LYMPHOCYTE SUBSETS IN RELATION TO INTERFERON GAMMA TESTING:
Immunology Perspective

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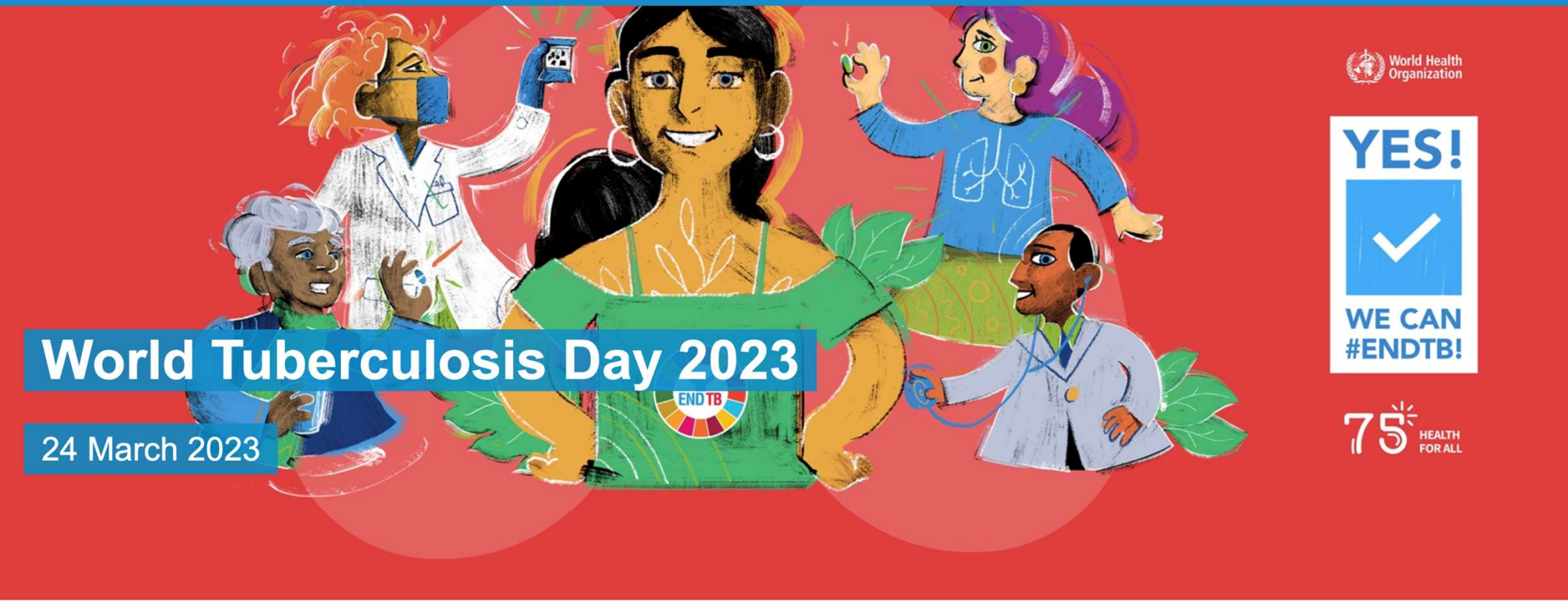


World Tuberculosis Day 2023

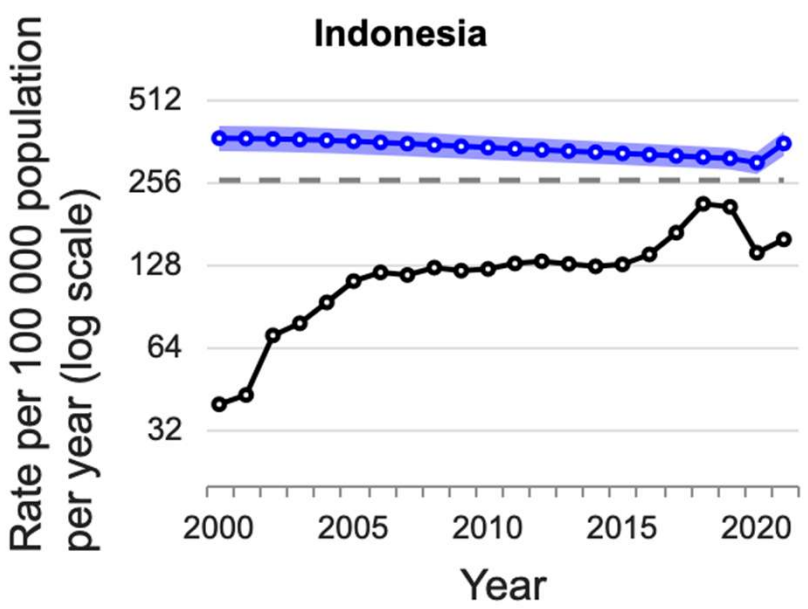
24 March 2023

74 million
lives saved since 2000 by global efforts to end TB

10.6 million
people fell ill with TB in 2021

1.6 million
people died of TB in 2021

INDONESIA SITUATION



Top 8 Countries with the Highest Number of New TB Infections:

India (26%)

China (8.5%)

Indonesia (8.4%)

Philippines (6.0%)

