KNCV TUBERCULOSIS FOUNDATION
To eliminate TB

aighd

The evolving concept of LTBI diagnosis

tests for incipient TB and tests for persistent infection

Frank Cobelens
f.cobelens@aighd.org

KNCV Tuberculosis Foundation
The Hague, Netherlands

Amsterdam Institute for Global Health and Development
Amsterdam, Netherlands

Liverpool, 26 October 2016

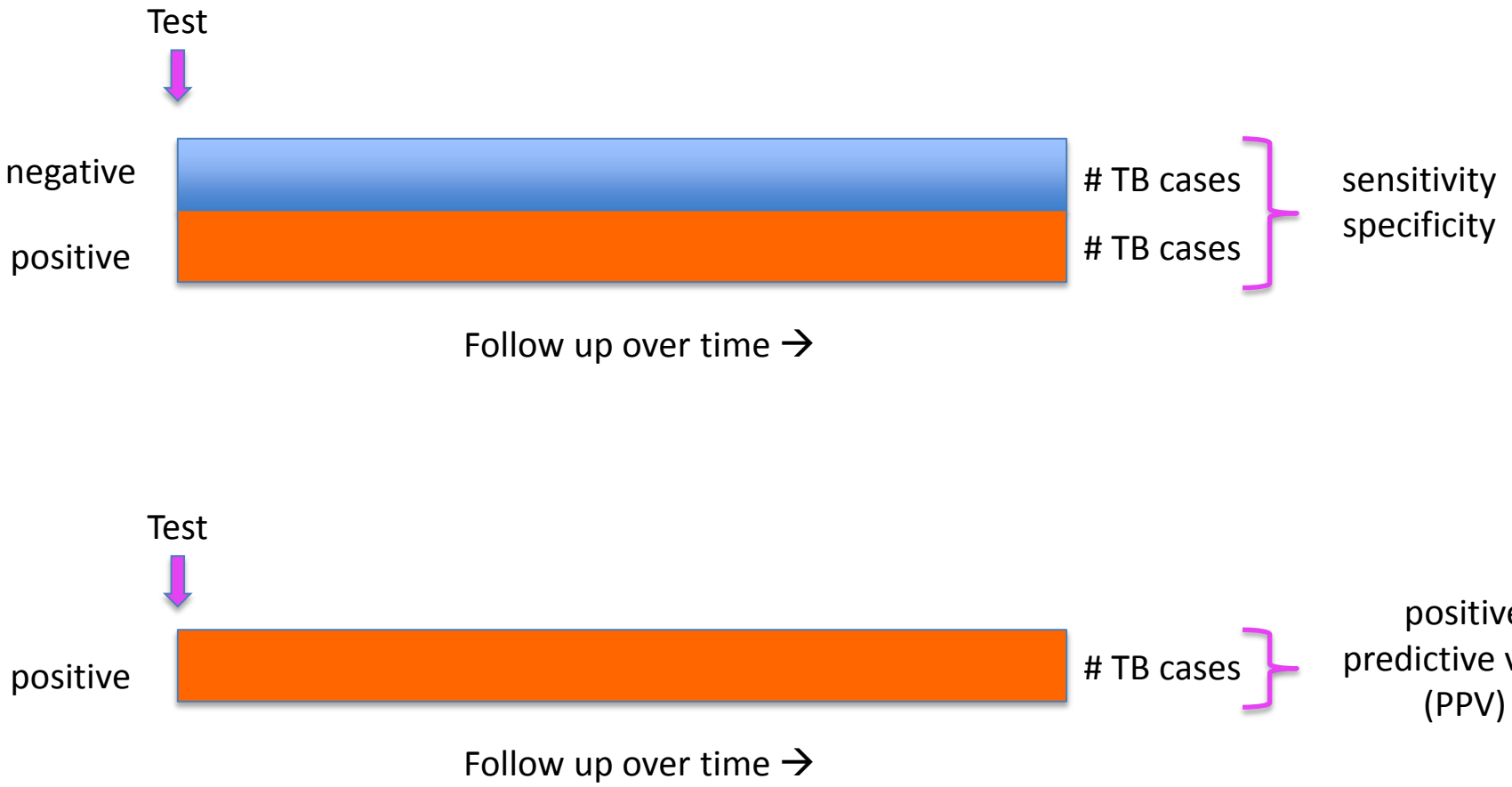
Conflict of interest disclosure

- I have the following, real or perceived direct or indirect conflicts of interest that relate to this presentation:

Affiliation / financial interest	Nature of conflict / commercial company name
Tobacco-industry and tobacco corporate affiliate related conflict of interest	
Grants/research support (to myself, my institution or department):	Qiagen is donating Quantiferon Plus testkits for the WHIP3TB trial on which i am a co-investigator
Honoraria or consultation fees:	
Participation in a company sponsored bureau:	
Stock shareholder:	
Spouse/partner:	
Other support or other potential conflict of interest:	

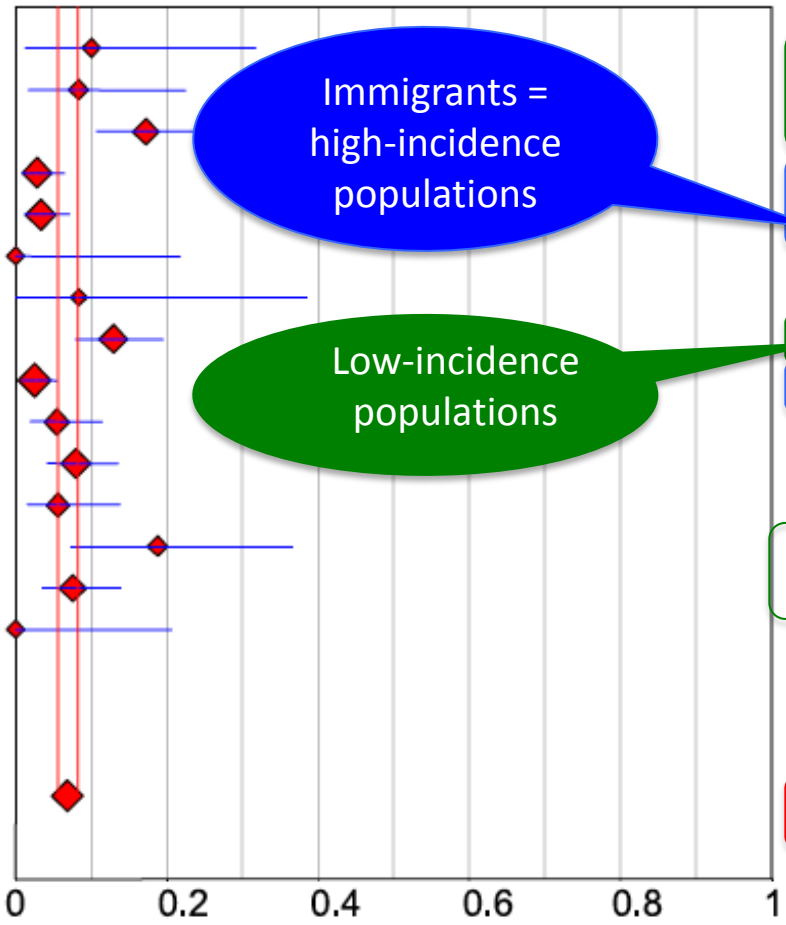
This event is accredited for CME credits by EBAP and speakers are required to disclose their potential conflict of interest going back 3 years prior to this presentation. The intent of this disclosure is not to prevent a speaker with a conflict of interest (any significant financial relationship a speaker has with manufacturers or providers of any commercial products or services relevant to the talk) from making a presentation, but rather to provide listeners with information on which they can make their own judgment. It remains for audience members to determine whether the speaker's interests or relationships may influence the presentation. Drug or device advertisement is strictly forbidden.

