Leiden University
Medical Center

Update TB immunology

EACCTB November 2019

Simone A. Joosten

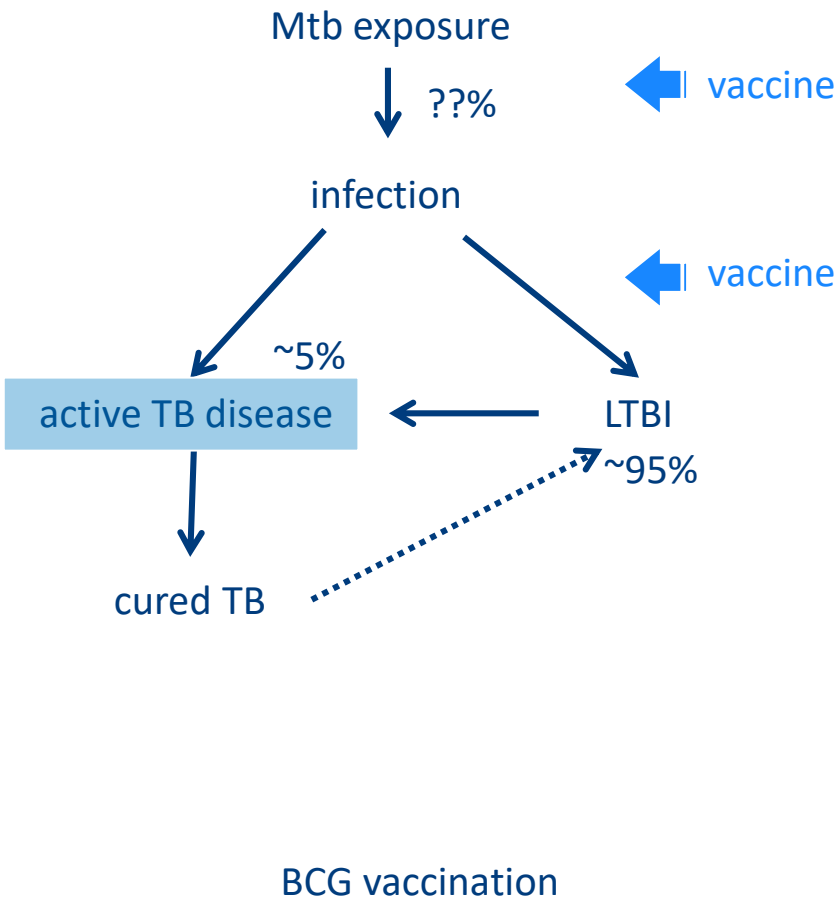
Dept. of Infectious Diseases

LEIDEN UNIVERSITY MEDICAL CENTER

Disclosure of speaker’s interests

No conflicts of interest

TB infection stages



Mtb infection and disease

BCG vaccination

Mtb exposure

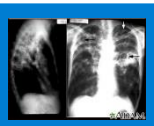
??%

infection

~95%

LTBI

~5%



active TB disease

Immune responses activated by Mtb

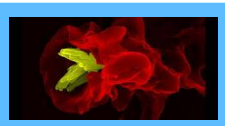
BCG vaccination

Adaptive immune responses,
mostly (CD4) T-cells (IFN-γ$^+$ or multifunctional T-cells)
Protection against other childhood infections,
activation of innate immunity?

Mtb exposure

??%

???

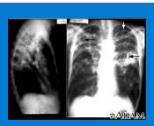


infection

~95%

~5%

LTBI



active TB disease

???

T-cell immunity to Mtb

Adaptive immune responses,
IFN-γ, multifunctional T-cells,
B-cells, antibodies
NK cells

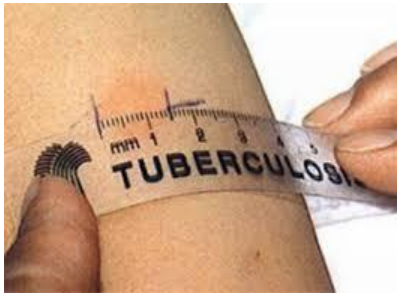
Detection of Mtb infection

Mtb exposure

→

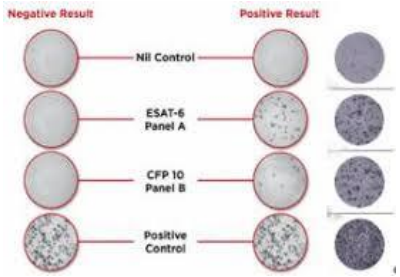
infection

→



Tuberculin skin test

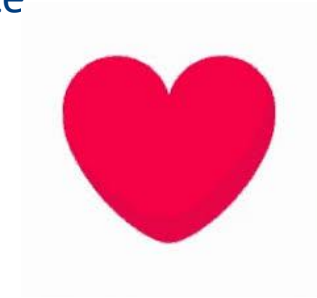
Quantiferon TB Gold

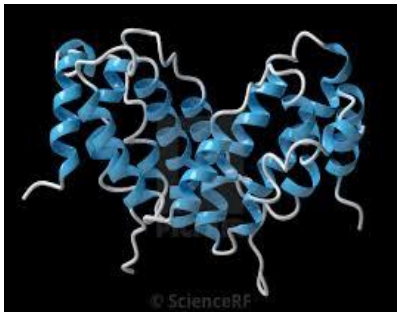


T-spot TB

Mtb not detectable in LTBI individuals

Rely on detection of host immunity to Mtb (antigens) to determine infection state