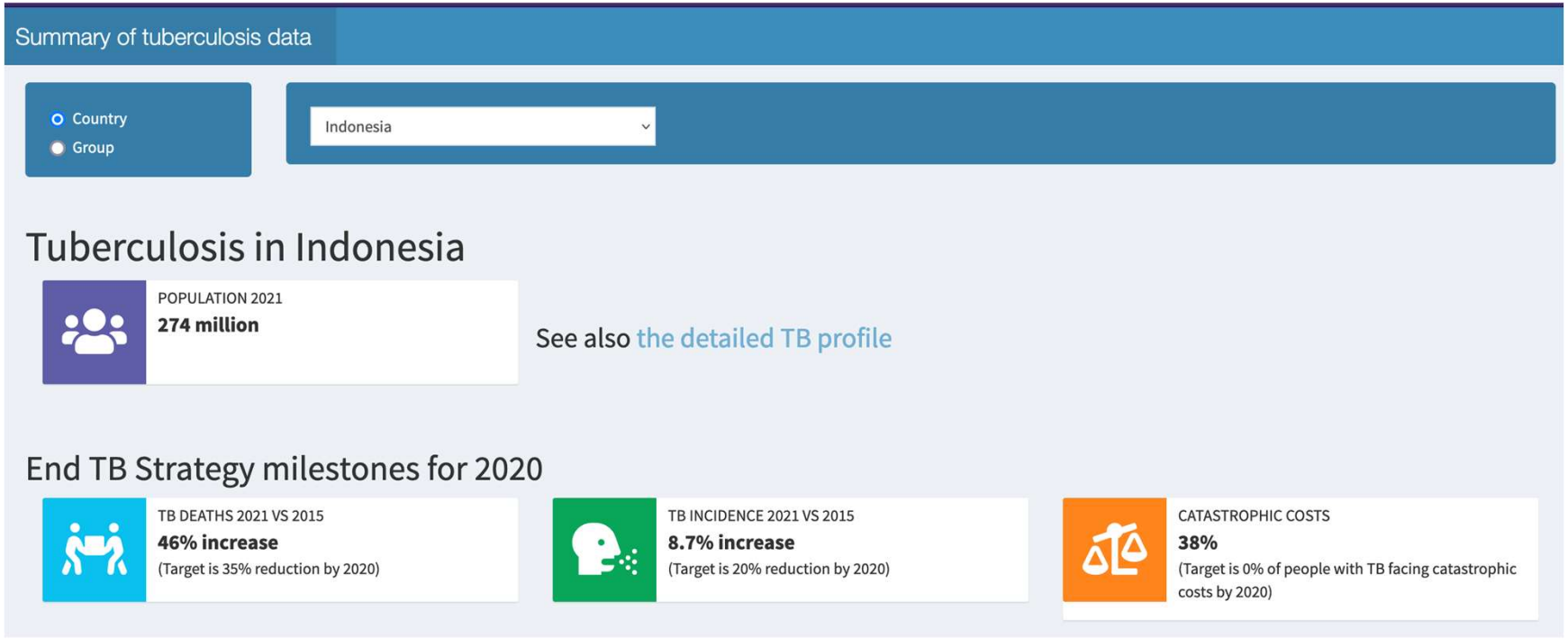
Pakistan (5.8%)

Nigeria (4.6%)

Bangladesh (3.6%)

South Africa (3.6%)

https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022/tb-disease-burden/2-1-tb-incidence



NUMBER OF TB DEATHS 2021
150 000 (one person every 4 minutes)
Range 132 000-169 000. (111 000 in 2020 ↑ +35%)

NUMBER FALLING ILL WITH TB (INCIDENCE NUMBER) 2021
969 000 (one person every 33 seconds)
Range 872 000-1 070 000

TB DEATH RATE 2021
55 per 100 000 population
Range 48-62

TB INCIDENCE RATE 2021
354 per 100 000 population
Range 318-391. (301 in 2020 ↑ +18%)

https://worldhealthorg.shinyapps.io/TBrief/?_inputs_&sidebarCollapsed=true&entity_type=%22country%22&iso2=%22ID%22&sidebarItemExpanded=null

IMMUNITY AGAINST M.tb

- BCG was first introduced in 1921, known to build protection against M.tb infection.
- the incidence of tuberculosis is increased with HIV infection
- Only 5-10% of immunocompetent individuals infected by M.tb progress to disease.

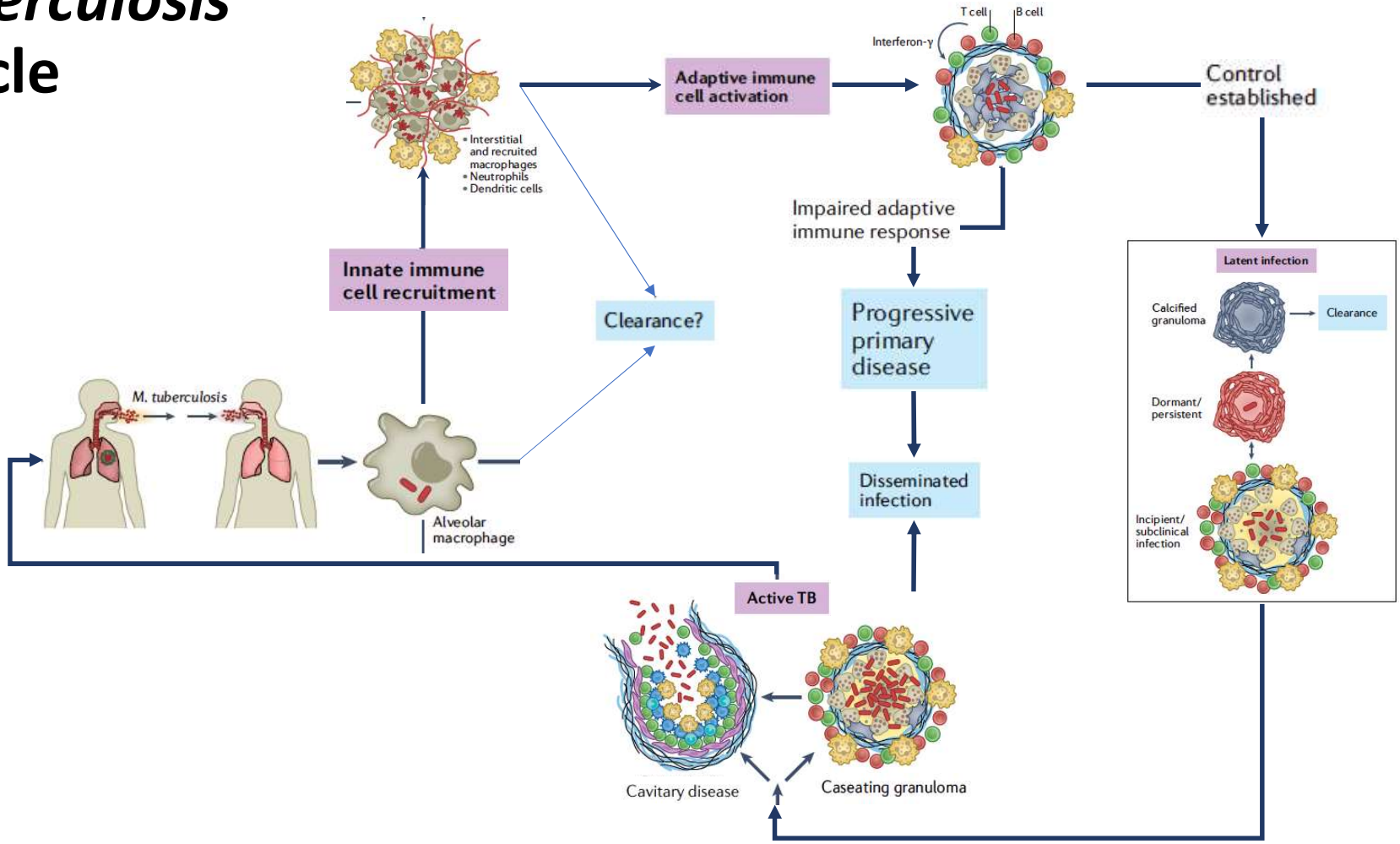
Reuben Erickson (left), the chief of the Division of Tuberculosis at Albany Hospital, administers BCG to babies in 1949.