What really matters: prediction of TB disease



IGRA as predictor of TB disease

Meta-analysis of prospective cohort studies
High-risk groups only

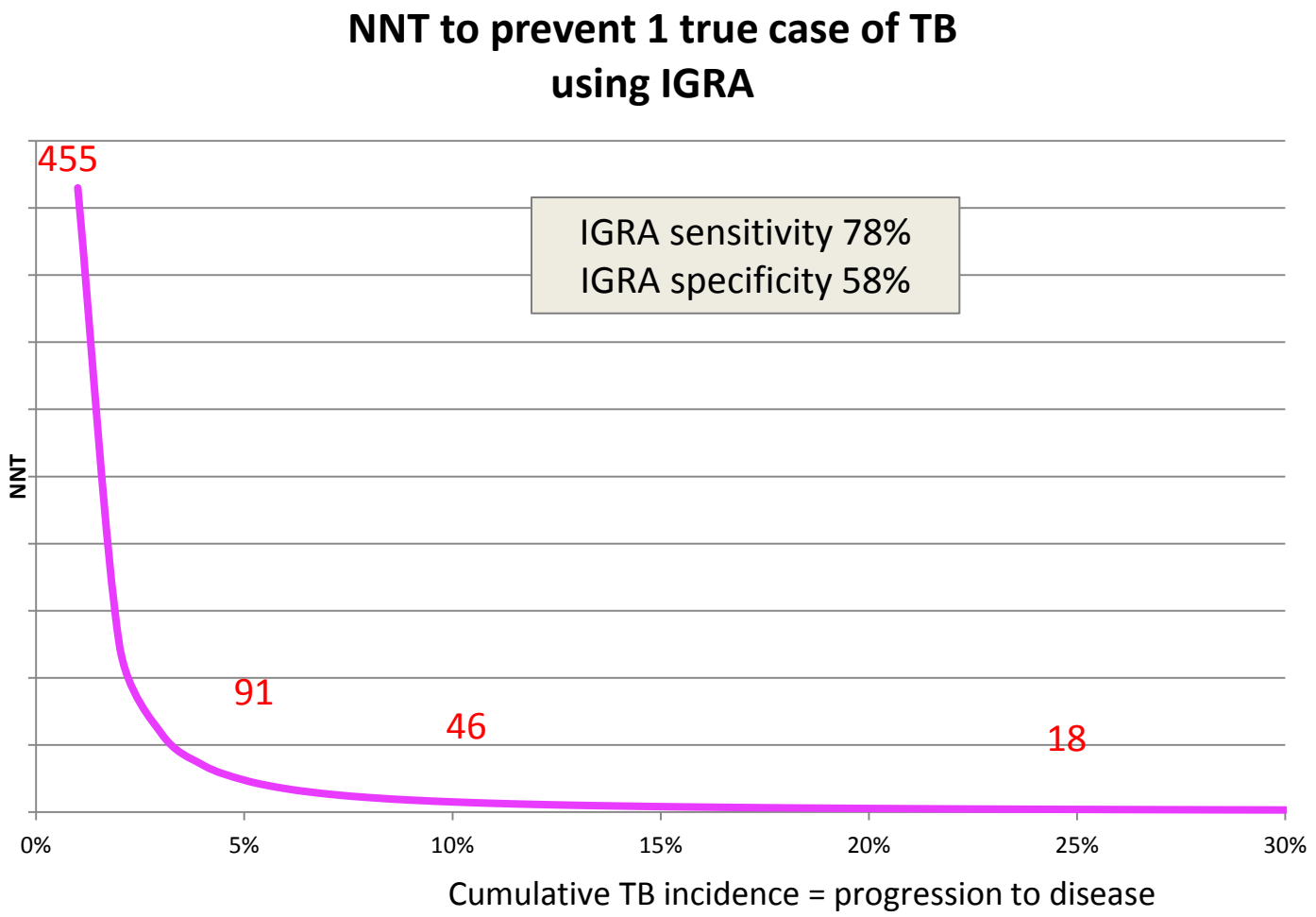


	PPV	(95% CI)	n/N
Clark 2007[36]	0.10	(0.01 – 0.32)	2/20
Aichelburg 2009[24]	0.08	(0.02 – 0.22)	3/36
Haldar 2009[25]	0.17	(0.11 – 0.26)	19/110
Kik 2009[14]	0.03	(0.01 – 0.06)	5/178
Kik 2009[14]	0.03	(0.01 – 0.07)	6/181
Lee 2009[13]	0.00	(0.00 – 0.22)	0/15
Lee 2009[13]	0.08	(0.00 – 0.38)	1/12
Diel 2011[27]	0.13	(0.08 – 0.19)	19/147
Harstad 2010[28]	0.03	(0.01 – 0.05)	6/238
Jonnalaggada 2010[37]	0.05	(0.02 – 0.11)	6/110
Leung 2010[38]	0.08	(0.04 – 0.13)	12/151
Kim 2011[39]	0.06	(0.02 – 0.14)	4/71
Song 2011[34]	0.19	(0.07 – 0.36)	6/32
Yoshiyama 2011[22]	0.08	(0.04 – 0.14)	9/119
Zhang 2011[40]	0.00	(0.00 – 0.21)	0/16

Pooled PPV for progression = 0.068 (0.056 to 0.083)
Chi-square = 50.30; df = 14 (p = 0.0000)
Inconsistency (I-square) = 72.2 %

