

Comparison of interferon-gamma production between TB1 and TB2 tubes of QuantiFERON-TB Gold Plus a meta-analysis

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Review

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Comparison of interferon-gamma production between TB1 and TB2 tubes of QuantiFERON-TB Gold Plus: a meta-analysis

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Abstract

Objectives: CD8 T-cells play an important role in interferon-gamma (IFN- γ) production as a host defense against tuberculosis (TB) infection. Therefore, QuantiFERON-TB Gold Plus (QFT-Plus) was developed by adding a TB2 tube beside the TB1 tube. This study aimed to compare and analyze the difference in IFN- γ production between the two tubes in general and specific populations.

Content: PubMed, Web of Science, and EBSCO were searched for studies reporting IFN- γ production levels in the TB1 and TB2 tubes. Statistical analysis was performed using RevMan 5.3.

Summary: A total of 17 studies met the inclusion criteria. The IFN- γ production in the TB2 tube was statistically higher than that in the TB1 tube (mean difference (MD)=0.02, 95 % confidence interval (95 % CI): 0.01–0.03). Further subgroup analysis in specific populations revealed that the MD of IFN- γ

production between the TB2 and TB1 tubes was significantly higher in active TB subjects than in latent TB infection (LTBI) subjects (MD=1.13, 95 % CI: 0.49–1.77, and MD=0.30, 95 % CI: 0.00–0.60, respectively). A similar finding was found in immune-mediated inflammatory disease subjects, but not statistically significant. Interestingly, IFN- γ production capacity was lower in active TB subjects than in LTBI subjects in each of the TB1 and TB2 tubes.

Outlook: This study is the first to systematically compare IFN- γ production between the TB1 and TB2 tubes. The IFN- γ production was higher in the TB2 tube than in the TB1 tube, representing the host's CD8 T-cell response magnitude to TB infection.

Keywords: CD8 T-cells; interferon-gamma; QuantiFERON-TB Gold Plus; TB1 tube; TB2 tube.

Introduction

Tuberculosis (TB), which is caused by *Mycobacterium tuberculosis* (MTB), is a crucial public health problem and the most common cause of death from a single infectious pathogen with approximately two million deaths yearly [1]. Almost one-third of the world's population is infected with MTB, and around 10 million people globally developed TB in 2019 [1, 2].

Interferon-gamma (IFN- γ) is a proinflammatory cytokine predominantly produced by activated T lymphocytes and plays an important role in regulating cellular immune response and inflammation in TB infection [3]. The host's IFN- γ response to TB is used as a surrogate for identifying TB infection in interferon-gamma release assays (IGRA), which is an immunodiagnostic test for TB [4]. The test measures T lymphocytes' IFN- γ concentration after *in vitro* whole-blood stimulation using highly immunogenic peptides from the region of difference (RD)-1 that is present in the genome of MTB [5, 6]. The QuantiFERON-TB Gold In-Tube assay (QFT-GIT) is the first commercially available IGRA, which is

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based on an enzyme-linked immunosorbent assay (ELISA). The third generation of QFT-GIT has MTB antigens ESAT-6, CFP-10, and TB-7.7 to induce IFN- γ secretion from CD4 T-cells [6, 7]. Recent studies have shown growing evidence of the crucial role of CD8 T-cells in MTB infection, especially in those who have active TB and are immunocompromised. Therefore, QuantiFERON-TB Gold Plus (QFT-Plus) has been developed to address this issue [8, 9]. The QFT-Plus included two TB antigen tubes. The first tube (TB1) contains long peptides of ESAT-6 and CFP-10 without TB-7.7 to stimulate the CD4 T-cell immune response. The second tube (TB2) contains six short peptides in addition to the peptides in TB1 to elicit both CD4 and CD8 T-cell immune responses [10, 11].

Recently, many studies have compared IFN- γ production in both TB1 and TB2 tubes, reflecting the contribution of the CD8 T-cell immune response. However, the subjects and results were varied. Thus, this study aimed to systematically ascertain the difference in IFN- γ production between the two tubes and investigate the differences in specific populations.