CORNELL CAPA/THE LIFE PICTURE COLLECTION VIA GETTY IMAGES

Diagnostic Problem

- Current tools to identify M.tb-infected individuals, specifically interferon-γ release assays (IGRAs) and the tuberculin skin test (TST), cannot distinguish between asymptomatic Mtb-infected individuals (latent Mtb infection (LTBI)) and those with TB
- Advancement of TB diagnostics and their application in TB-endemic settings requires an assay that distinguishes between individuals with LTBI and TB.

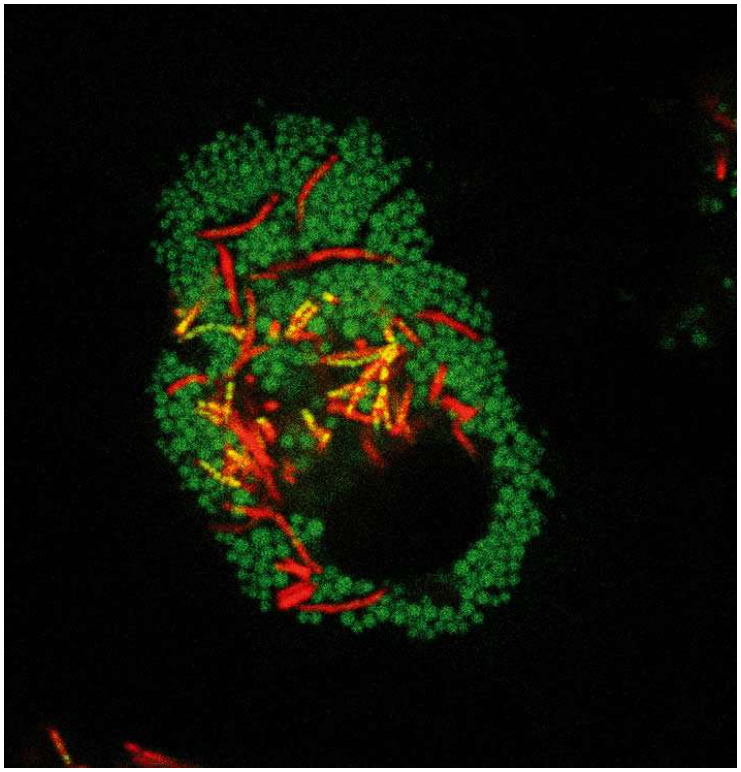
M.tuberculosis life cycle



Chandra, P., et al. Immune evasion and provocation by *Mycobacterium tuberculosis*. *Nat Rev Microbiol* **20**, 750–766 (2022). https://doi.org/10.1038/s41579-022-00763-4

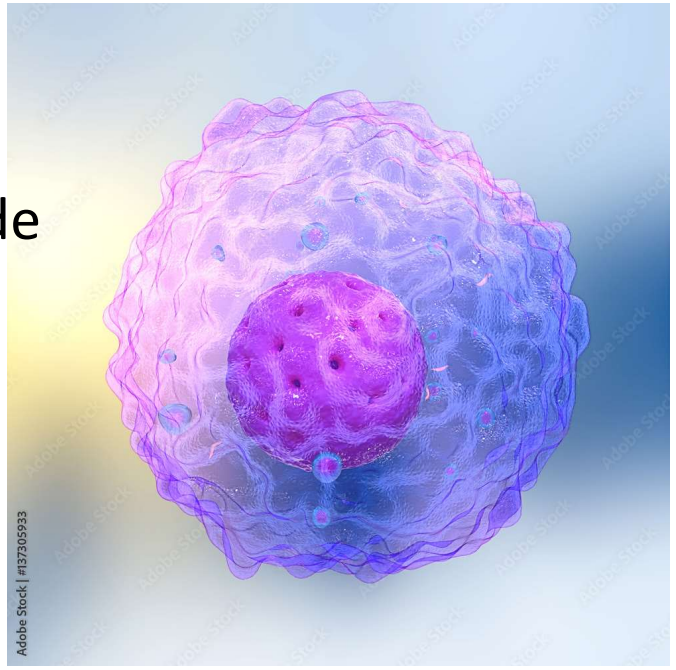
INNATE IMMUNE RESPONSE AGAINST M.tb.

