR "interferon-gamma release assay*"[tiab] OR "Quantiferon*"[tiab] OR "QFT"[tiab] OR "Interferon-gamma release test*"[tiab]) AND ("reactivation"[tiab] OR "reactivity"[tiab] OR "activation"[tiab] OR "predictive"[tiab] OR "risk"[tiab]) AND ("tuberculosis"[MeSH] OR "tuberculosis"[tiab]) AND ("prospective"[tiab] OR "cohort"[tiab] OR "follow up"[tiab]) (“2001/01/01”[PDAT] : "2020/05/10"[PDAT]) Embase search terms: (‘Interferon-gamma Release Tests’/de OR ‘IGRA’:ab,ti OR ‘interferon-gamma release assay*’:ab,ti OR ‘Quantiferon*’:ab,ti OR ‘QFT’:ab,ti OR ‘Interferon-gamma release test*’:ab,ti) AND (‘reactivation’:ab,ti OR ‘reactivity’:ab,ti OR ‘activation’:ab,ti OR ‘predictive’:ab,ti OR ‘risk’:ab,ti) AND (‘tuberculosis’/de OR ‘tuberculosis’:ab,ti) AND (‘prospective’:ab,ti OR ‘cohort’:ab,ti OR ‘follow up’:ab,ti) AND [1-1-2001]/sd NOT [5-10-2020]/sd

Table S3. Newcastle-Ottawa quality assessment scale adopted for quality assessment

Criteria Number	Criteria Domain	Criteria	Score
1	Cohort selection	Representativeness of the exposed cohort	Truly or somewhat representative of the community (*) Selected groups No clear description
2	Cohort selection	Selection of the non-exposed cohort	Drawn from the same community as exposed cohort (*) Drawn from a different source No clear description
3	Cohort selection	Ascertainment of exposure	Secured records or structured interviews (*) Written self-report No clear description
4	Cohort selection	Demonstration that focal outcome was not present at start of study	Yes (*) No
5	Comparability of cohort	Comparability: study excluded participants with preventive treatment for LTBI	Yes (*) No
6	Comparability of cohort	Comparability: study excluded participants with HIV-infection	Yes (*) No
7	Outcome	Assessment of outcome	All TB cases were bacteriologically confirmed (*) Clinically diagnosed No clear description
8	Outcome	Sufficient follow-up for outcome to occur	3 years $\geq$ (*) < 3 years No clear description
9	Outcome	Adequate follow-up of cohort	Loss to follow-up $\leq$ 20% (*) Loss to follow-up > 20% No clear description

Note: For studies where the study population was HIV-positive individuals criteria number 6 was not considered instead studies would be awarded 2 points for criteria number 5 if requirements are met.
Answers with a (*) indicate that study quality improved, while answers without the (*) indicate no improvement in quality.

6.1. Estimating the relative risks of developing active TB by interferon gamma levels

Our mixed-effects regression model can be represented as the following:

$$ln(relative\ risk) = (\frac{\ln(1 + X_{comp}\beta) - \ln(1 + X_{ref}\beta)}{X_{comp} - X_{ref}} + u)(X_{comp} - X_{ref})$$

Where X_{comp} and X_{ref} are the design matrices for the comparison and reference groups; β is a vector of regression coefficients; u is the study random effect assuming a random slope.

The risk function occurring within the design matrices is defined by:

$$relative\ risk(s, e, \beta) = \sum_{i=1}^{m} \beta_i \frac{1}{e - s} \int_s^e f_i\ (t)dt$$

where s is the lower bound of interferon gamma levels (IU/ml) for a data point; e is the upper bound of interferon gamma levels (IU/ml) for a data point; β is the regression coefficient at i. Particularly, we use a set of spline bases to parametrize the relative risk function of interferon gamma levels. Each f_i is one of the bases and β_i are the corresponding coefficients.