8 Materials and methods

Study search strategy and selection

The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement guidelines [12]. The study was registered on PROSPERO, an international prospective register of systematic reviews, with registration number CRD42022364596. PubMed, Web of Science, and EBSCO were searched for all relevant published studies up to September 30, 2022. The search strategy was designed by combining the medical subject headings (MeSH) and text words: “interferon gamma” and “interferon gamma release test”. Several text words were used for “interferon gamma” (“ifng” and “interferon gamma production”) and “interferon gamma release test” (“igra,” “igra assay,” “quantiferonTB gold plus,” “QFT-Plus,” “TB1,” and “TB2”). Both text words and MeSH identified were used together using “OR,” and the results were further combined using “AND” to obtain the result. An additional manual search was performed to identify the relevant studies. Study selection and quality assessment were performed independently by reviewers. Any disagreements were resolved through discussion.

Eligibility criteria

Inclusion criteria included (i) published observational studies (cross-sectional, case-control, or cohort); (ii) studies clearly defining the population; (iii) studies clearly defining the IGRA examination method; (iv) studies presenting outcomes of interest: the IFN- γ production level by calculating the IFN- γ values for TB1 minus nil (IU/mL) and TB2 minus nil (IU/mL). The level was measured using the ELISA technique. Active TB subjects were diagnosed based on a combination of clinical presentations and available radiographic and bacteriological

examinations. The diagnosis of latent TB infection (LTBI) was confirmed based on a positive IGRA test. For studies with the same subjects or duplicate populations, only the one with the most updated or largest sample size was included. Exclusion criteria included non-human studies, protocols, meeting abstracts, editorials, commentaries, reviews, small studies having subjects less than 10, case reports, or case series.

Data extraction

Data, including title, author's names, publication year, origin country, number of subjects, baseline characteristics of subjects (including sex, mean age, and disease status), IGRA method, and IFN- γ production in each tube, were extracted by two authors. If the values for the meta-analysis were not sufficiently reported, the corresponding author was contacted to provide the data.

11 Quality assessment

The quality of each study was assessed using the Newcastle-Ottawa Scale (NOS) [13]. Only studies with good and fair quality were included in the analysis. Disagreements and discrepancies between the reviewers were discussed to achieve a final consensus.

Statistical analysis

A minimum of two studies with a similar outcome measurement was required to perform the meta-analyses. Means and standard deviations (SD) were combined. A formula was used to estimate the mean and SD by any reported and interquartile range data [14]. The difference between the mean value in two different groups was calculated as the mean difference (MD), and forest plots were used to display the pooled MD with the corresponding 95% confidence interval (95% CI). The heterogeneity between studies was quantified using I^2 values. I^2 values ranged from 0% (no heterogeneity) to 100% and were interpreted according to the Cochrane Consumers and Communication Review Group. A fixed-effect model approach was employed if $I^2 < 50\%$; otherwise, a random-effect model was used. If significant heterogeneity was detected, sensitivity analysis (leave-one-out procedure) was performed to explore the possible source of it. Additional subgroup analyses were performed based on disease conditions. Publication bias was evaluated through funnel plot visual analysis. Statistical analysis was performed using Review Manager 5.3. A p-value of less than 0.05 was considered statistically significant. Studies included in this review were approved previously by each Institutional Ethical Review Board. Therefore, the requirement for ethical approval was waived.

16 Results

Study selection

A total of 410 articles were identified from the initial database search. After a thorough screening and review, 17 studies were eligible for inclusion. Figure 1 shows the detailed process of study selection. The included studies'

characteristics are shown in Table 1. The studies were published between 2016 and 2022 from various countries of origin, including the United States [7], Italy [15, 16], Spain [17], the Netherlands [18], Germany [19], Indonesia [20], China [21], Korea [2, 22, 23], Japan [24], and South Africa [25, 26]. Based on the World Health Organization's global list of high TB burden countries, three countries were high TB burden countries [17]. Together, these studies included 4,050 subjects, with the number of participants in each study ranging from 79 to 1,031. Seven studies included subjects with latent TB [11, 15, 16, 18, 21, 23, 25], five studies included subjects with active TB [16, 23, 24, 26, 28], and eight studies included immunocompromised subjects [7, 11, 15, 17, 18, 20, 22, 26].