We  IFN-γ



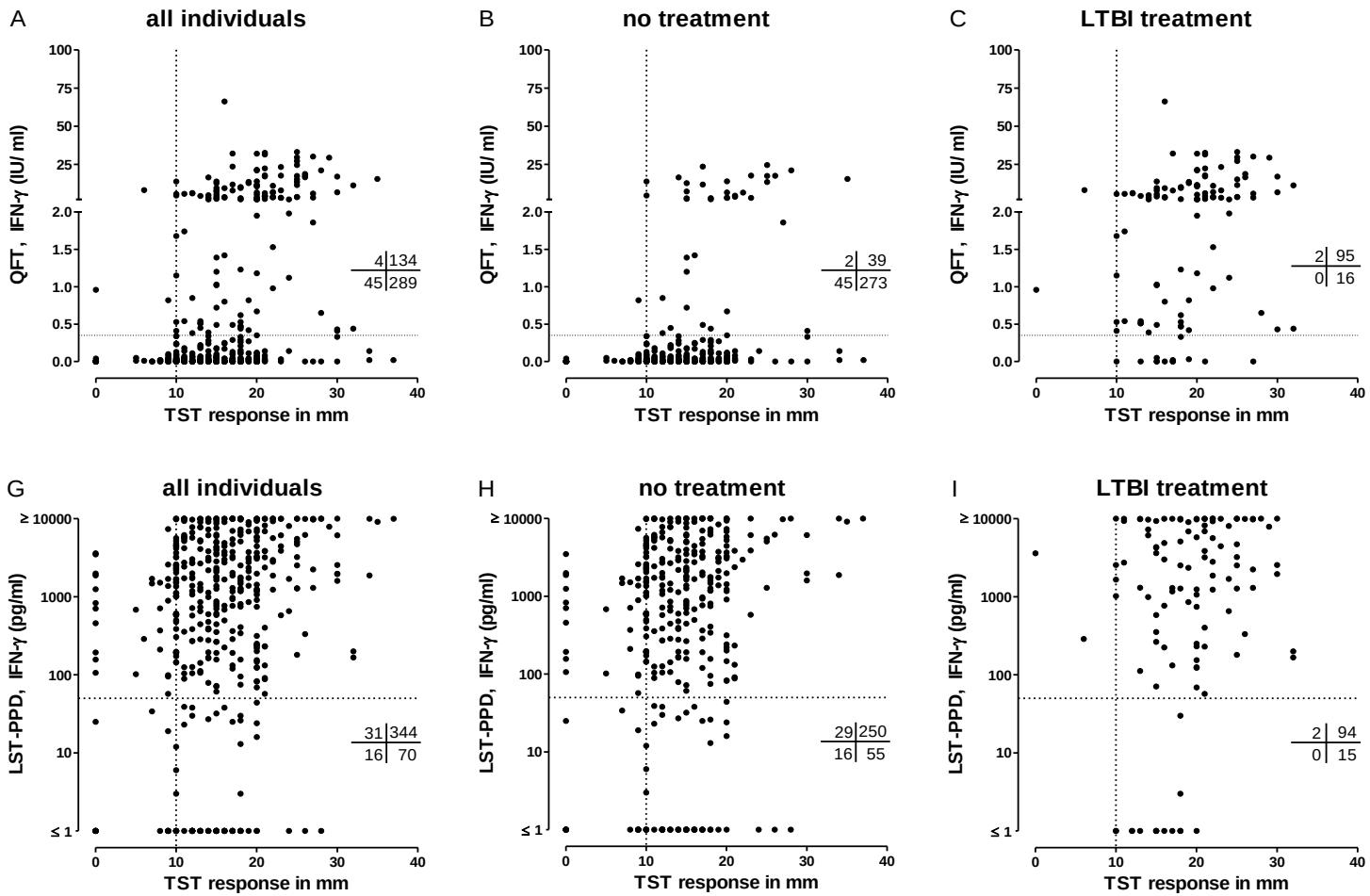
IFN-γ

TB induced immunity

Screening of Th1 immune responses in individuals with a positive TST in a low endemic country (2007-2013), 2 year follow up

QFT-Gold in tube ~24 hrs stimulation

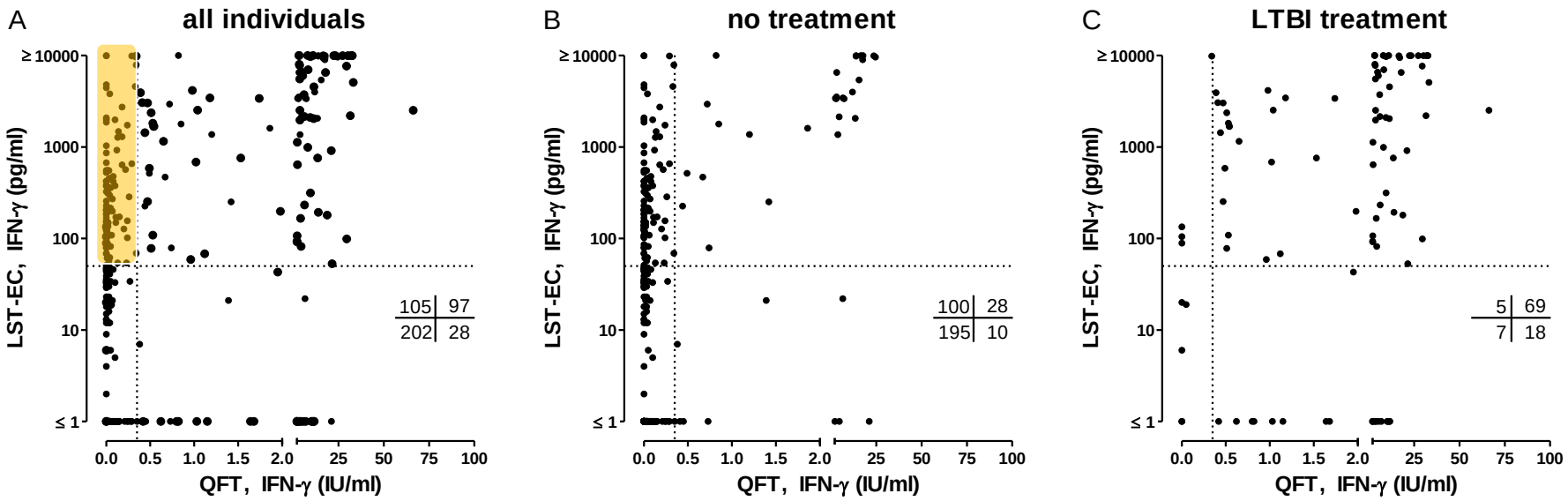
6 day PBMC stimulation assay



Mtb specific memory responses detected in majority of individuals using prolonged stimulation

de Paus et al
Tuberculosis (2017), 106:62-72

Memory immunity



	Contact investigation N=196	Immigrant screening N=48	Screening for other indications [a] N=251	Total N=495
QFT- TST-	15 (8%)	4 (8%)	26 (10%)	45 (9%)
QFT- TST+	106 (54%)	10 (21%)	173 (69%)	289 (58%)
QFT+ TST-	2 (1%)	1 (2%)	1 (0.4%)	4 (0.8%)
QFT+ TST+	68 (35%)**	26 (54%)**	40 (16%)	134 (27%)
Missing	5 (3%)	7 (15%)	11 (4%)	23 (5%)
LSTEC- TST-	9 (4%)	2 (4%)	18 (7%)	29 (6%)
LSTEC- TST+	70(36%)	11 (23%)	109 (43%)	190 (38%)
LSTEC+ TST-	8 (4%)	3 (6%)	5 (2%)	16 (3%)
LSTEC+ TST+	77 (39%)	21 (44%)*	79 (31%)	177 (36%)
Missing	32 (16%)	11 (23%)	40 (16%)	83 (17%)

Recent contact not associated with high EC recognition

de Paus et al
Tuberculosis (2017), 106:62-72

QFT borderline results: infection or assay variation?

AGORA
RESEARCH LETTER

CrossMark

Proof of concept that most borderline Quantiferon results are true antigen-specific responses

~3000 anonymized QFT results from Tertiary Care Hospital in the Netherlands – 2010-2016

Borderline QFT results mostly reflected MTB-specific responses rather than random assay variability:

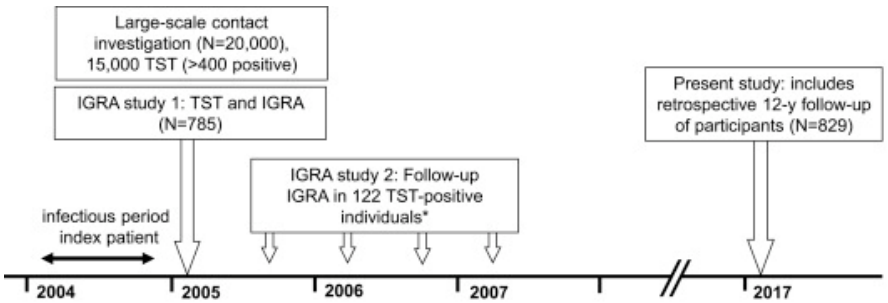
1. QFT results below the cut-off occurred in three-fold excess over the number expected based on random assay variability

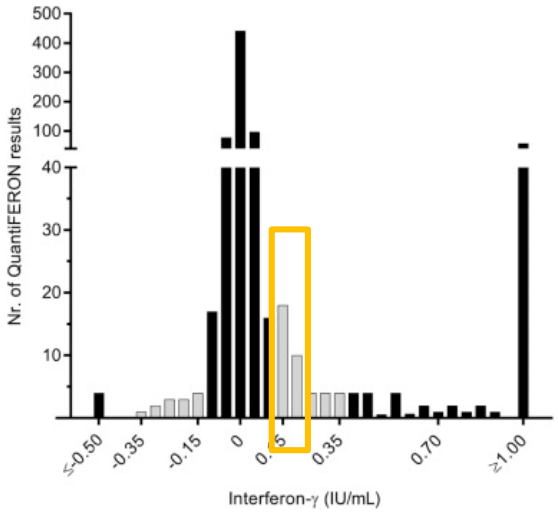
2. patients with borderline results were similar to those with positive results with regard to all other available evidence of TB infection rather than to the negative QFT group