- Macrophages are the first line of defense, but only if the ratio of forces lies to their advantage and the intervention is immediate.
- Otherwise, they become first a niche for the slow replication of the Mtb and then the sanctuary for the persistence of the infection inside the phagosome.
- IFN-γ is a key element in the containment of M.tb within the macrophages



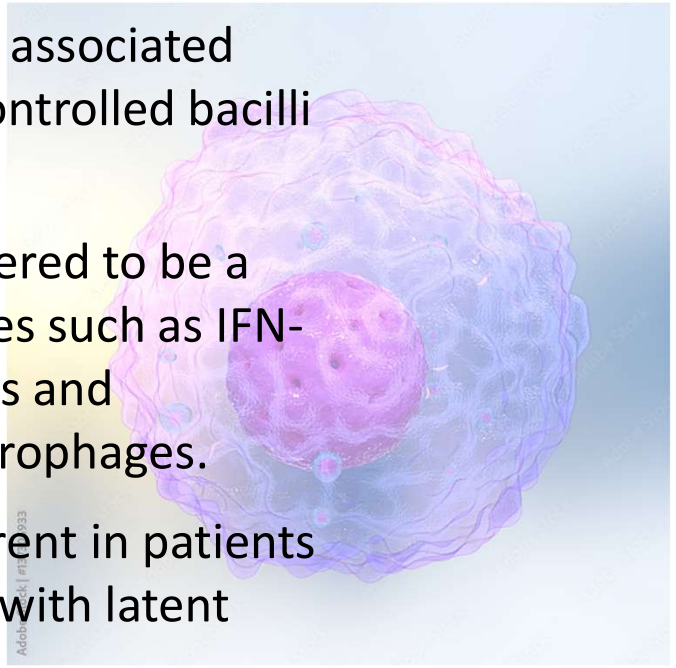
ADAPTIVE IMMUNE RESPONSE AGAINST M.tb

- T cells are required for containment of primary M.tb infection, and most TB vaccines in development elicit T cell responses
- T lymphocytes activation when M.tb spreads inside the lymph nodes but started the innate immune system.
- Maturation of the phagosome of macrophage is facilitated and increased by IFN- γ, mostly dependent on the T lymphocytes CD4+ with a minor support of CD8+ and gd T lymphocytes



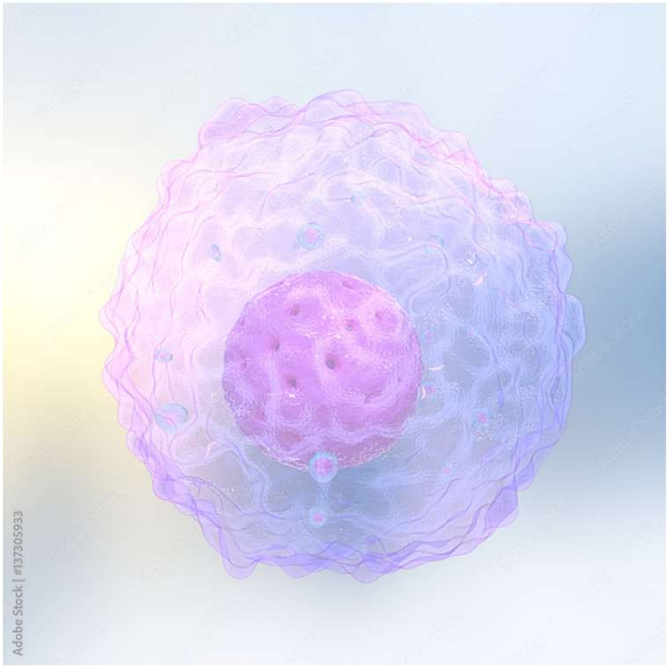
CD4+ T Lymphocytes

- Several studies have underscored the essential role of CD4+ T cells in protection against M.tb, since CD4+ T-cell depletion is also associated with M.tb reactivation in HIV-infected individuals and uncontrolled bacilli growth.
- The protective Mtb-specific CD4+ T-cell response is considered to be a typical T H 1 response with CD4+ T cells producing cytokines such as IFN-γ or TNF-α that contribute to the recruitment of monocytes and granulocytes and activate the antimicrobial activity of macrophages.
- Mtb-specific CD4+ T-cell responses were functionally different in patients with active TB disease as compared with those in subjects with latent Mtb infection (LTBI).
- Several studies also suggested a role of TH 17 cells in the control of TB

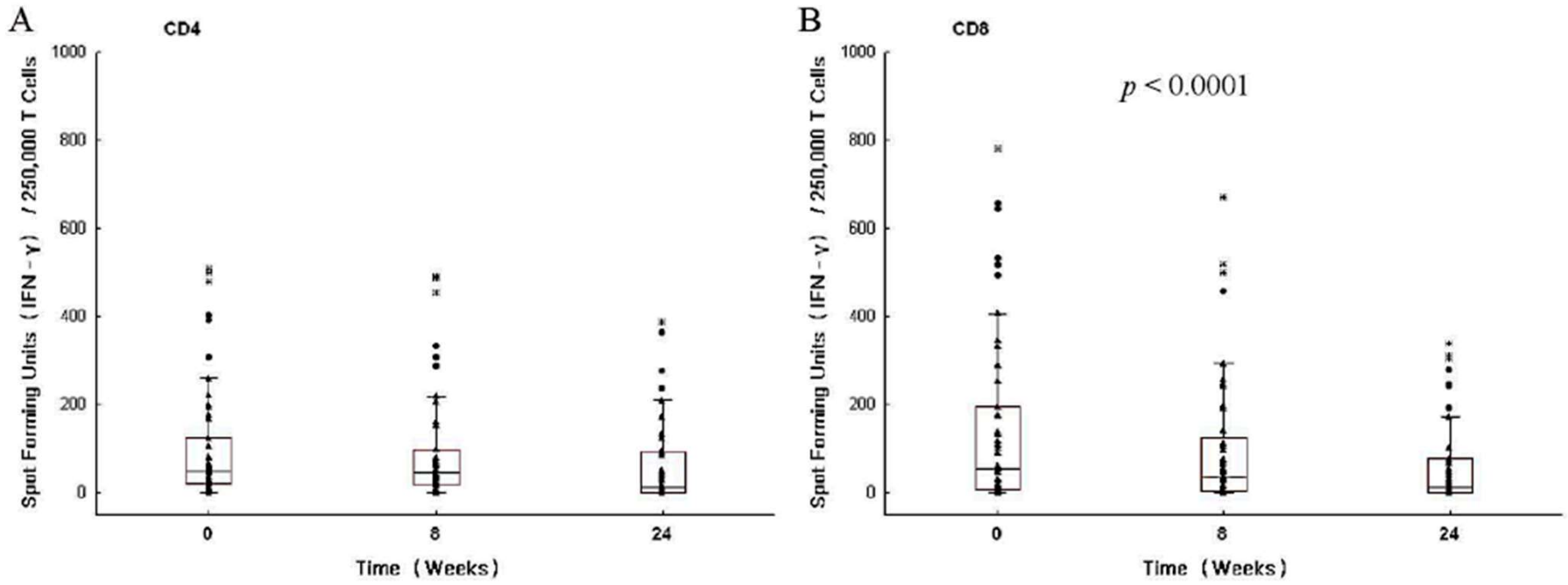


CD8+ T Lymphocytes

- The importance and the role of M.tb-specific CD8+ T cells in the control of M.tb and their mechanism of action remain highly controversial.
- A number of secreted immunodominant M.tb antigens can be processed by cytosolic pathways and presented by MHC class I molecules