Quality assessment

The NOS was performed in all the 17 studies, with an average score of 6.59. Most studies were good quality, whereas only two studies got an NOS score of 5 (Table 1).

Risk of bias

Most of these studies were at a low risk of bias based on the overall bias (11 of 17) and outcome bias (15 of 17). The risk of

bias due to selection and comparability was classified as low in 10 and 9 studies, respectively (Supplementary Material).

Meta-analysis result

Overall MD of IFN- γ production between TB1 and TB2 tubes

The IFN- γ production in the TB2 tube was statistically higher than in the TB1 tube in the 17 studies with high heterogeneity (pooled MD=0.02, 95 % CI: 0.01–0.03; $I^2=95\%$). Subgroup analysis was performed based on disease conditions and sensitivity analysis to explore the heterogeneity source.

Infection status of TB

Based on the TB status, the subgroup analysis showed that the MD of IFN- γ production between the TB2 and TB1 tubes was significantly higher in active TB subjects than in LTBI subjects (Figure 2A). Pooled MD in active TB subjects from five studies showed that the IFN- γ production was significantly higher in the TB2 tube than in the TB1 tube with high heterogeneity (MD=1.13, 95 % CI: 0.49–1.77; $I^2=94\%$). Meanwhile, the IFN- γ production in LTBI subjects was higher in the TB2 tube than in the TB1 tube with moderate heterogeneity (MD=0.30, 95 % CI: 0.00–0.60; $I^2=58\%$).

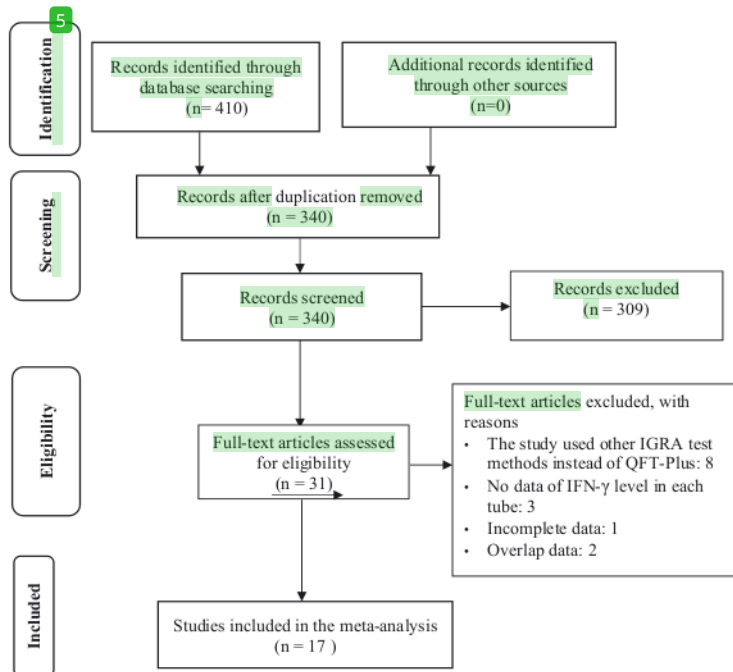


Figure 1: Flow chart of study selection. IGRA, interferon-gamma release assays; QFT-Plus, QuantiFERON-TB Gold Plus; IFN- γ , interferon- γ .

Table 1: Characteristics of studies included in the current meta-analysis on the comparison of IFN- γ production between TB1 and TB2 tubes.