6.2. References of studies included in the meta-analysis

1 Abdulkareem FN, Merza MA, Salih AM. First insight into latent tuberculosis infection among household contacts of tuberculosis patients in Duhok, Iraqi Kurdistan: using tuberculin skin test and QuantiFERON-TB Gold Plus test. Int J Infect Dis 2020;96:97–104. doi:10.1016/j.ijid.2020.03.067

2 Ahmed A, Feng P-JI, Gaensbauer JT, et al. Interferon-γ Release Assays in Children <15 Years of Age. Pediatrics 2020;145:e20191930. doi:10.1542/peds.2019-1930

3 Aichelburg MC, Rieger A, Breitenecker F, et al. Detection and Prediction of Active Tuberculosis Disease by a Whole□Blood Interferon□γ Release Assay in HIV□1–Infected Individuals. Clin Infect Dis 2009;48:954–62. doi:10.1086/597351

4 Altet N, Dominguez J, Souza-Galvão M-L de, et al. Predicting the Development of Tuberculosis with the Tuberculin Skin Test and QuantiFERON Testing. Ann Am Thorac Soc 2015;12:680–8. doi:10.1513/AnnalsATS.201408-394OC

5 Andrews JR, Nemes E, Tameris M, et al. Serial QuantiFERON testing and tuberculosis disease risk among young children: an observational cohort study. Lancet Respir Med 2017;5:282–90. doi:10.1016/S2213-2600(17)30060-7

6 Bergot E, Haustraete E, Malbruny B, et al. Observational Study of QuantiFERON®-TB Gold In-Tube Assay in Tuberculosis Contacts in a Low Incidence Area. PLoS One 2012;7:e43520. doi:10.1371/journal.pone.0043520

7 Torres Costa J, Silva R, Ringshausen FC, et al. Screening for tuberculosis and prediction of disease in Portuguese healthcare workers. J Occup Med Toxicol 2011;6:19. doi:10.1186/1745-6673-6-19

8 Diel R, Loddenkemper R, Niemann S, et al. Negative and Positive Predictive Value of a Whole-Blood Interferon-γ Release Assay for Developing Active Tuberculosis. Am J Respir Crit Care Med 2011;183:88–95. doi:10.1164/rccm.201006-0974OC

9 Doyle JS, Bissessor M, Denholm JT, et al. Latent Tuberculosis Screening Using Interferon-Gamma Release Assays in an Australian HIV-Infected Cohort. JAIDS J Acquir Immune Defic Syndr 2014;66:48–54. doi:10.1097/QAI.0000000000000109

10 Giri P, Basu S, Sargeant T, et al. Pre-placement screening for tuberculosis in healthcare workers. Occup Med (Chic Ill) 2014;64:524–9. doi:10.1093/occmed/kqu107

11 Gupta RK, Lipman M, Jackson C, et al. Quantitative IFN-γ Release Assay and Tuberculin Skin Test Results to Predict Incident Tuberculosis. A Prospective Cohort Study. Am J Respir Crit Care Med 2020;201:984–91. doi:10.1164/rccm.201905-0969OC

12 Haldar P, Thuraisingam H, Patel H, et al. Single-step QuantiFERON screening of adult contacts: a prospective cohort study of tuberculosis risk. Thorax 2013;68:240–6. doi:10.1136/thoraxjnl-2011-200956

13 Harstad I, Winje BA, Heldal E, et al. Predictive values of QuantiFERON-TB Gold testing in screening for tuberculosis disease in asylum seekers. Int J Tuberc lung Dis 2010;14:1209–11.http://www.ncbi.nlm.nih.gov/pubmed/20819271

14 Jonsson J, Westman A, Bruchfeld J, et al. A borderline range for Quantiferon Gold In-Tube results. PLoS One 2017;12:e0187313. doi:10.1371/journal.pone.0187313

15 Joshi R, Narang U, Zwerling A, et al. Predictive value of latent tuberculosis tests in Indian healthcare workers: a cohort study. Eur Respir J 2011;38:1475–7. doi:10.1183/09031936.00014611

16 Kruczak K, Duplaga M, Sanak M, et al. Comparison of IGRA tests and TST in the diagnosis of latent tuberculosis infection and predicting tuberculosis in risk groups in Krakow, Poland. Scand J Infect Dis 2014;46:649–55. doi:10.3109/00365548.2014.927955

17 Lee S, Lee JE, Kang JS, et al. Long-term performance of the IGRA to predict and prevent active tuberculosis development in HIV-infected patients. Int J Tuberc Lung Dis 2019;23:422–7. doi:10.5588/ijtld.18.0198

18 Lu P, Liu Q, Zhou Y, et al. Predictors of Discordant Tuberculin Skin test and QuantiFERON-TB Gold In-Tube Results in Eastern China: A Population-based, Cohort Study. Clin Infect Dis 2020;15:1056–61. doi:10.1093/cid/ciaa519