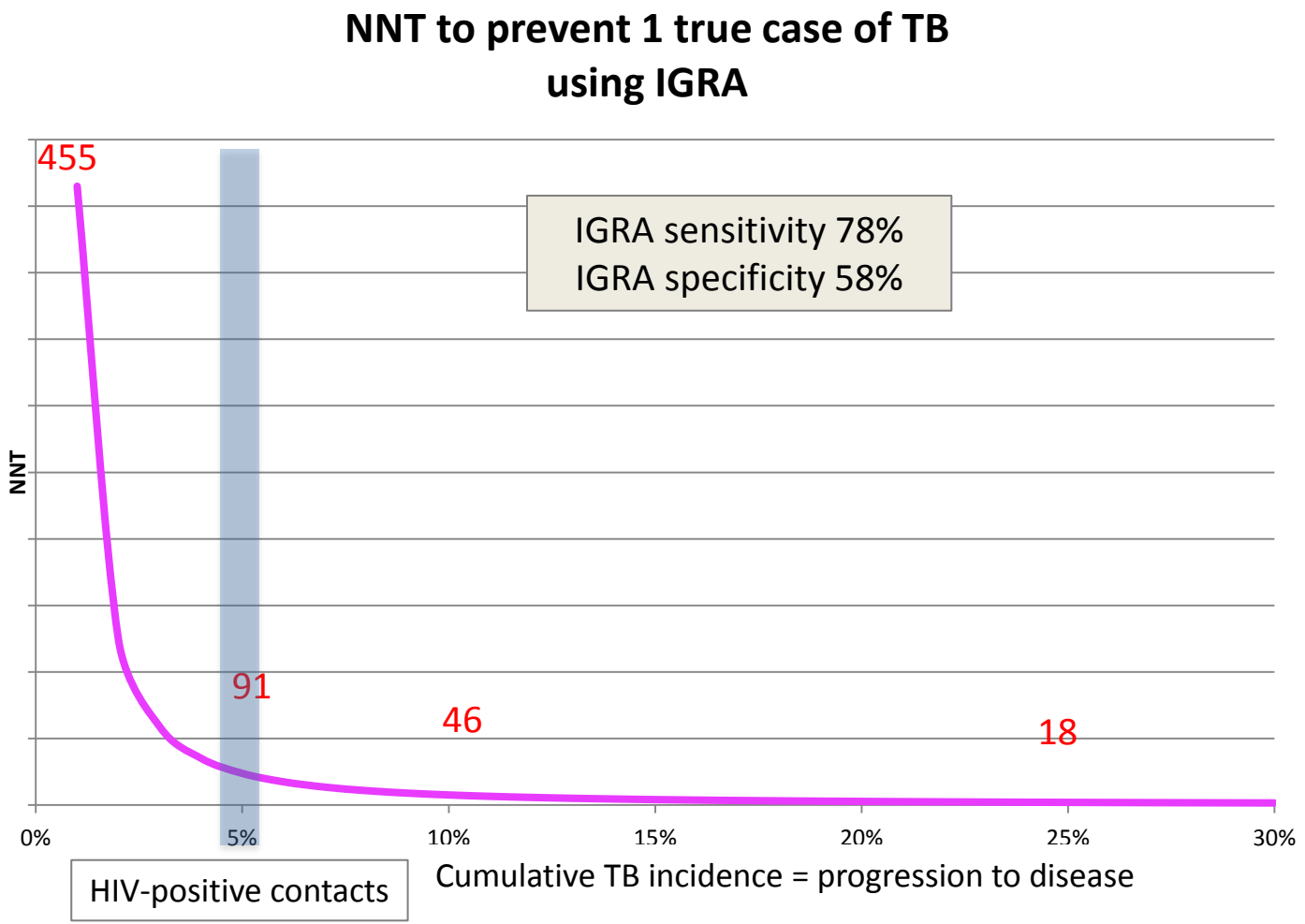
Diel et al. Chest 2012

Number needed to treat



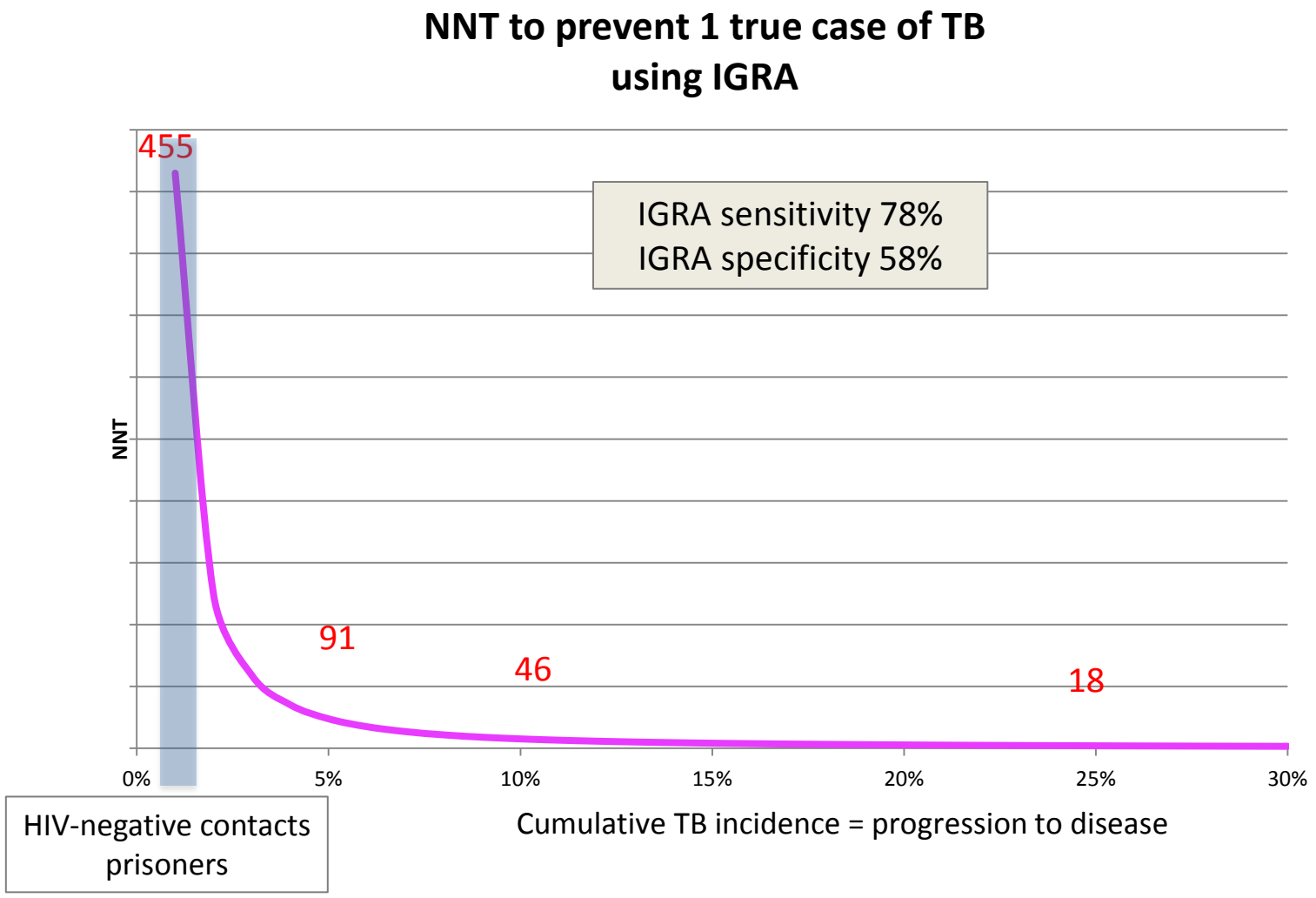
Kik et al., in prep

Number needed to treat



Rangaka, Kik et al, in prep

Number needed to treat



Kik et al., in prep

The need

So we need a test that has better positive (and negative) predictive value for TB disease occurring in the future

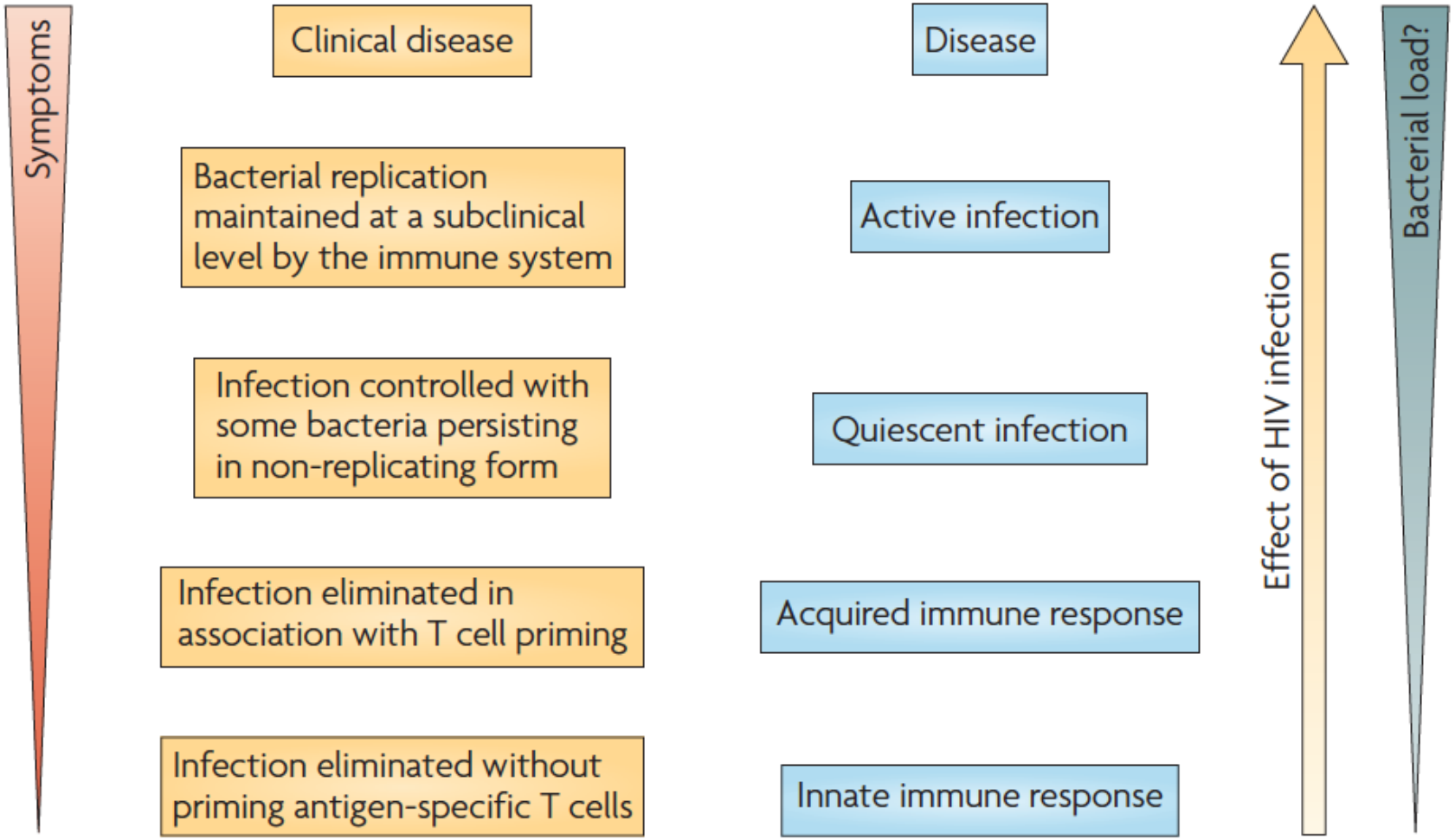
~~*LTBI test*~~

~~*TB risk stratification test*~~

"TB prediction test"