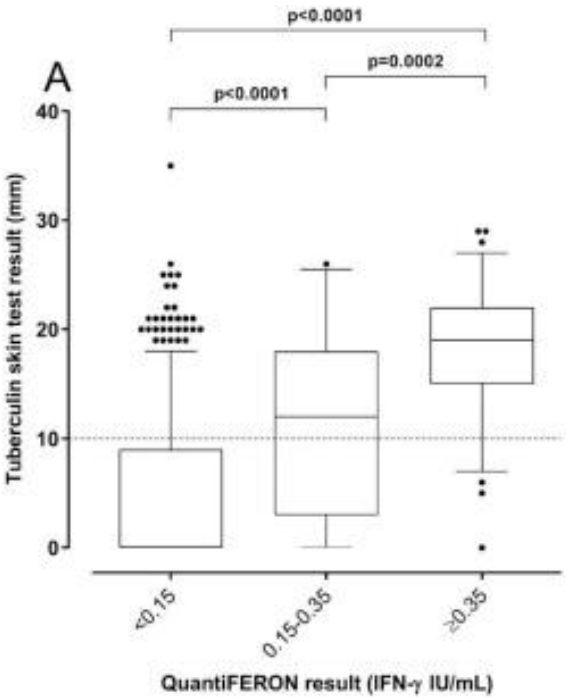
> apply different cut-off depending on the risk of TB, analogous to the graded cut-off for the interpretation of the TST at 5, 10 or 15 mm depending on setting and immune status?

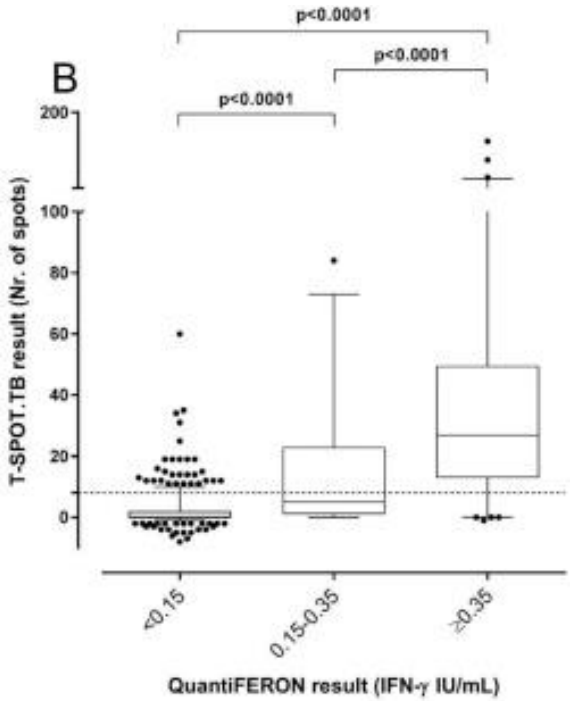
Uzorka et al
Eur Respir J (2017), 50(5): pii 1701630

Most borderline QFT reflect true infection









Unexpected high frequency of QFT results between 0,15-0,35

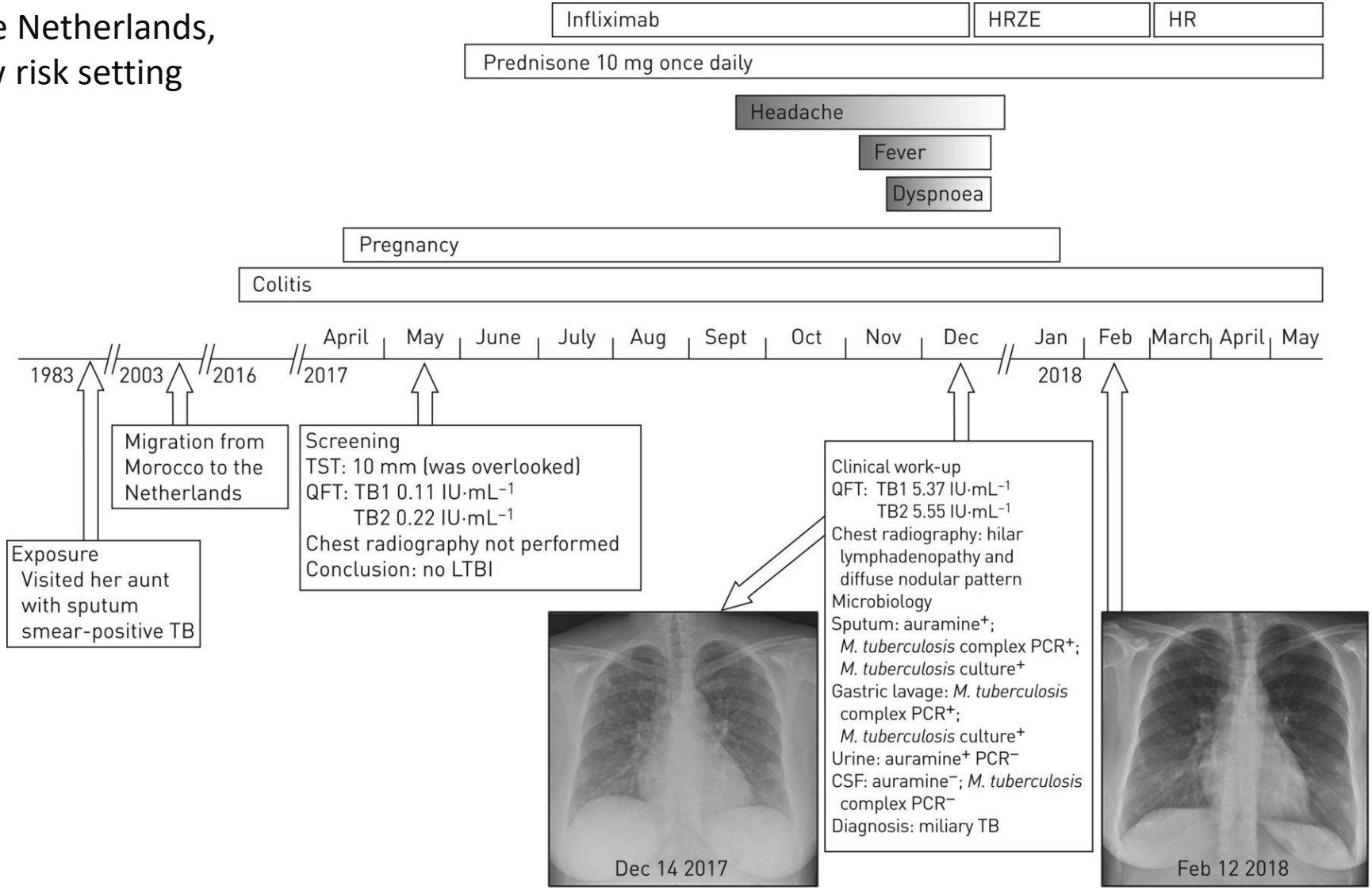
Most individuals with borderline QFT have positive TST or T-SPOT