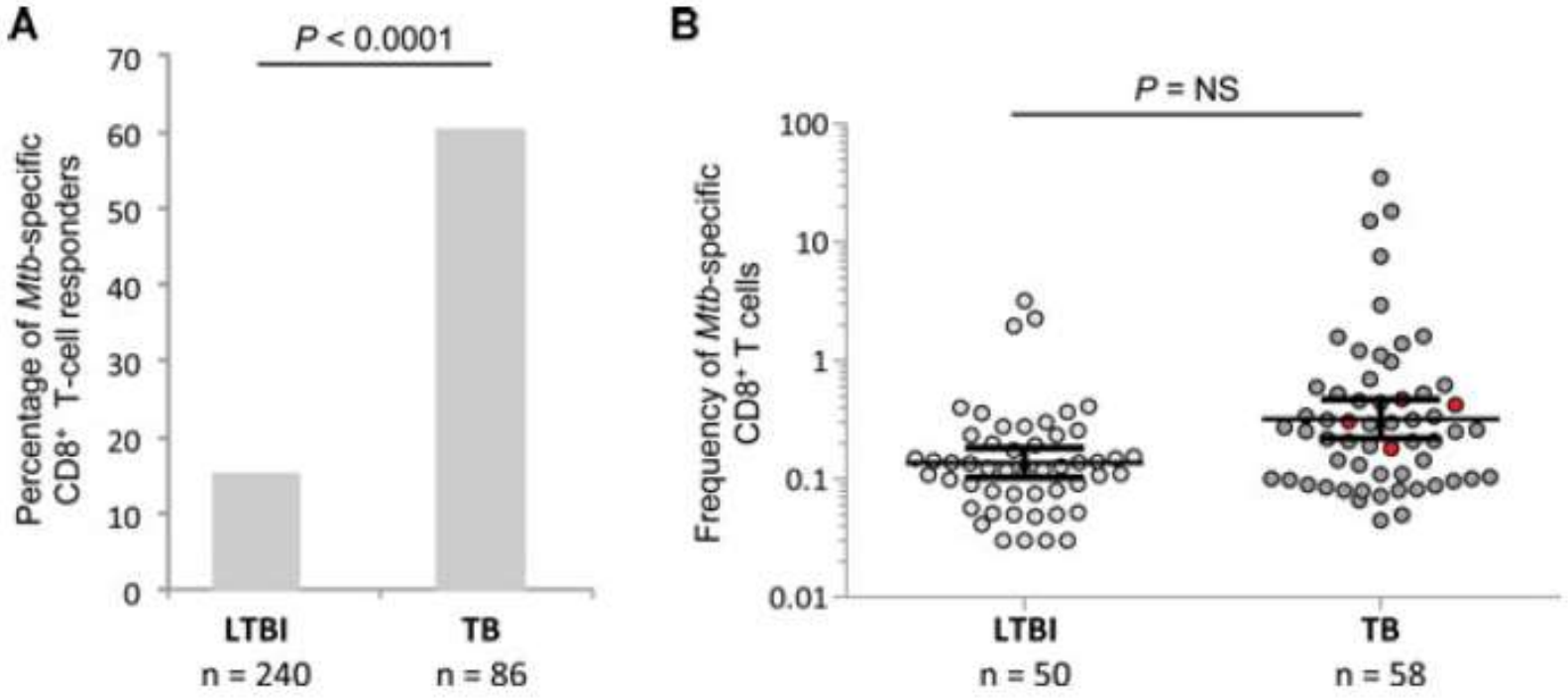


M.tb specific CD4+ and CD8+ T Lymphocyt count with antituberculosis treatment



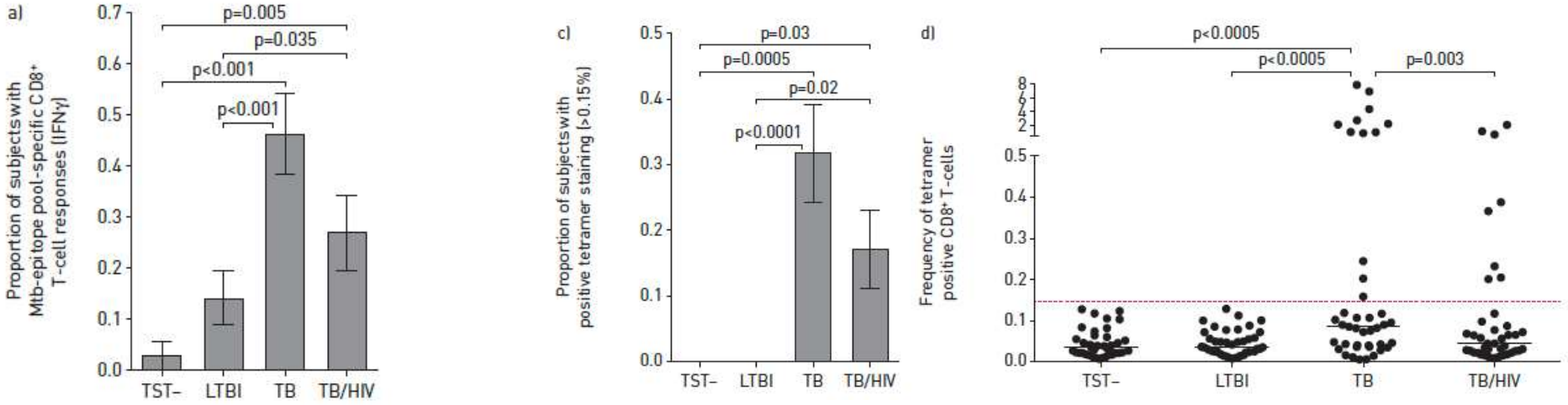
Nyendak MR, Park B, Null MD, Baseke J, Swarbrick G, et al. (2013) Mycobacterium tuberculosis Specific CD8+ T Cells Rapidly Decline with Antituberculosis Treatment. PLoS ONE 8(12): e81564. doi:10.1371/journal.pone.0081564