No.	Author, year	Country	Population	Mean or median IFN- γ production level in TB1 and TB2 tubes, IU/mL	Quality (based on NOS)
1.	Barcellini 2016	Italy	119 adult TB contacts Age: 38 (30–79) years old – Immunocompromised or under immunosuppressants: 11 – Immunocompetent: 108	TB1-nil: 0.74 (0.01–9.65) TB2-nil: 0.67 (0.04–8.94) LTBI: TB1-nil: 10.6 (2.94–16.57) TB2-nil: 11.00 (3.32–17.75)	Fair
2.	Petruccioli 2017	Italy	HIV-uninfected adults – Active TB: 69 Age: 35 (28–44) years old – LTBI: 58 Age: 42 (31.75–57) years old – Cured TB: 33 Age: 35 (28.5–42.5) years old – Healthy controls: 19 Age: 43 (33–48) years old	Active TB TB1-nil: 1.9 (0.7–6.8) TB2-nil: 2.5 (0.9–7.5) LTBI TB1-nil: 5.6 (2–10) TB2-nil: 7.3 (1.9–10.0)	Good
3.	Kim 2019	Korea	137 adults (included immunocompromised or under immunosuppressants) Age: 46.8 \pm 16.3 years old – Active TB: 14 – LTBI: 45	Overall TB1-nil: 2.62 (1.06–7.91) TB2-nil: 3.15 (1.08–8.30) LTBI TB1-nil: 4.93 (1.15–10.00) TB2-nil: 4.17 (1.28–10.00)	Good
4.	Won 2020	Korea	220 subjects Age: 47 (28–58) years old – Immunocompromised or under immunosuppressants: 125 – Healthy individuals: 25 – TB infection: 63 – Exposure to TB: 7	Overall TB1-nil: 0.025 (0–0.20) TB2-nil: 0.04 (0.01–0.28)	Good
5.	Siegel 2018	USA	Adult (included immunocompromised or under immunosuppressants) – NTM: 51 Age: 65 (18–78) years old – Non-NTM: 211 Age: 34 (18–75)	Overall TB1-nil: 0.018 (–0.08, 0.37) TB2-nil: 0.043 (–0.15, 0.46)	Fair
6.	Perez-Recio 2021	Spain	Adult: 318 Consists of: – Immune-mediated inflammatory disease: 229 Age: 55.8 (\pm 13.6) years old – Asylum seekers & people from abroad: 89 Age: 28.5 (\pm 11.9) years old	Immune-mediated inflammatory disease: TB1-nil: 1.76 (0.67;6.48) TB2-nil: 1.83 (0.74;6.56) Asylum seekers & people from abroad: TB1-nil: 2.59 (0.91;7.07) TB2-nil: 2.78 (0.84;7.26)	Good
7.	Chien 2018	Taiwan	Elderly: 244 Age: 80 (60–102) years old – LTBI: 66 – Others: 163 – Excluded: 15 (1 died, 13 withdrew, 1 persistent indeterminate QFT)	LTBI TB1-nil: 2.38 \pm 2.67 TB2-nil: 2.6 \pm 2.79 Non LTBI TB1-nil: 0.07 \pm 0.26 TB2-nil: 0.11 \pm 0.33	Good
8.	Lee 2021	Korea	Active TB: 63 Age: 58.3 \pm 13.4 years old LTBI: 77 Age: 49.1 \pm 12.8 years old	Active TB TB1-nil: 8.43 \pm 1.41 TB2-nil: 10.66 \pm 1.65 LTBI TB1-nil: 11.37 \pm 1.753 TB2-nil: 11.38 \pm 1.705	Good

Table 1: (continued)