> Most borderline QFT results truly reflect Mtb infection

Uzorka et al
Tuberculosis (2018), 111: 102-108

Immunosuppression in QFT borderline patient

The Netherlands,
low risk setting

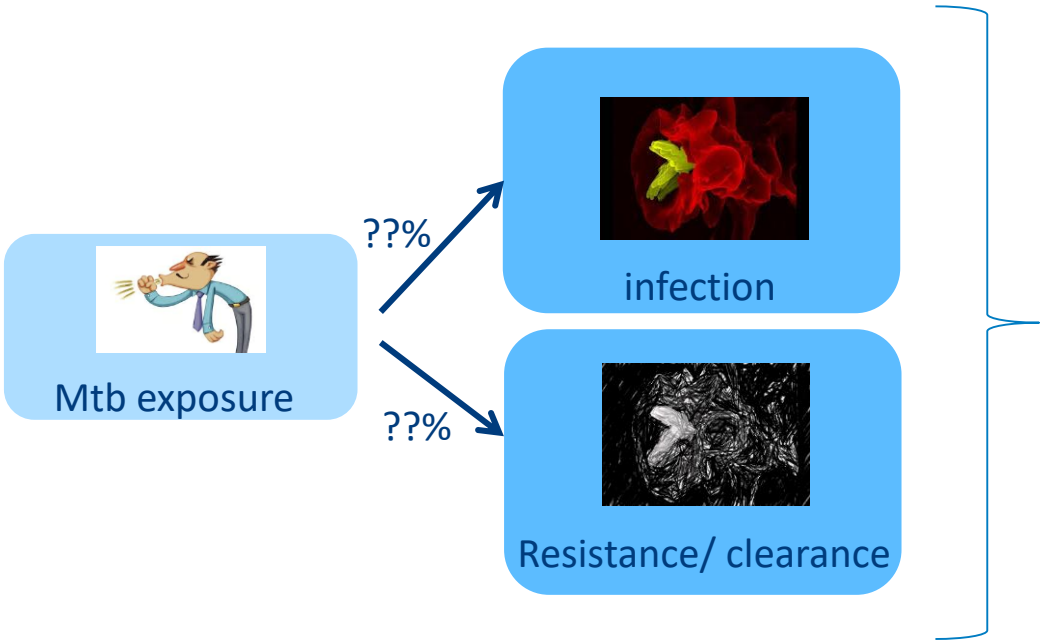


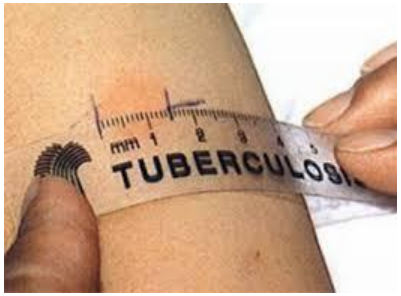
hilar lymphadenopathy and a diffuse nodular pattern, suspicious of miliary TB

Uzorka et al
Eur Respir J (2018), 52 (2): pii 1800913

Mtb exposure: infection vs clearance

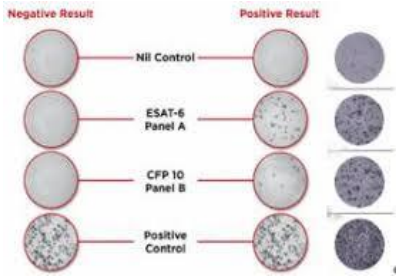
Resistance to infection vs early (innate) clearance



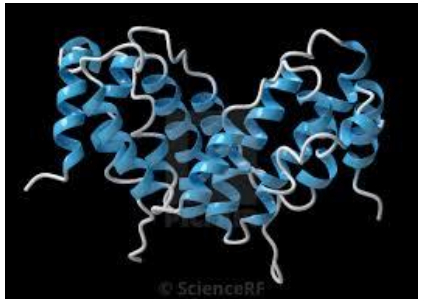


Tuberculin skin test

Quantiferon TB Gold



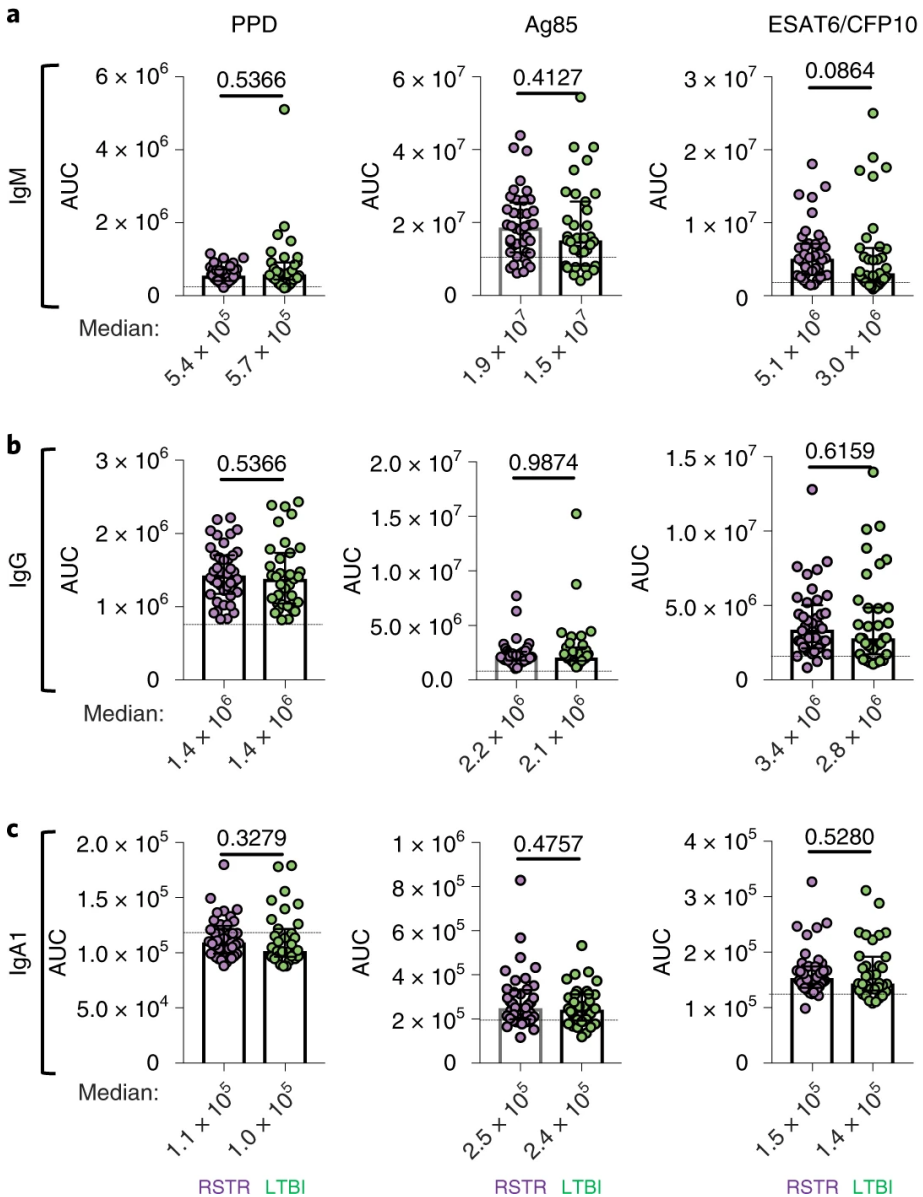
T-spot TB



IFN-γ

Mtb exposure: alternative markers of infection?

Ugandan HHC of TB patients: exposed but persistently negative in TST and/ or QFT > resistors?