M.tb specific CD8+ T lymphocyte: TB vs LTBI



Eur. J. Immunol. 2013. 43: 1568–1577

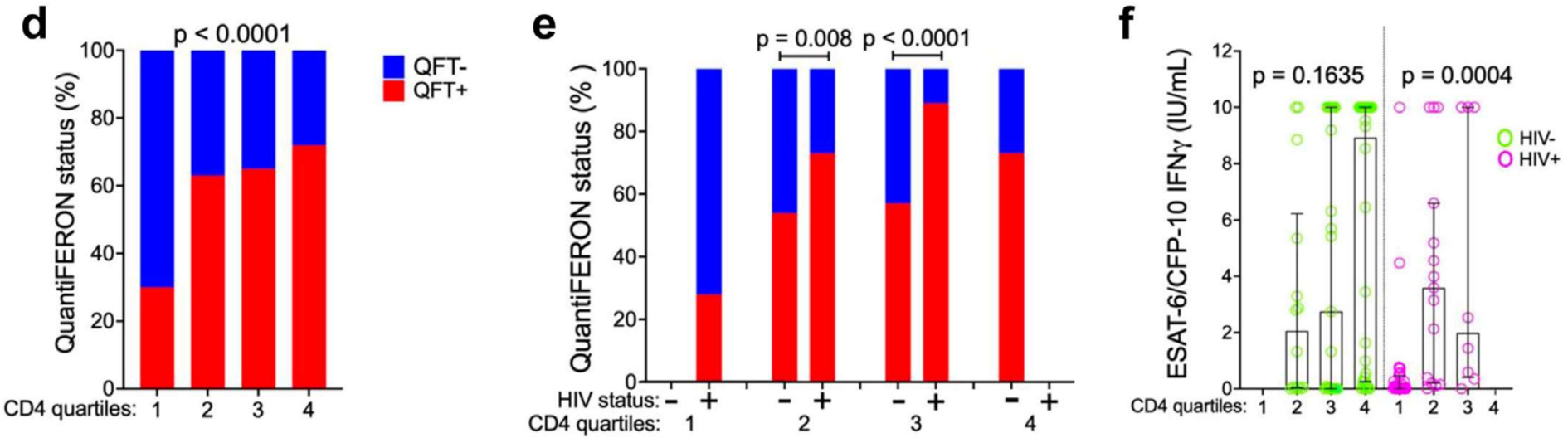
In TB-endemic Setting



CD8+ T-cell cytokine and tetramer responses to Mycobacterium tuberculosis (Mtb)-epitope pool distinguishes latent tuberculosis infection (LTBI) from tuberculosis (TB).

Lancioni C, Swarbrick GM, Park B, et al. Recognition of CD8+ T-cell epitopes to identify adults with pulmonary tuberculosis. Eur Respir J 2019; 53: 1802053 [https://doi.org/10.1183/13993003.02053-2018].

IFN–γ Positivity: CD4 count & HIV status



CD4 T cell count (cells/mm^3) median (IQR)

1st quartile (0–428) n (median)

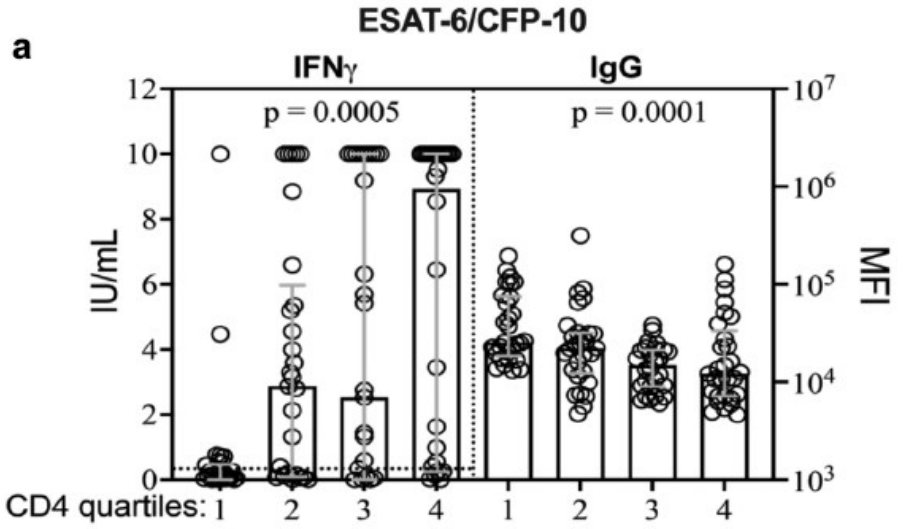
2nd quartile (429–685) n (median)