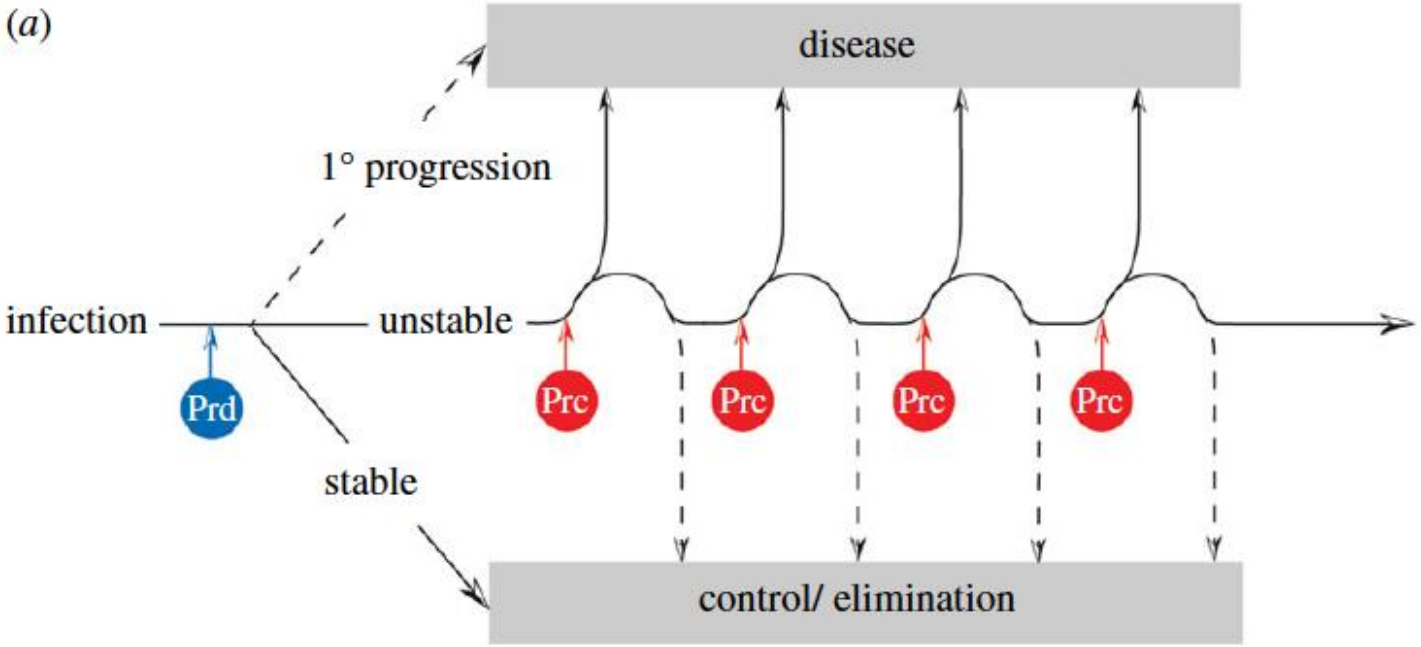
Can high positive predictive values be attained?

LTBI: changing paradigm



Barry et al. Nat Rev Microbiol 2009

LTBI: changing paradigm

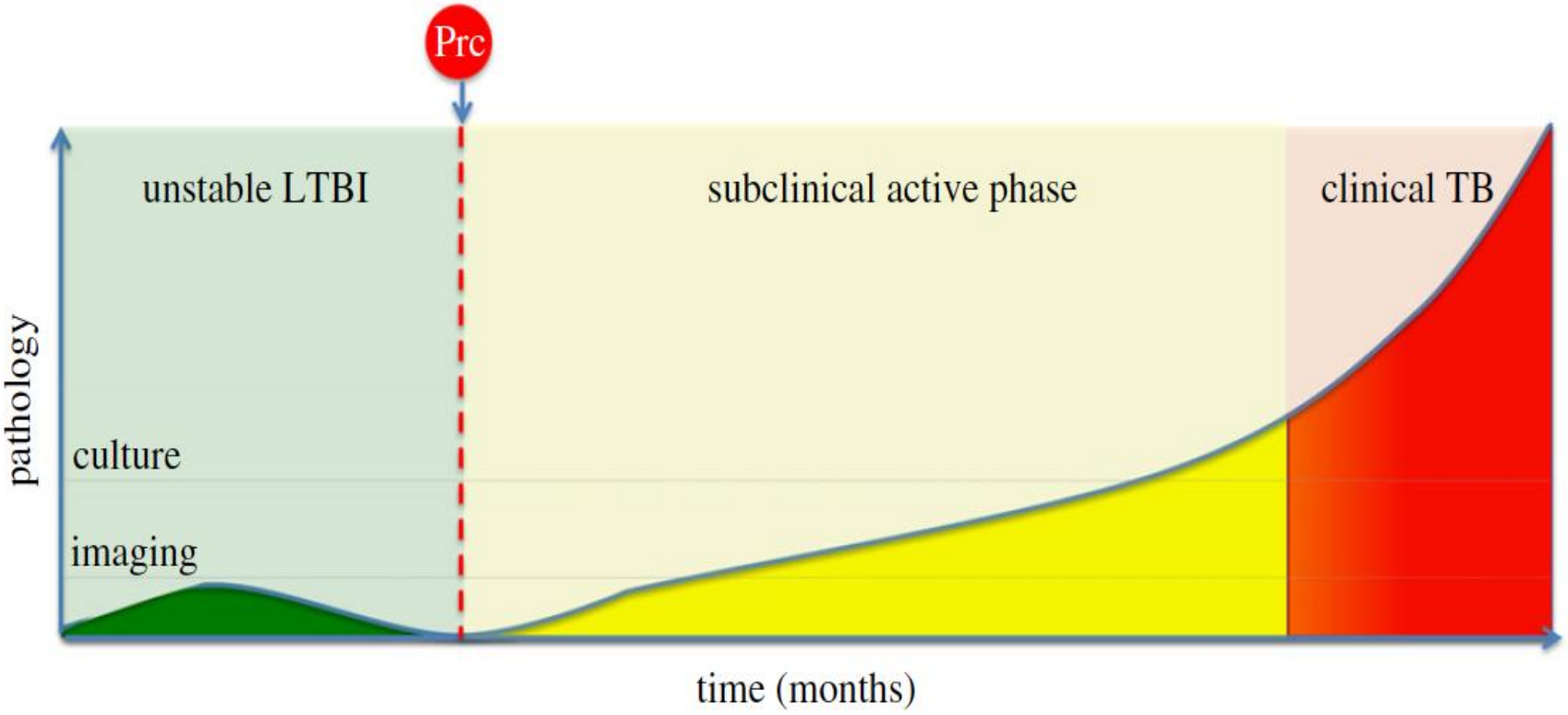


possible predisposing factors
HIV
malnutrition
diabetes
alcoholism
pro/anti inflammatory imbalance

possible precipitating factors
HIV
anti-TNF therapy
malnutrition
Vit D deficiency
viral infection