Resistors have antibodies against Mtb, including against ESAT-6/ CFP10

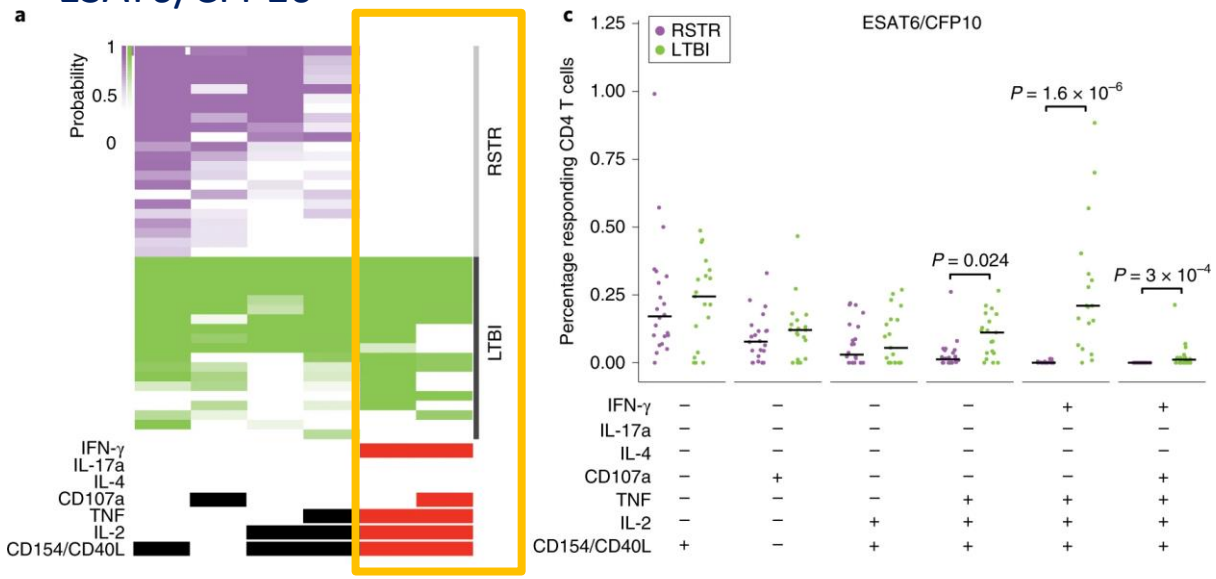
Antibodies have class-switched > suggests long-term antigen exposure

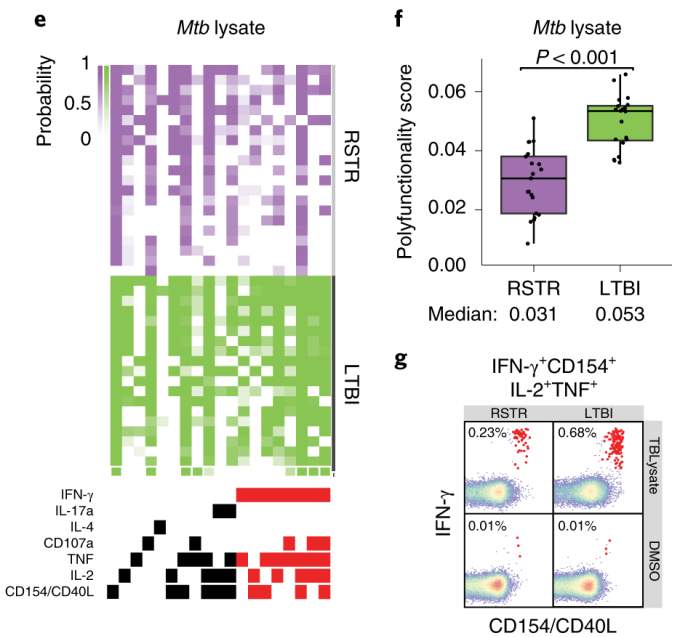
Antibodies have same functional profile as in LTBI

Lu et al
Nat Med (2019), 25: 977-987

Resistors have Mtb specific T-cell responses

ESAT6/CFP10





Resistors have T-cells that recognized Mtb antigens, including ESAT-6/ CFP-10

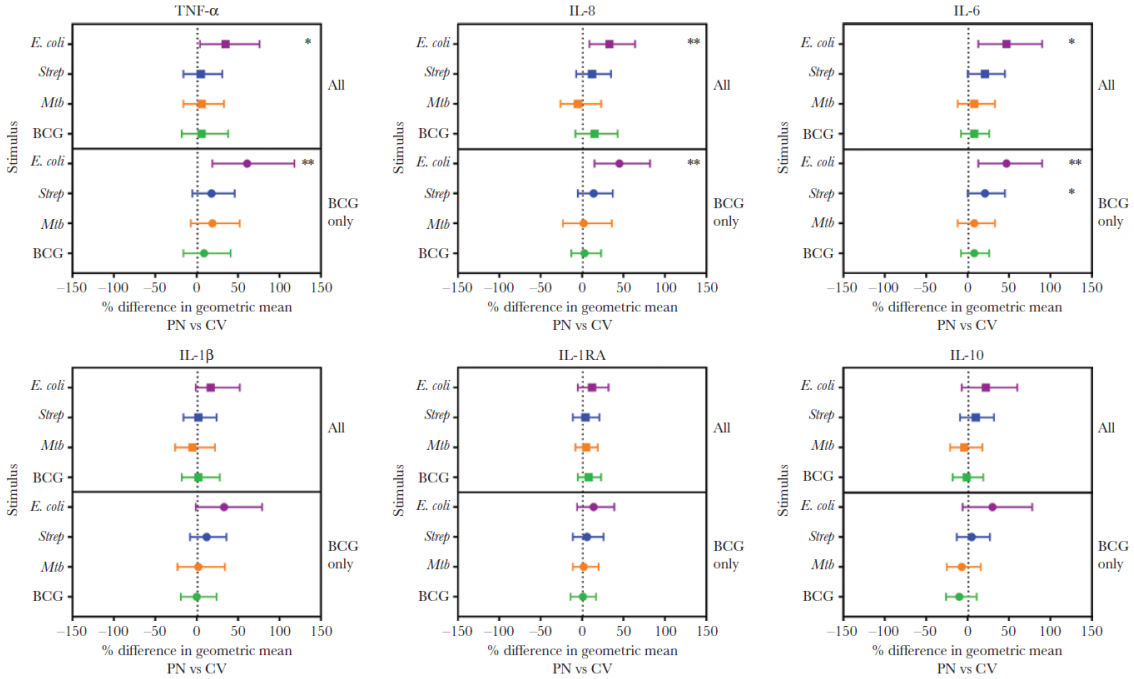
T-cells become activated and produce multiple cytokines, but not IFNg in response to ESAT-6/ CFP-10

>> Antigen specific T-cells in resistors
Early clearance possibly prevented switch to IFNγ producing cells?

Lu et al
Nat Med (2019), 25: 977-987

Early Mtb clearance in persistently negative HHC?

- Indonesian household contacts of TB cases, IGRA baseline and 14 weeks post recruitment
- persistently IGRA-negative contacts:
  - resolving innate cellular response from 2 to 14 weeks in but not converters
  - more proinflammatory cytokines following heterologous stimulation with *E. coli* and *S. pneumoniae*.



- Early clearance of *M. tuberculosis* is associated with enhanced heterologous innate immune responses similar to those activated during induction of trained immunity

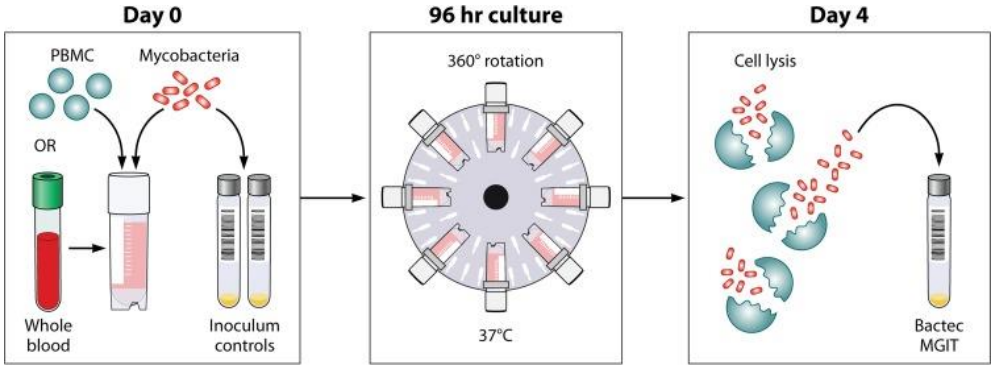
Verall, J Infect Dis, 2019, doi: 10.1093/infdis/jiz147