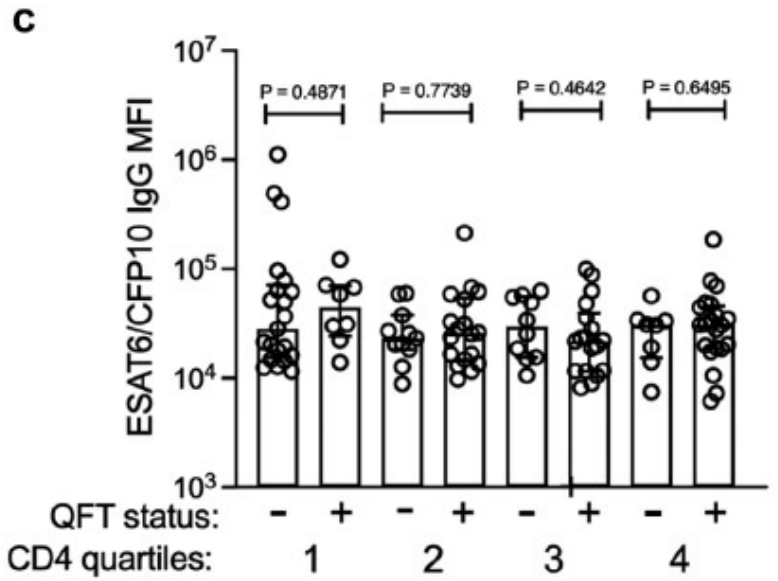
3rd quartile (686–923) n (median)

4th quartile (923–2043) n (median)

Mthembu M. et al.
eBioMedicine 2023;90: 104504 https://doi.org/10.1016/j.ebiom.2023.104504
www.thelancet.com Vol 90 April, 2023

IFN–γ vs IgG: ESAT-6/CFP-10 induced by CD4-count group





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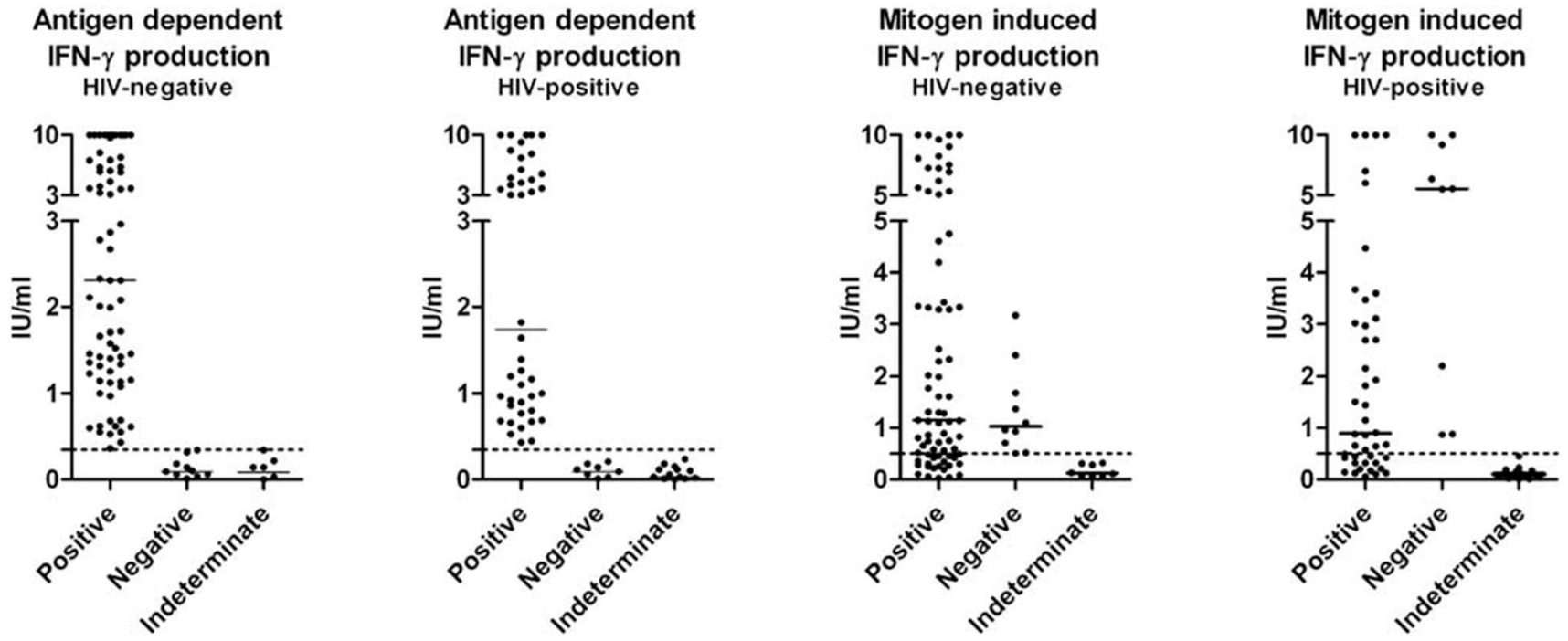
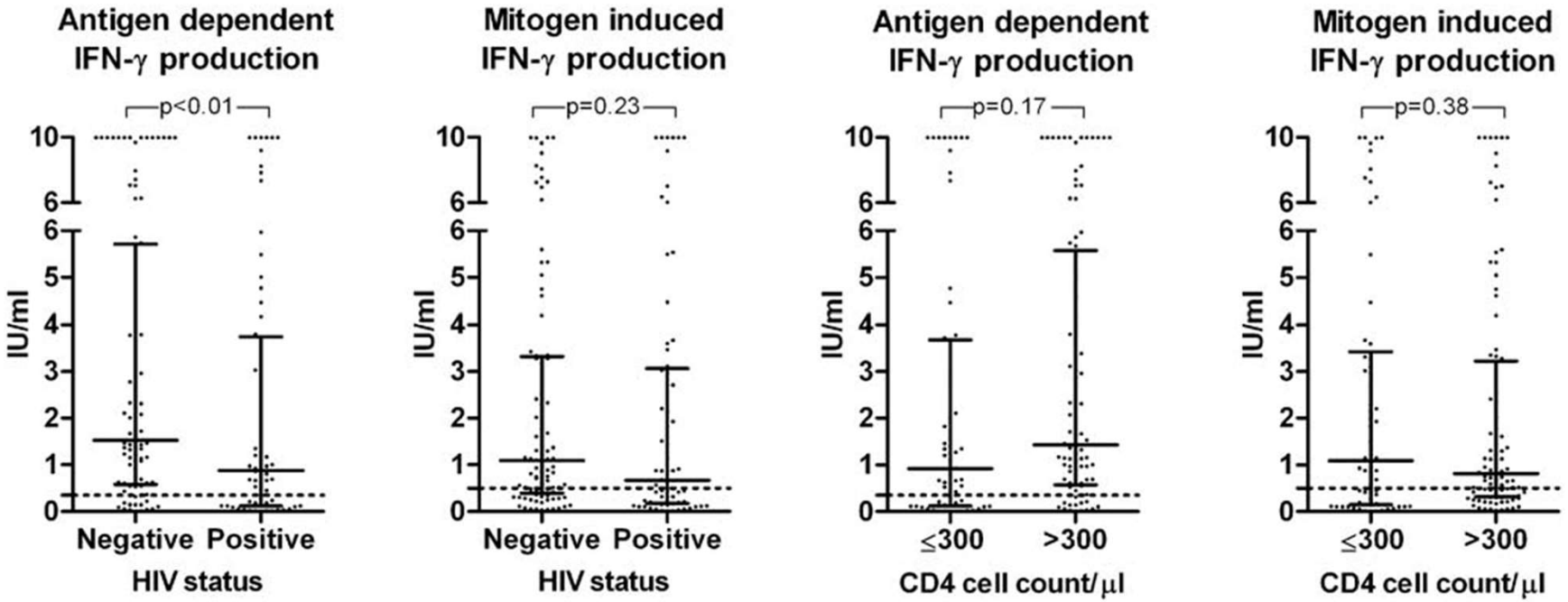
Antigen dependent and mitogen induced absolute IFN-γ levels in HIV negative and HIV-positive patients