Esmail et al. Phil Trans Roy Soc 2015

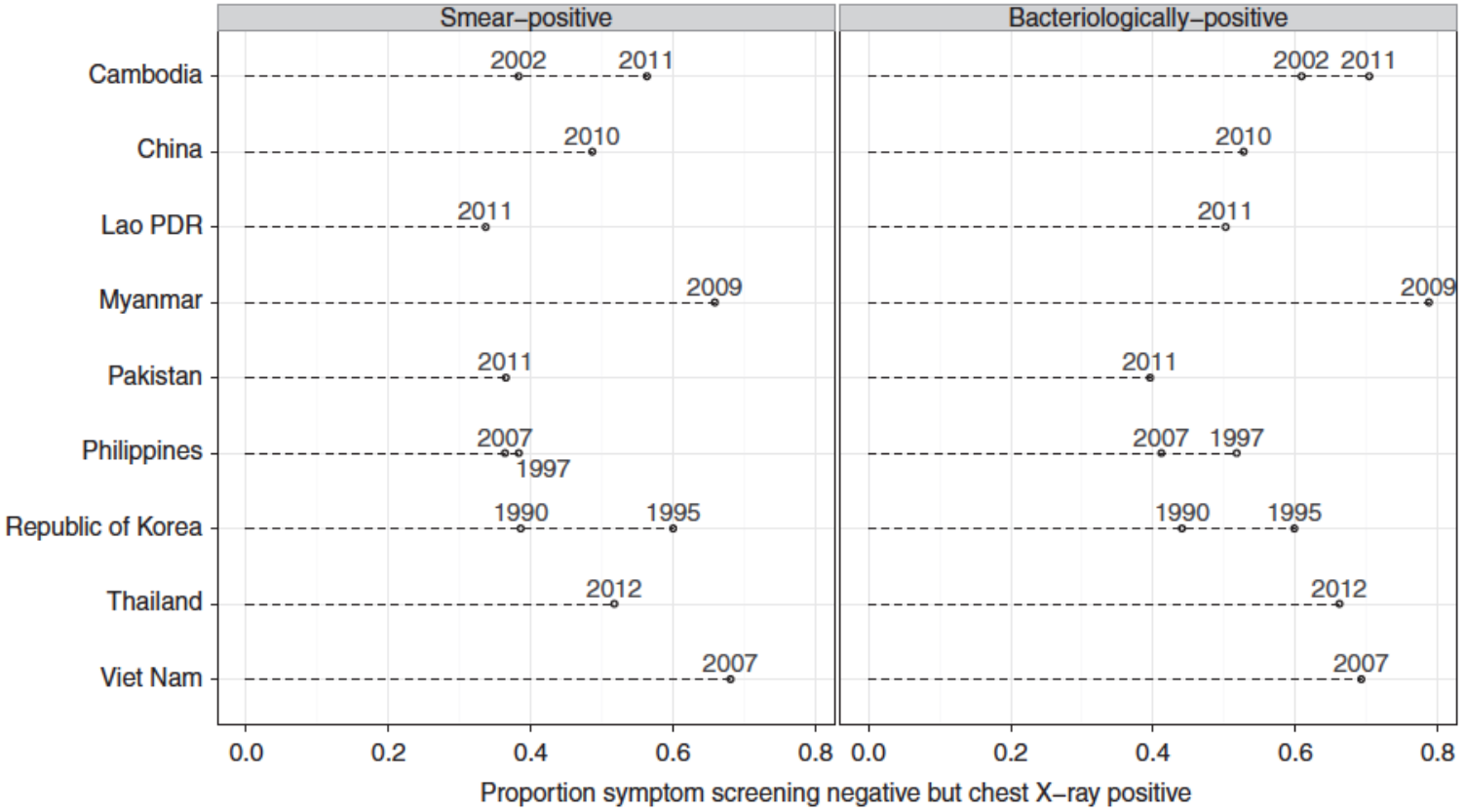
LTBI: changing paradigm



Esmail et al. Phil Trans Roy Soc 2015

Subclinical active phase

Overview of national TB prevalence surveys conducted in Asia, 1990-2012
Proportion of all detected prevalent TB cases that did not report cough

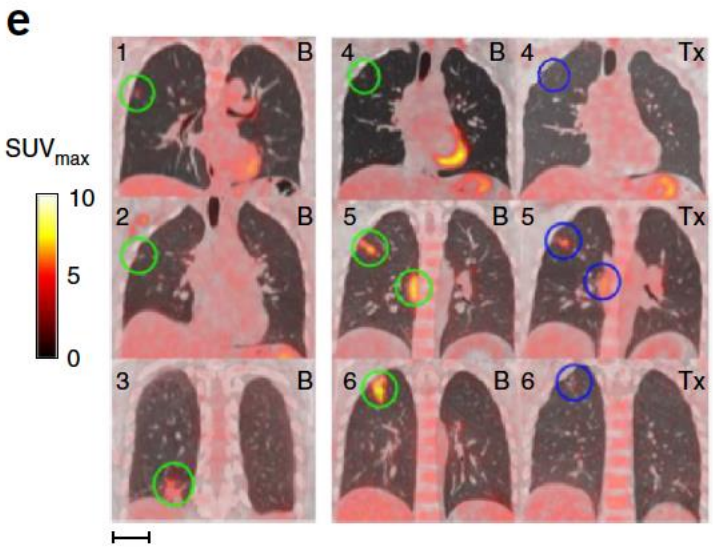


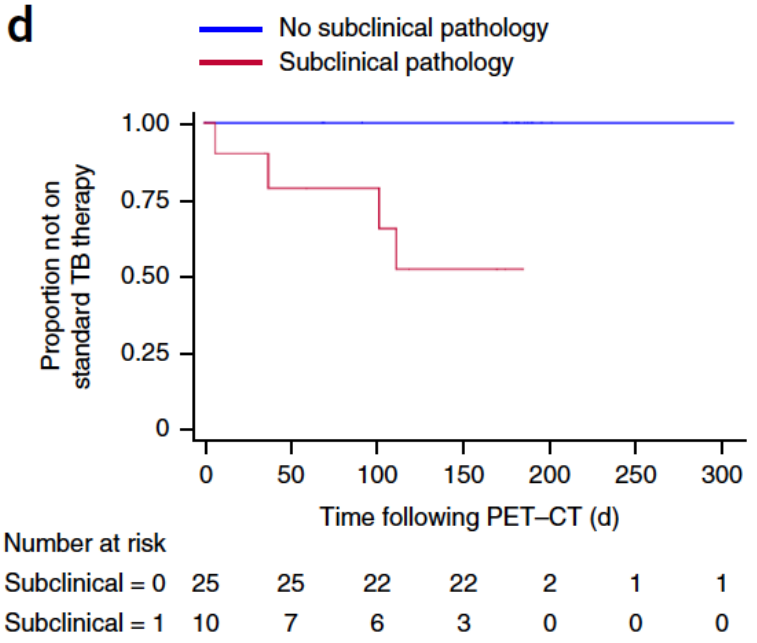
Onozaki et al. TMIH 2015

Subclinical active phase

35 patients with LTBI (QFN-GIT+, culture -), HIV infected, ART naive (CD4>350)
PET-scans (2-deoxy-2-[^{18}F]fluoro-d-glucose positron emission and computed tomography)
6 months follow-up

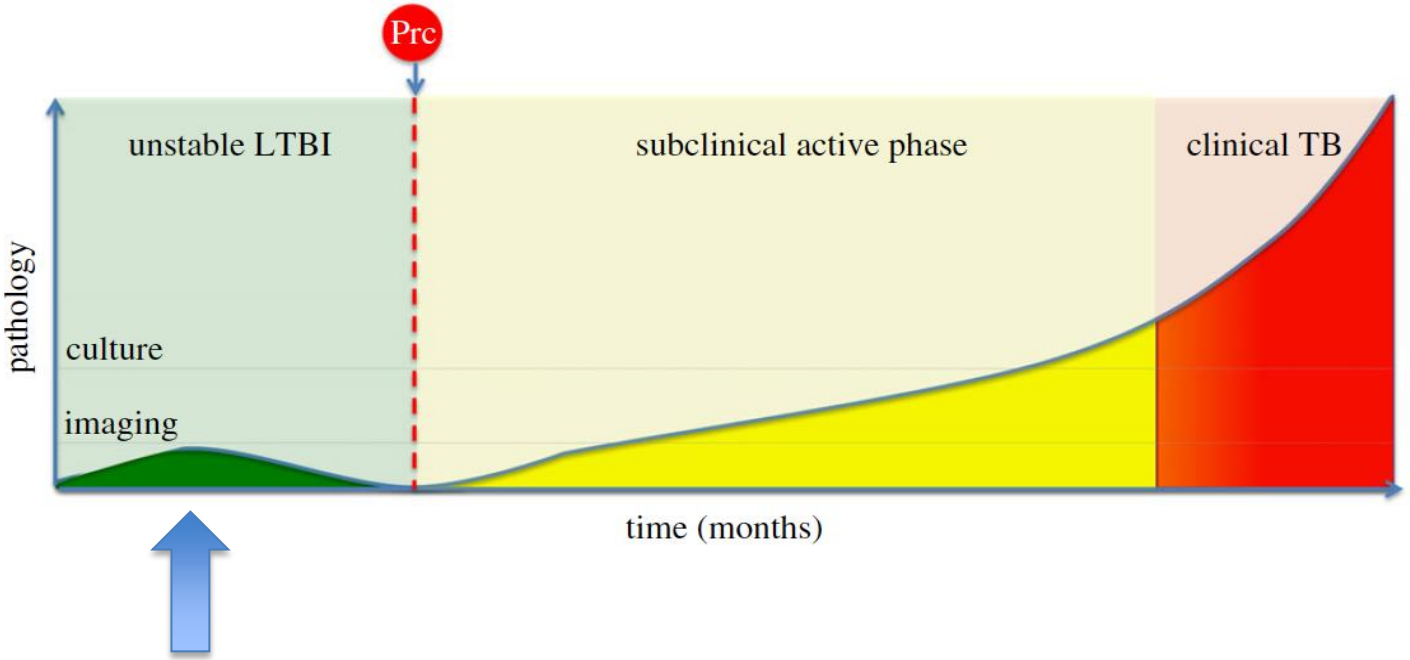
→ 10 patients with subclinical disease more likely to progress to active disease