Functional assessment of immune response to Mtb

Unbiased approaches: Analyse immune system as a whole rather than isolated components

- Whole blood transcriptome studies
- Functional assays to assess the capacity to eliminate mycobacteria >

Mycobacterial Growth Inhibition Assay (MGIA)



Hoft et al, J Infect Dis. 2002;186(10):1448-57
Tanner et al, Vaccine. 2016;34(39):4656-4665
Brennan et al, Clin Vaccine Immunol. 2017, 24(9)

Lack of control during latency

BCG vaccination

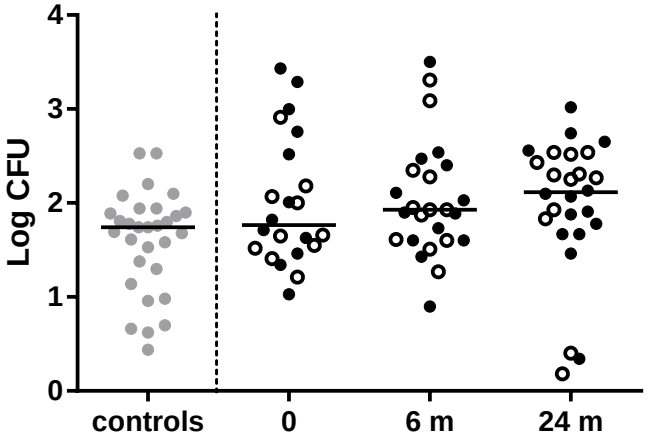
Mtb exposure

infection

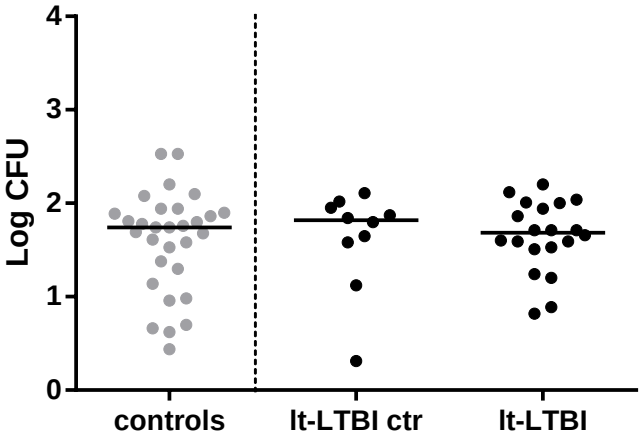
LTBI

active TB disease

LTBI cohort, The Netherlands,
2 year follow up



LTBI cohort, Norway,
> 30 years of LTBI



No control observed in (long-term) LTBI, despite presence of strong adaptive immune responses and control of the infection *in vivo*

Joosten, J Clin Invest, 2018, 128(5): 1837-1851

Recently exposed individuals control BCG outgrowth

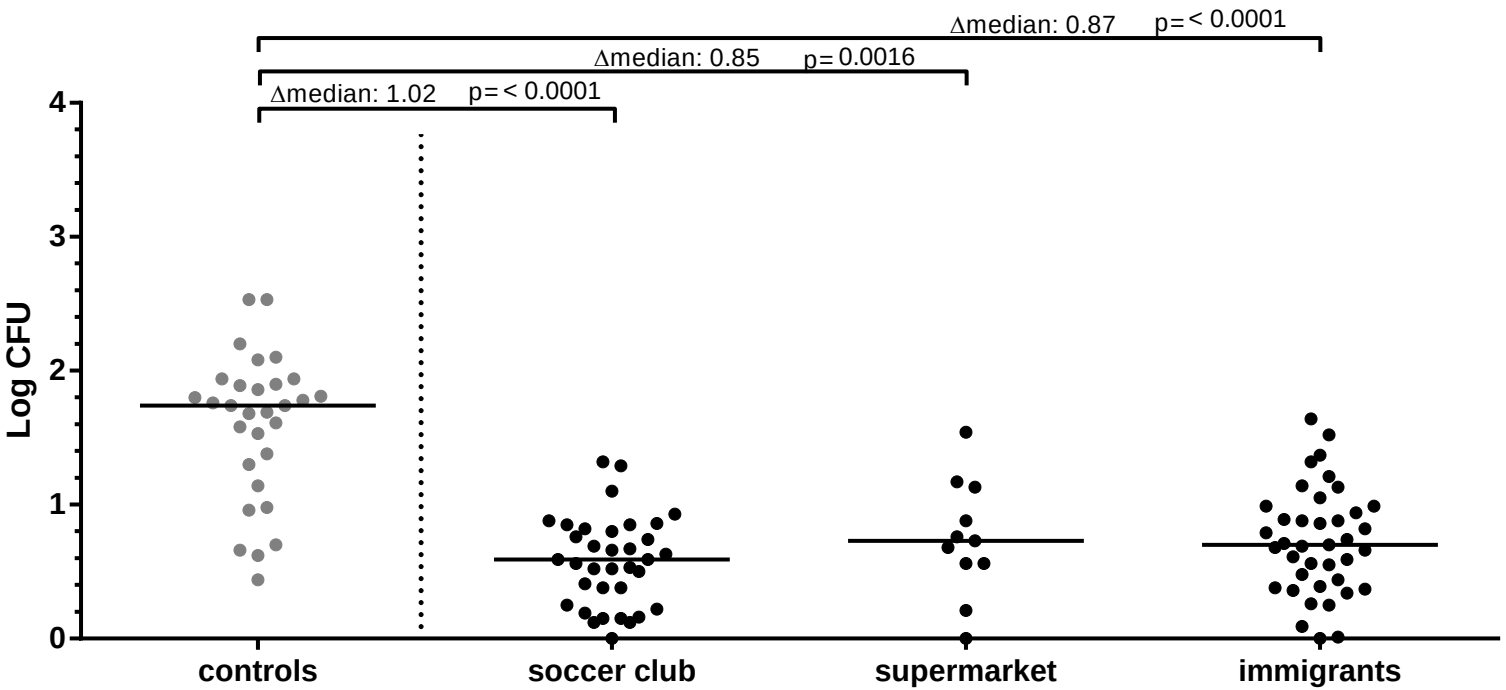
BCG vaccination

Mtb exposure

infection

LTBI

active TB disease



born in TB endemic country and recent exposure to active TB case

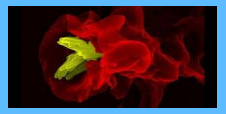
Strong control in most individuals after recent exposure to patient with active TB
Not all individuals are 'infected' (TST/ QFN)