(QuantiFERON-TBH Gold In-tube test)



Aabye MG, Ravn P, PrayGod G, Jeremiah K, Mugomela A, et al. (2009) The Impact of HIV Infection and CD4 Cell Count on the Performance of an Interferon Gamma Release Assay in Patients with Pulmonary Tuberculosis. PLoS ONE 4(1): e4220. doi:10.1371/journal.pone.0004220

Antigen dependent and mitogen induced absolute IFN- γ levels by HIV-status and CD4 cell count group.



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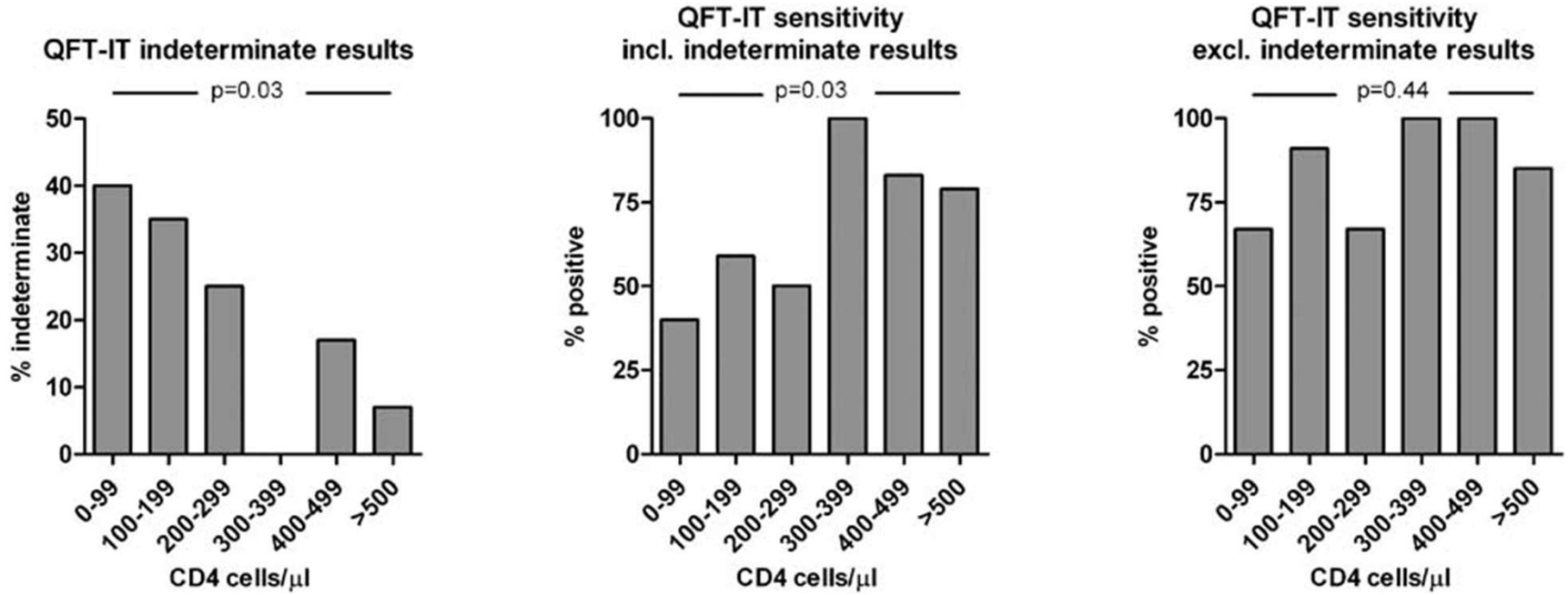
Influence of CD4 cell count on performance of the QuantiFERON-TBH Gold In-tube test in HIV-positive patients



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SUMMARY

- Tuberculosis remains a global major health problem. Indonesia is one among top countries with highest new TB infection.
- Immune system may play an important role in TB pathogenesis, as vaccination reduced the disease burden, and only 5-10% of immunocompetent infected with M.tb progressed to disease.
- Macrophages are among those innate immune system that first encounter M.tb infection. They may be successfully in infection elimination, otherwise may be a sanctuary for the pathogens.
- CD4+ T lymphocytes are known to play important roles in M.tb elimination, one among others by secreting IFN-γ, that helps phagosome to mature and eliminate the pathogens inside.
- CD8+ T lymphocytes role in TB eliminations remains unclear. However, the number of M.tb specific CD8+ T lymphocytes frequencies decreased with antituberculosis treatment, suggestively the usage to differentiate active TB infection.
- IFN-γ release assay may be a useful modality to establish TB diagnosis. IFN-γ release by CD8+ T lymphocytes may differentiate LTBI and TB.
- Care must be taken when using IFN-γ release assay on HIV infected patient with low CD4+ T lymphocyte count.