No.	Author, year	Country	Population	Mean or median IFN- γ production level in TB1 and TB2 tubes, IU/mL	Quality (based on NOS)
9.	Ntshiqqa 2022	South Africa	349 total participants LTBI: 304 Age: 48 (44–52) years old	Overall TB1-nil: 2.89 (1.18–6.97) TB2-nil: 2.95 (1.17–7.79) LTBI TB1-nil: 3.06 (1.31–7) TB2-nil: 3.25 (1.53–8.02) Negative IGRA TB1-nil 0.35 (0.18–0.53) TB2-nil 0.37 (0.28–0.45)	Good
10.	Pieterman 2018	Netherlands	1,031 participants Age: 44 \pm 18 years old – Immunocompromised: 178 – Immunocompetent: 57 – Unknown immune state: 279	LTBI TB1-nil: 2.01 (0.385–6.195) TB2-nil: 2.47 (0.57–6.07) Negative IGRA TB1-nil: 0.00 (–0.01–0.02) TB2-nil: 0.005 (–0.01–0.03)	Fair
11.	Takasaka 2017	Japan	– Active TB: 99 Age: 42 (29–55) years old – Healthy controls: 106 Age: 20 (20–21) years old	Active TB TB1-nil: 4.08 (2.20–8.74) TB2-nil: 4.70 (2.4–9.46) Healthy controls TB1-nil: 0.02 (0.00–0.06) TB2-nil: 0.01 (–0.01–0.06)	Good
12.	Hoffmann 2016	Germany	163 subjects – Active TB: 57 – No TB: 106	Overall TB1-nil: 0.31 \pm 3.2 TB2-nil: 0.37 \pm 3.4	Fair
13.	Yi 2016	Japan	Active TB: 162 – Age: 59 (39–70) years old Control (low-risk subjects): 212 – Age 20 (19–21) years old	Active TB TB1-nil: 2.359 (1.040–5.840) TB2-nil: 2.85 (1.147–6.365) Healthy controls TB1-nil: 0.003 (–0.006–0.012) TB2-nil: 0.009 (–0.003–0.029)	Good
14.	Venkatappa 2019	USA	508 subjects (high risk for LTBI and/or progression to TB) Age: 32 (19–44.5) years old LTBI: 94	LTBI TB1-nil: 2.55 (0.98–9.87) TB2-nil: 2.90 (1–9.87)	Good
15.	Theel 2018	USA	161 subjects – TB clinic patients: 42 Age 36 (18–79) years old – Active TB: 3 – LTBI no Tx: 28 – LTBI complete Tx: 1 – No LTBI: 10 – Health care workers: 119 Age 41 (25–62) years old	LTBI TB1-nil: 2.22 (0.31–6.2) TB2-nil: 2.44 (0.21–6.31)	Fair
16.	Maharani 2020	Indonesia	All female: 79 – SLE patients (LTBI: 10) – Active: 33 Age 29 (22–47) years old – Quiescent: 26 Age 34 (25–63) years old – Healthy controls: 20 (LTBI: 6)	Overall TB1-nil: 0.3096 \pm 1.17 TB2-nil: 0.2572 \pm 0.96 Overall LTBI TB1-nil: 1.76 \pm 1.88 TB2-nil: 1.39 \pm 1.515 SLE subjects TB1-nil: 0.2917 \pm 1.26 TB2-nil: 0.2705 \pm 1.08 Healthy control TB1-nil: 0.3625 \pm 0.88 TB2-nil: 0.218 \pm 0.455	Good

Table 1: (continued)

No.	Author, year	Country	Population	Mean or median IFN- γ production level in TB1 and TB2 tubes, IU/mL	Quality (based on NOS)
17.	Telisinghe 2017	Africa	108 pulmonary TB patients – Age: 32 (27–38) years old – HIV +: 68 – HIV -: 40	HIV (-) TB1-nil: 1.61 (0.43–5.74) TB2-nil: 2.47 (0.67–10.0) HIV (+) TB1-nil: 2.32 (0.45–7.87) TB2-nil: 4.42 (0.58–9.77)	Good

IFN, interferon; TB, tuberculosis; LTBI, latent tuberculosis infection; NTM, nontuberculous mycobacterial; QFT, QuantiFERON; IGRA, interferon gamma release assay; SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus; NOS, Newcastle-Ottawa Scale.