Esmail et al. Nature Med 2016

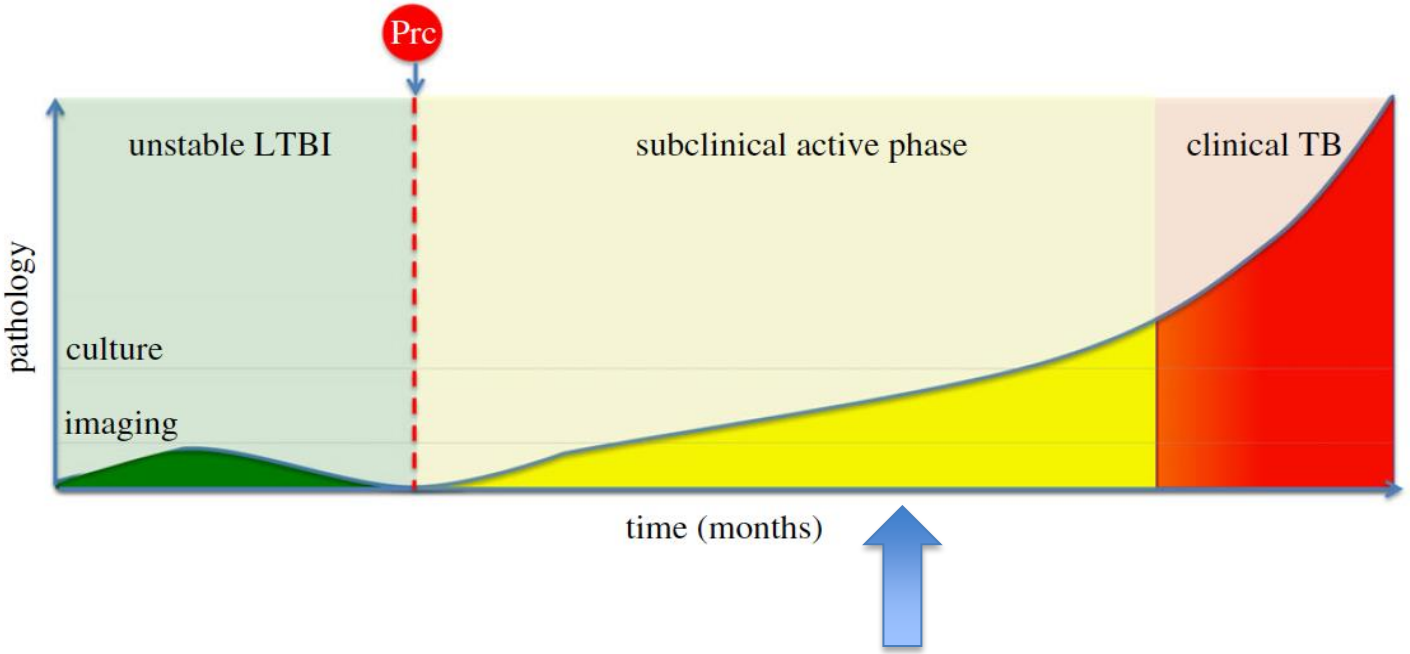
LTBI: changing paradigm



In this stage we cannot predict if and when a precipitating event will occur
→ we cannot predict who will become diseased

→ **PPVs will be relatively low**

LTBI: changing paradigm

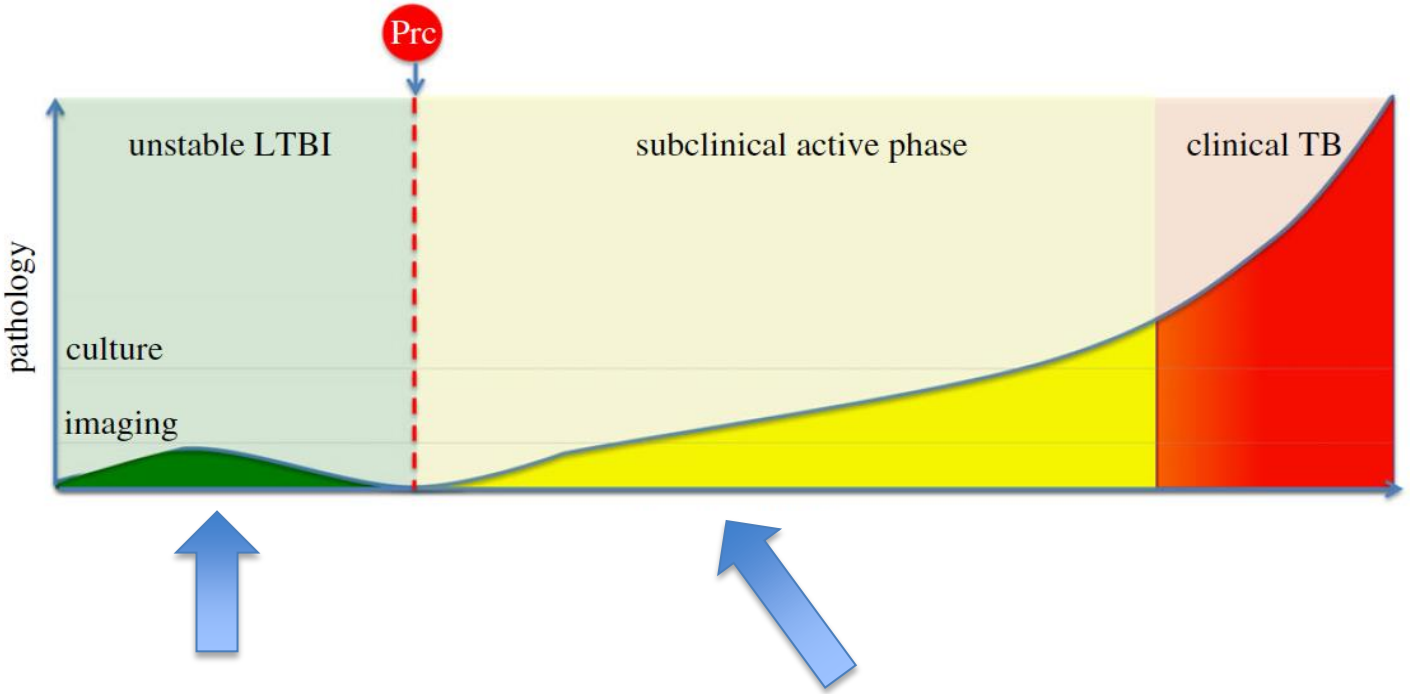


In this stage there is active bacterial multiplication with high probability of leading to TB disease

→ **PPVs can be relatively high**

What does the test measure?