Joosten, J Clin Invest, 2018, 128(5): 1837-1851

Strongest BCG control upon recent exposure

BCG vaccination

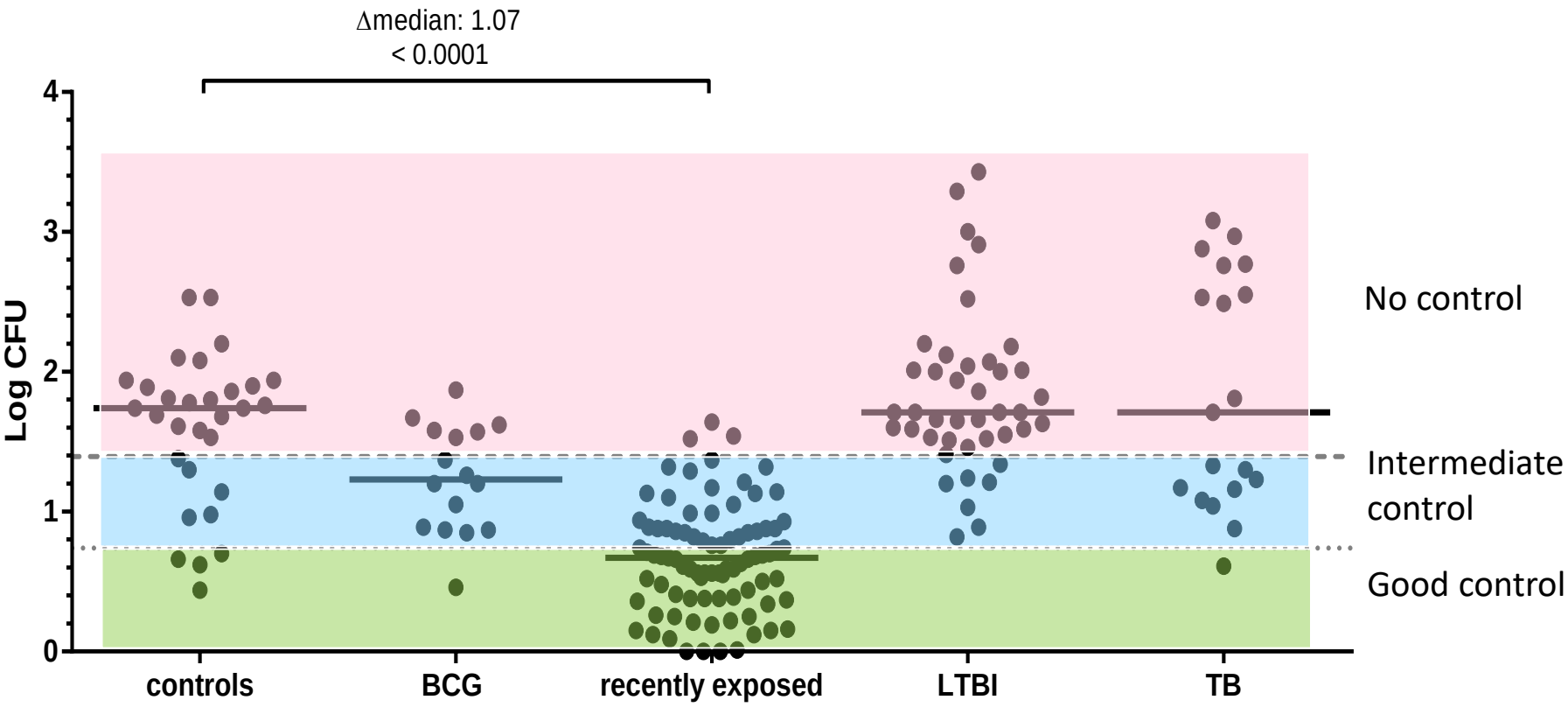
Mtb exposure



infection

LTBI

active TB disease



Highest control of BCG outgrowth observed in recently exposed individuals

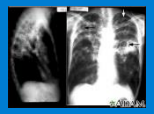
Adaptive responses and control of mycobacterial growth

BCG vaccination

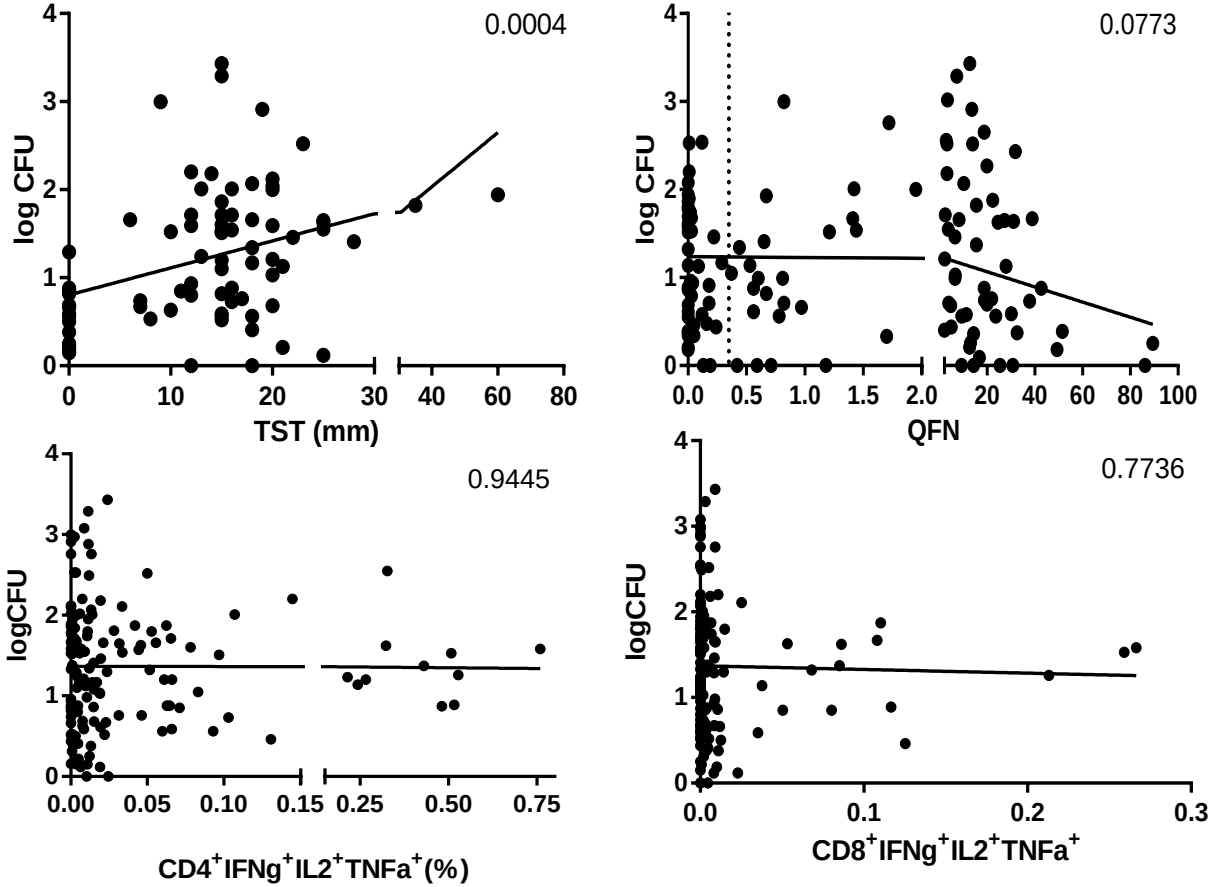
Mtb exposure

infection

LTBI



active TB disease



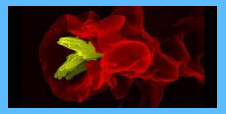
Antigen specific responses do not correlate with control of BCG outgrowth