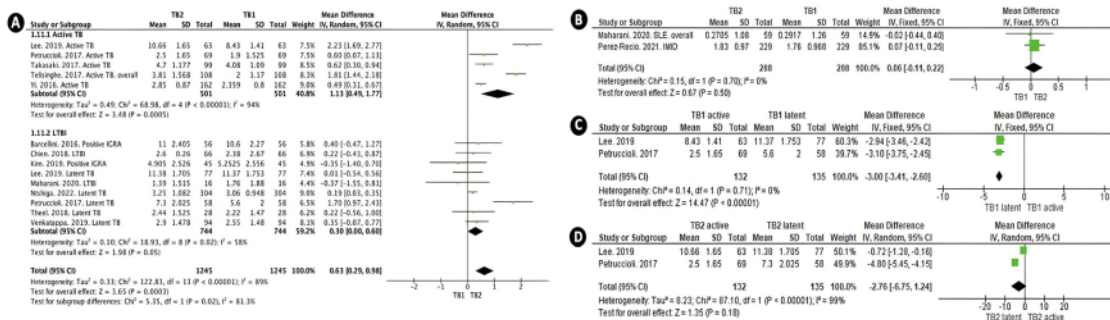


Figure 2: Forrest plot of each subgroup. (A) Forrest plot of mean difference IFN- γ production in TB1 and TB2 tubes in active and LTBI subjects; (B) Forrest plot of mean difference IFN- γ production in TB1 and TB2 tubes in immune-mediated inflammatory diseases subjects; (C) Forrest plot of mean difference IFN- γ production in TB1 between active and LTBI subjects; (D) Forrest plot of mean difference IFN- γ production in TB2 between active and LTBI subjects.

Immunocompromised subjects due to immune-mediated inflammatory disease

Two studies have reported data on immune-mediated inflammatory subjects. One study included patients with systemic lupus erythematosus as a case group [20], and the other did not mention the diagnosis of immune-mediated inflammatory disease included in the study. Pooled MD showed higher IFN- γ production in the TB2 tube than in the TB1 tube. However, no statistical significance was observed. No significant heterogeneity was detected (MD=0.06, 95% CI: -0.11 to 0.22; I²=0%) (Figure 2B).

Grouping the studies based on TB burden countries resulted in no decline in heterogeneity (I² were 97 and 94% in the pooling of three high TB burden countries and seven non-high TB burden countries, resp.). No significant differences were observed between the two groups.

Furthermore, the IFN- γ production in each tube was compared between active TB and LTBI subjects. Interestingly, the IFN- γ production was lower in active TB subjects than in LTBI subjects in both the TB1 (MD=-3.00, 95% CI: -3.41 to -2.60; I²=0%) and TB2 tubes (MD=-2.45, 95% CI: -2.87 to -2.03; I²=99%) (Figure 2C and D).

Sensitivity analyses and publication bias

Sensitivity analyses by excluding fair-quality studies exhibited significantly higher IFN- γ production levels in the TB2 tube than in the TB1 tube. Additionally, a single study from the 17 studies was sequentially excluded. The findings were statistically higher in the TB2 tube than in the TB1 tube, except when excluding a study by Telisinghe et al., which did not achieve statistical significance. These sensitivity analyses showed the robustness of our meta-analysis.

Publication bias for the 17 studies was assessed using a funnel plot, which showed no convincing evidence of publication bias.

Discussion

IFN- γ plays an essential role in protecting against TB infection and is mainly secreted by CD4 and CD8 T-cells [29]. The result of this extensive review demonstrated a higher IFN- γ production level in the TB2 tube than in the TB1 tube, which might serve as a surrogate marker for the magnitude of the CD8 T-cell response in the overall population. The evidence

of the association between CD4 T-cells and TB infection is well documented, such as in patients with human immunodeficiency virus (HIV) infection with CD4 immunodeficiency who are dramatically more vulnerable to TB infection [30]. The role of CD8 T-cells in TB infection is less prominent than that of CD4 T-cells since few specifically CD8 T-cell-deficient conditions have been observed in humans. Nevertheless, CD8 T-cells may serve as cytotoxic cells killing the pathogen and cells producing various cytokines, including IFN- γ [31, 32]. This study supports the emerging data that CD8 T-cells play an important role in host immunity against MTB, which is reflected by the difference in IFN- γ production levels between the TB2 and TB1 tubes [15]. Moreover, adding newly designed short peptides to elicit CD8 T-cell immune response provides some advantages, such as higher accuracy in immunocompromised subjects and higher response in active TB subjects [23, 33]. Both conditions were evaluated through subgroup analyses.