19 Mahomed H, Hawkridge T, Verver S, et al. The Tuberculin Skin Test versus QuantiFERON TB Gold in Predicting Tuberculosis Disease in an Adolescent Cohort Study in South Africa. PLoS One 2011;6:e17984. doi:10.1371/journal.pone.0017984

20 Nienhaus A, Costa JT. Screening for tuberculosis and the use of a borderline zone for the interpretation of the interferon-γ release assay (IGRA) in Portuguese healthcare workers. J Occup Med Toxicol 2013;8:1. doi:10.1186/1745-6673-8-1

21 Noorbakhsh S, Mousavi J, Barati M, et al. Evaluation of an interferon-gamma release assay in young contacts of active tuberculosis cases. East Mediterr Heal J 2011;17:714–8.http://www.ncbi.nlm.nih.gov/pubmed/22259925

22 Ringshausen FC, Nienhaus A, Schablon A, et al. Predictors of persistently positive Mycobacterium-tuberculosis-specific interferon-gamma responses in the serial testing of health care workers. BMC Infect Dis 2010;10:220. doi:10.1186/1471-2334-10-220

23 Rose W, Kitai I, Kakkar F, et al. Quantiferon Gold-in-tube assay for TB screening in HIV infected children: influence of quantitative values. BMC Infect Dis 2014;14:516. doi:10.1186/1471-2334-14-516

24 Santin M, Casas S, Saumoy M, et al. Detection of latent tuberculosis by the tuberculin skin test and a whole-blood interferon-γ release assay, and the development of active tuberculosis in HIV-seropositive persons. Diagn Microbiol Infect Dis 2011;69:59–65. doi:10.1016/j.diagmicrobio.2010.09.005

25 Schablon A, Peters C, Diel R, et al. Serial IGRA testing of trainees in the healthcare sector in a country with low incidence for tuberculosis - a prospective cohort study. GMS Hyg Infect Control 2013;8:Doc17. doi:10.3205/dgkh000217

26 Sharma SK, Vashishtha R, Chauhan LS, et al. Comparison of TST and IGRA in Diagnosis of Latent Tuberculosis Infection in a High TB-Burden Setting. PLoS One 2017;12:e0169539. doi:10.1371/journal.pone.0169539

27 Tsou P, Huang W-C, Huang C, et al. Quantiferon TB-Gold conversion can predict active tuberculosis development in elderly nursing home residents. Geriatr Gerontol Int 2015;15:1179–84. doi:10.1111/ggi.12416

28 Verhagen LM, Maes M, Villalba JA, et al. Agreement between QuantiFERON-TB Gold In-Tube and the tuberculin skin test and predictors of positive test results in Warao Amerindian pediatric tuberculosis contacts. BMC Infect Dis 2014;14:383. doi:10.1186/1471-2334-14-383

29 A. Whitaker J, Mirtskhulava V, Kipiani M, et al. Prevalence and Incidence of Latent Tuberculosis Infection in Georgian Healthcare Workers. PLoS One 2013;8:e58202. doi:10.1371/journal.pone.0058202

30 Winje BA, White R, Syre H, et al. Stratification by interferon-γ release assay level predicts risk of incident TB. Thorax 2018;73:652–61. doi:10.1136/thoraxjnl-2017-211147

31 Yoshiyama T, Harada N, Higuchi K, et al. Use of the QuantiFERON ® -TB Gold in Tube test for screening TB contacts and predictive value for active TB. Infect Dis (Auckl) 2015;47:542–9. doi:10.3109/23744235.2015.1026935

32 Yoshiyama T, Harada N, Higuchi K, et al. Use of the QuantiFERON-TB Gold test for screening tuberculosis contacts and predicting active disease. Int J Tuberc lung Dis 2010;14:819–27.http://www.ncbi.nlm.nih.gov/pubmed/20550763

33 Zellweger J-P, 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. doi:10.1164/rccm.201502-0232OC

34 Zenner D, Loutet MG, Harris R, et al. Evaluating 17 years of latent tuberculosis infection screening in north-west England: a retrospective cohort study of reactivation. Eur Respir J 2017;50:1602505. doi:10.1183/13993003.02505-2016