Conceptually, the test either…



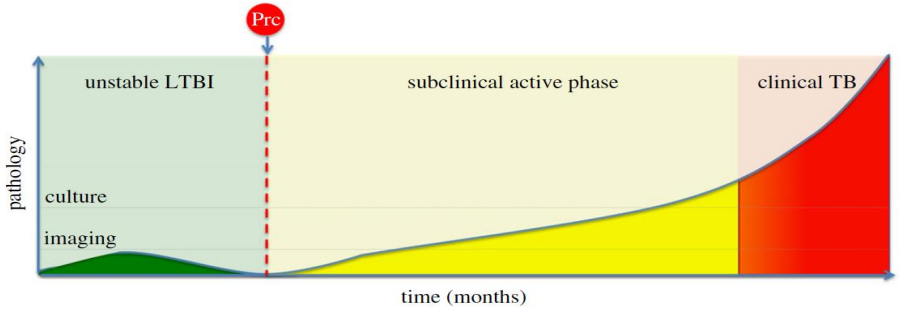
… predicts that disease cannot happen *because there is no persistent infection*

"persistent infection test"

... or predicts that disease will occur *because it has already started….*

"incipient TB test"

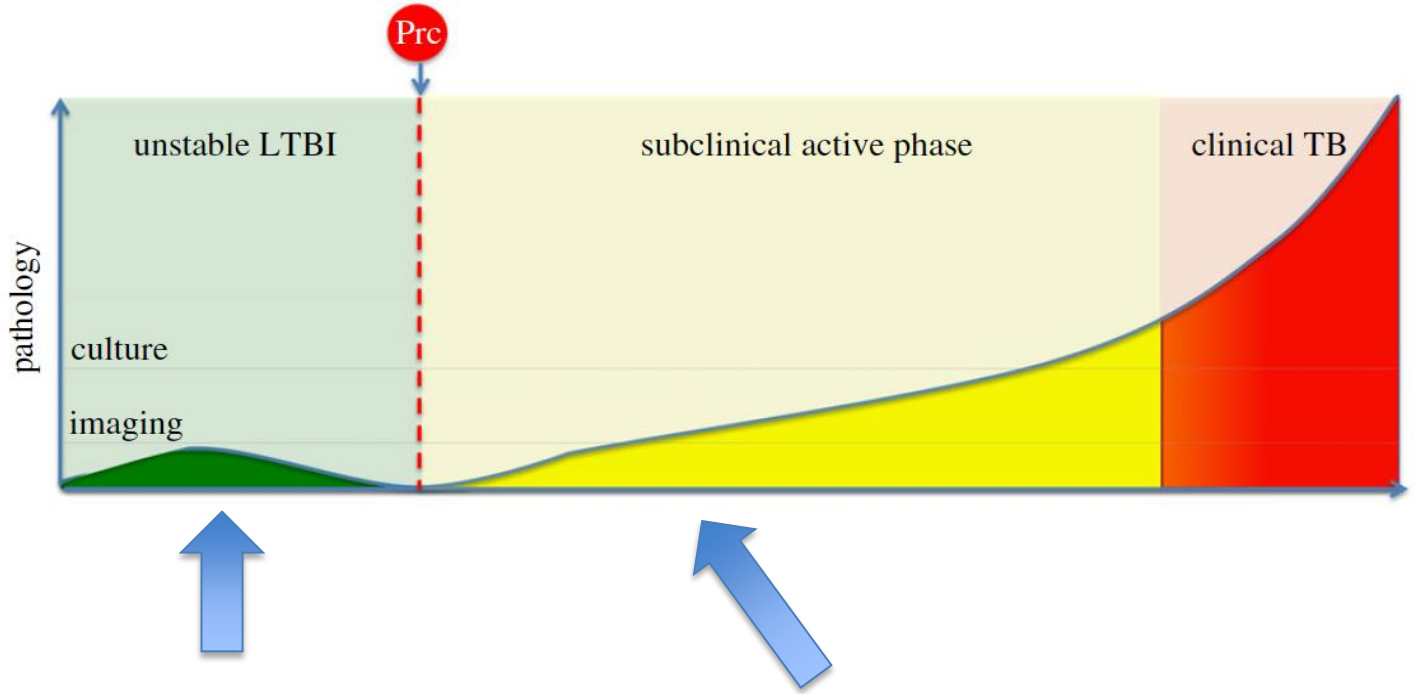
So what…?



This dichotomy matters because it has implications for:

- Test development
- Test performance
- Test utilization
- Test design

Implications for test development



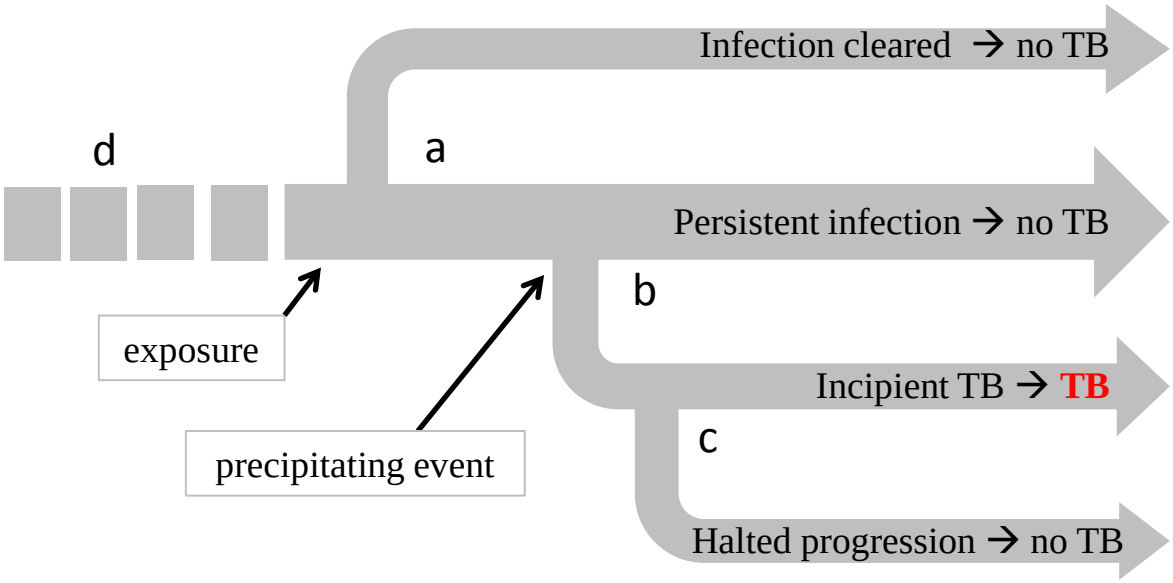
“persistent infection test”

CD4 response
mRNA?

“incipient TB test”

bacterial multiplication?
mRNA?
inflammatory response?
CD8 response?

Implications for test performance

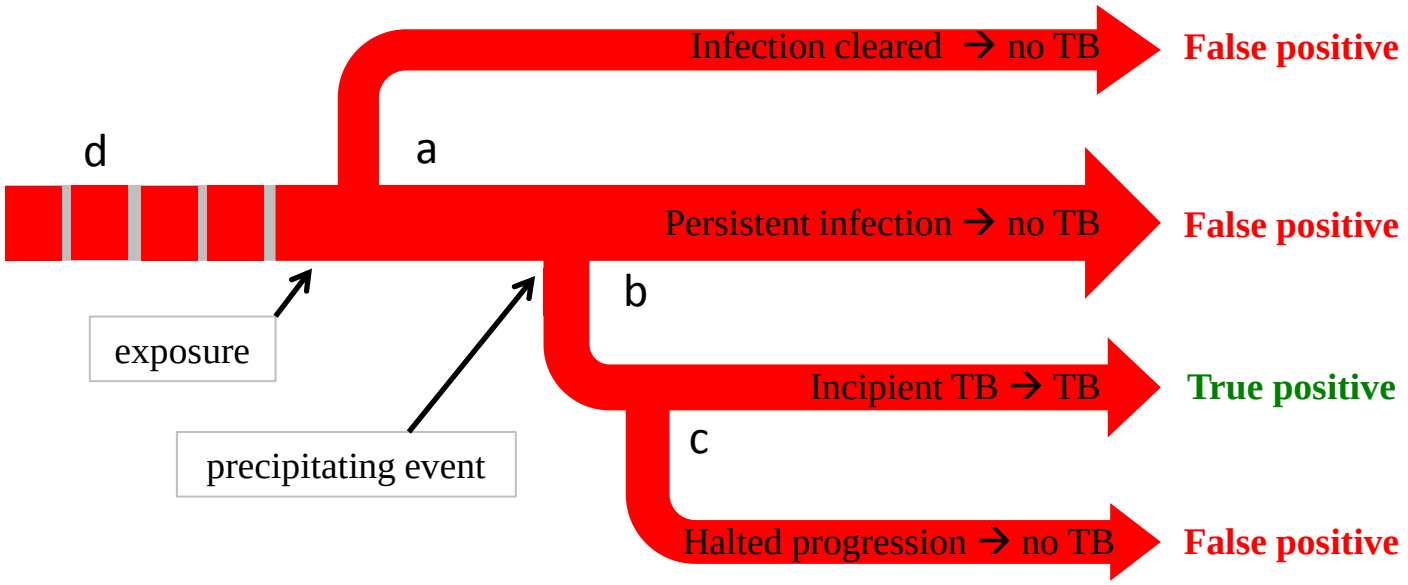


a probability that infection is cleared spontaneously
b probability that infection leads to incipient TB
c probability that incipient TB leads to TB disease
d probability that infection existed before the (recent) exposure