Joosten, J Clin Invest, 2018, 128(5): 1837-1851

Monocytes correlate with control upon recent exposure

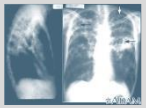
BCG vaccination

Mtb exposure

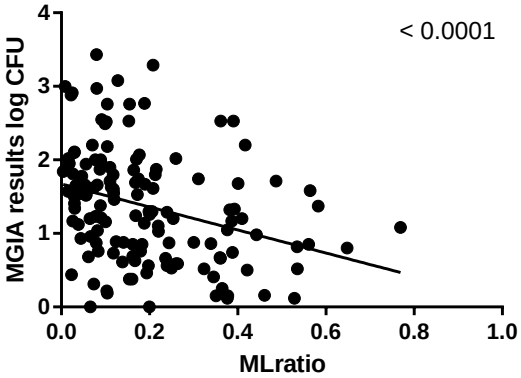


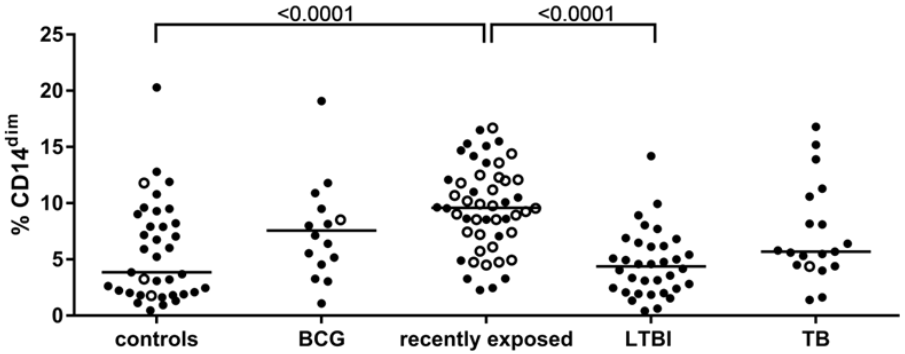
infection

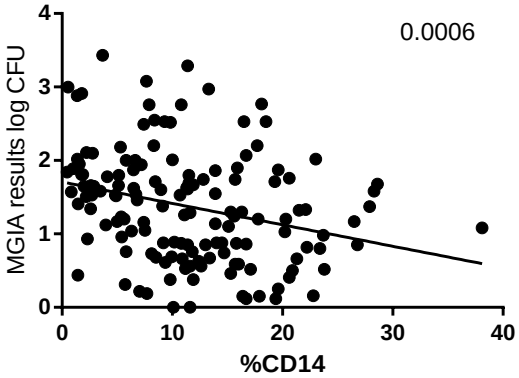
LTBI

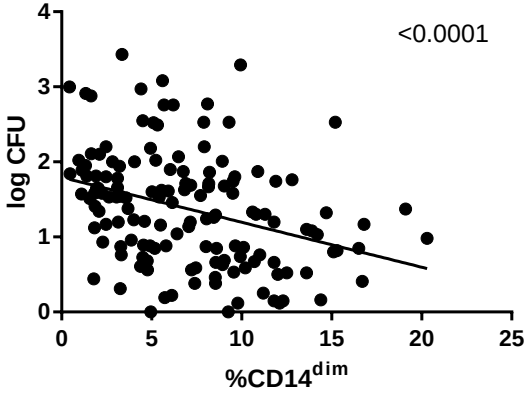


active TB disease









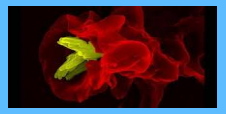
BCG growth control is associated with a non-classical monocyte population

Joosten, J Clin Invest, 2018, 128(5): 1837-1851

Non classical monocytes derived CXCL10 mediates growth control

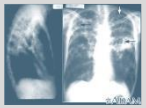
BCG vaccination

Mtb exposure

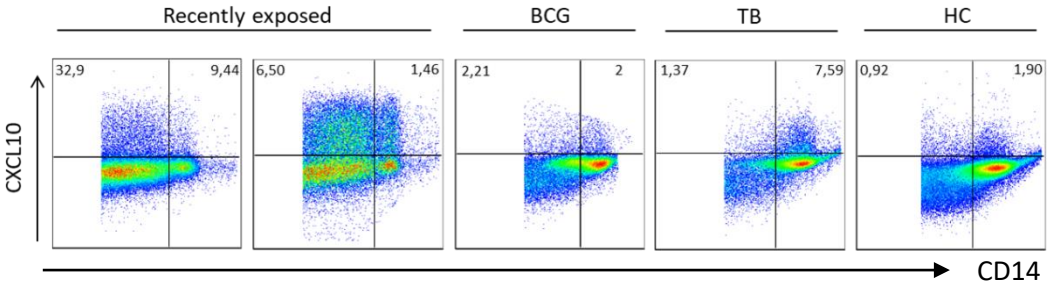


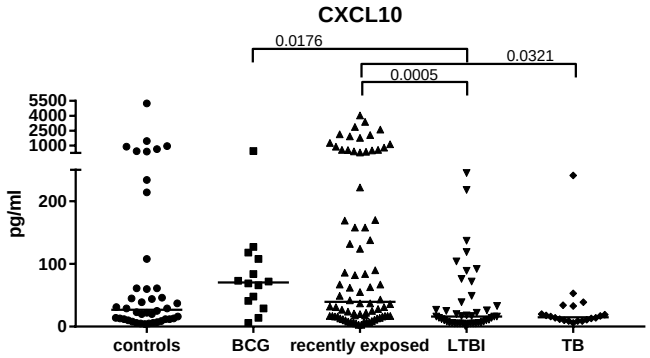
infection

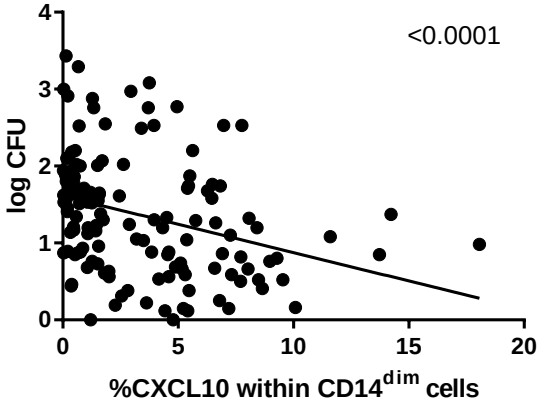
LTBI

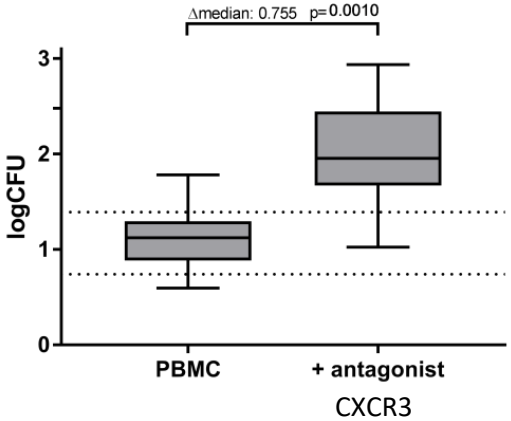


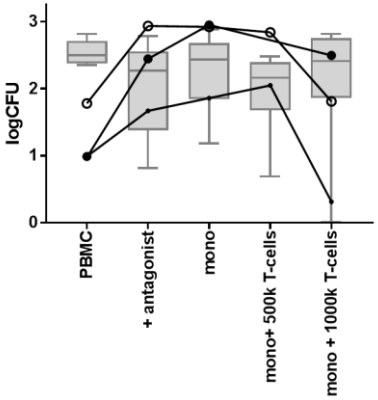
active TB disease











CXCL10 is produced by non-classical monocytes mostly in exposed individuals
CXCR3 receptor blockade reversed mycobacterial growth control
T-cells are required to mediated growth control

Joosten, J Clin Invest, 2018, 128(5): 1837-1851

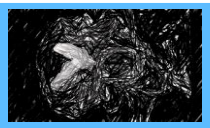
Immune responses activated by Mtb

BCG vaccination

Mtb exposure

??%

infection



Resistance/ clearance

~95%

~5%

LTBI

active TB disease

Borderline QFT responses may indicate Mtb infection

Trained innate immunity
Functional control of mycobacterial outgrowth

'Resistors' to QFT conversion can have T-cells and Abs reactive with Mtb > but lack IFN-γ producing T-cells

Early Mtb clearance does not always result in activation of T-cell immunity

Acknowledgements

LUMC, Dept of Infectious Diseases

Jonathan Uzorka
Krista E van Meijgaarden
Anne MHF Drittij
Louis Wilson
Sandra M Arend
Corine Prins
Kees LMC Franken
Tom HM Ottenhoff
Simone A Joosten

Norwegian Institute of Public Health

Fredrik Oftung
Gro Ellen Korsvold

KNCV Dutch Tuberculosis Foundation

Sandra Kik

Radboud UMC, Nijmegen

Reinout van Crevel
Rob Arts
Mihai Netea

EURIPRED

European Commission

TBVAC 2020

TBVI