This study showed a higher MD of IFN- γ response between the TB2 and TB1 tubes in the active TB subjects than in the LTBI subjects. This finding was in line with previous flow cytometry studies that reported a predominant CD8 T-cell response in active TB subjects compared with LTBI subjects, which might be related to bacterial load [34, 35]. Hence, the functional profile of CD4 and CD8 T-cells reflects the disease stage of TB. CD8 T-cell response is associated with active TB [36]. Nevertheless, the QFT-Plus test does not discriminate between active and LTBI.

In this study, seven studies included subjects under immunosuppressive agents or having immunocompromised diseases. Nonetheless, only four studies reported data of interest. One study shared the data of immunocompromised subjects but included subjects with various causes of immunosuppression state, such as history of malignancy, diabetes mellitus, and organ transplant recipients. Unfortunately, only one study reported the MD IFN- γ data in subjects with CD4 immunodeficiency, that is, HIV infection. Therefore, we could not present a pooled evaluation biomolecular mechanism of IFN- γ production in CD4-deficient subjects. Two of four studies reported the data in a relatively similar population, that is, immune-mediated inflammatory disease subjects. This study demonstrated that samples from immune-mediated inflammatory disease subjects behaved in the same manner as IFN- γ response between the TB1 and TB2 tubes. However, functional impairment of CD8 T-cells might underlie the higher risk of infection in patients with immune-mediated inflammatory diseases [37, 38].

When comparing the IFN- γ production level in each tube, a significantly higher IFN- γ response was demonstrated in LTBI subjects than in active TB subjects. These results suggest a higher immunological ability to respond to

the MTB antigen stimulation in LTBI subjects than in active TB subjects [16, 23]. Immunological studies comparing pulmonary TB, LTBI, and healthy control demonstrated that pulmonary TB subjects had the lowest frequencies of CD4 and CD8 T-cells producing IFN- γ among the groups [39]. A previous study from Indonesia showed findings similar to those of our study: depression of IFN- γ production capacity in active TB subjects, which correlated with disease severity and recovered after therapy [40]. The findings of this study, in harmony with the previous studies, provide ample evidence of the pivotal role of IFN- γ in protective immunity against MTB and dysregulated IFN- γ production as one of the risk factors for developing active TB.

The novelty of this study lies in the fact that it is the first study that systematically reviewed the difference in IFN- γ response between the TB1 and TB2 tubes from multinational studies consisting of numerous subjects with different disease conditions. Furthermore, subgroup analyses were performed to accommodate the heterogeneity across the studies and specifically evaluate the difference in IFN- γ production capacity in specific disease states.

This study has several limitations. This study included only literature in English. Thus, language bias may exist. Some studies have reported the data in medians, and information might be lost in the transfer process. The included studies had potential confounders, such as age, and nutritional status, which might affect the cytokine production capacity. Substantial heterogeneity was noted in this study. Subgroup analyses were conducted, some of which decreased heterogeneity. However, the number of studies in each group was small.

Conclusions

This is the first study that systematically demonstrated a higher level of IFN- γ production in the TB2 tube than in the TB1 tube, reflecting the role of CD8 T-cells in response to TB infection. This study showed the potential usefulness of the TB2 tube in certain populations, such as immunocompromised subjects, especially those having CD4 T-cell immunodeficiency. Further studies on more specific and homogeneous immunocompromised subjects are needed to confirm the difference in IFN- γ response between the two tubes in such a population.

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Competing interests: Authors state no conflict of interest.

Informed consent: Not applicable. All included studies declared having obtained informed consent from all inclusion subjects.

Ethical approval: Studies included in this review were approved previously by each Institutional Ethical Review Board; therefore, ethical approval was not required for the present study.

Data availability: The data that support the findings of this study are available on request. Any questions or comments should be addressed to the corresponding authors.

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