PPV = true positives out of all positives

Cobelens et al. Lancet Resp Med, accepted

Performance for anamnestic response (TST?)



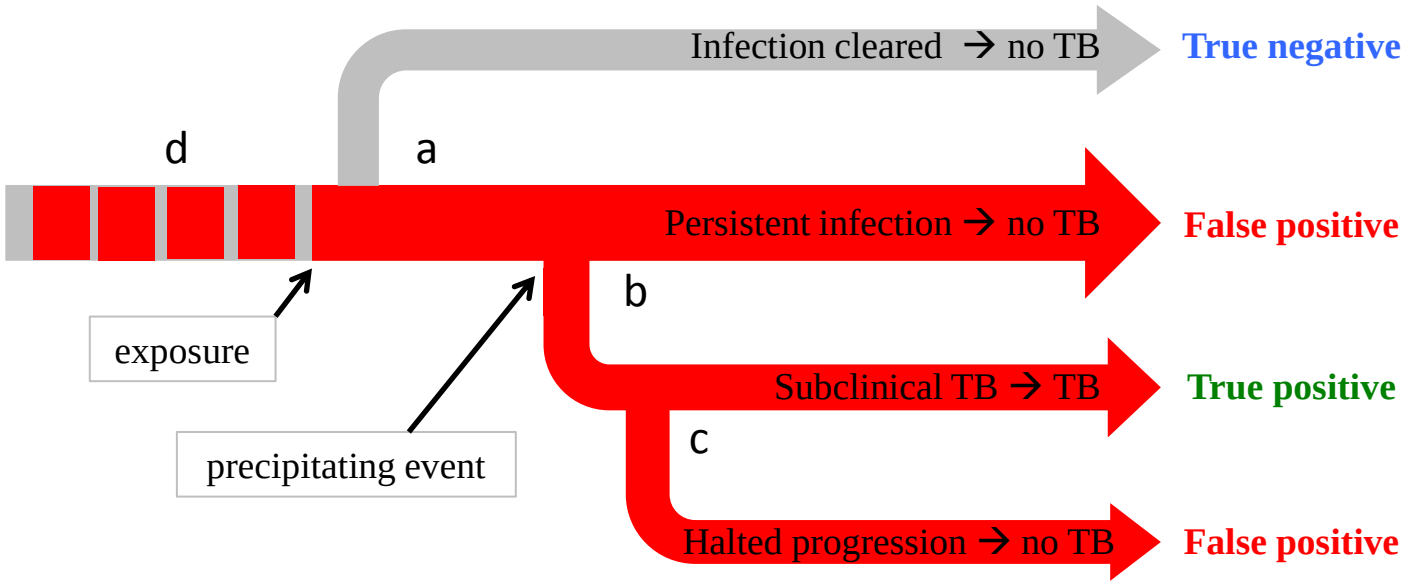
Test result negative

Test result positive

PPV for predicting TB disease is very low

Cobelens et al. Lancet Resp Med, accepted

Performance for a test for *persistent infection*

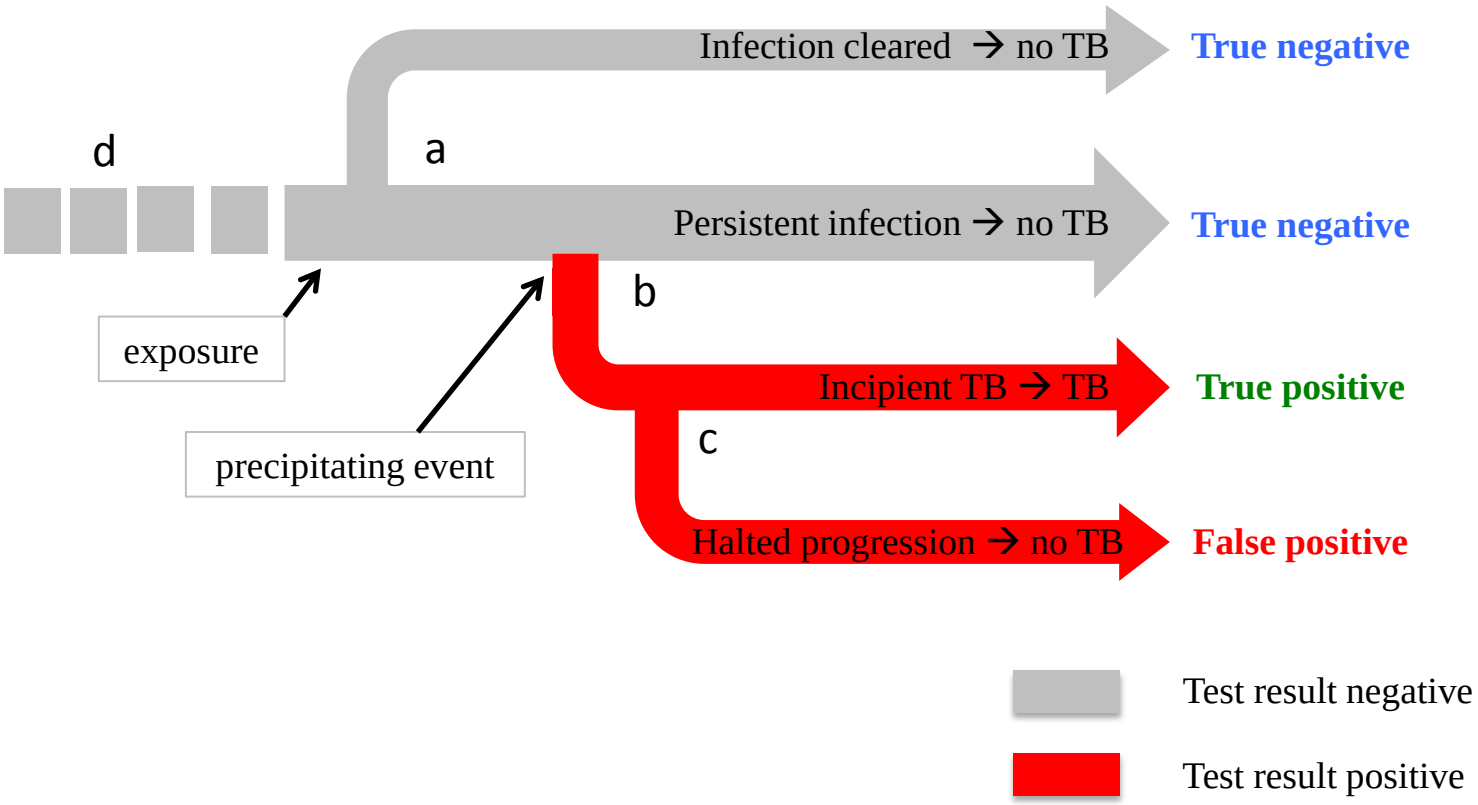


PPV depends on b and c (risk of disease progression)
PPV depends on d (previous exposure)

→ **PPV is population-dependent and lower in high-transmission settings (IGRA!)**

Cobelens et al. Lancet Resp Med, accepted

Performance for a test for *incipient TB*

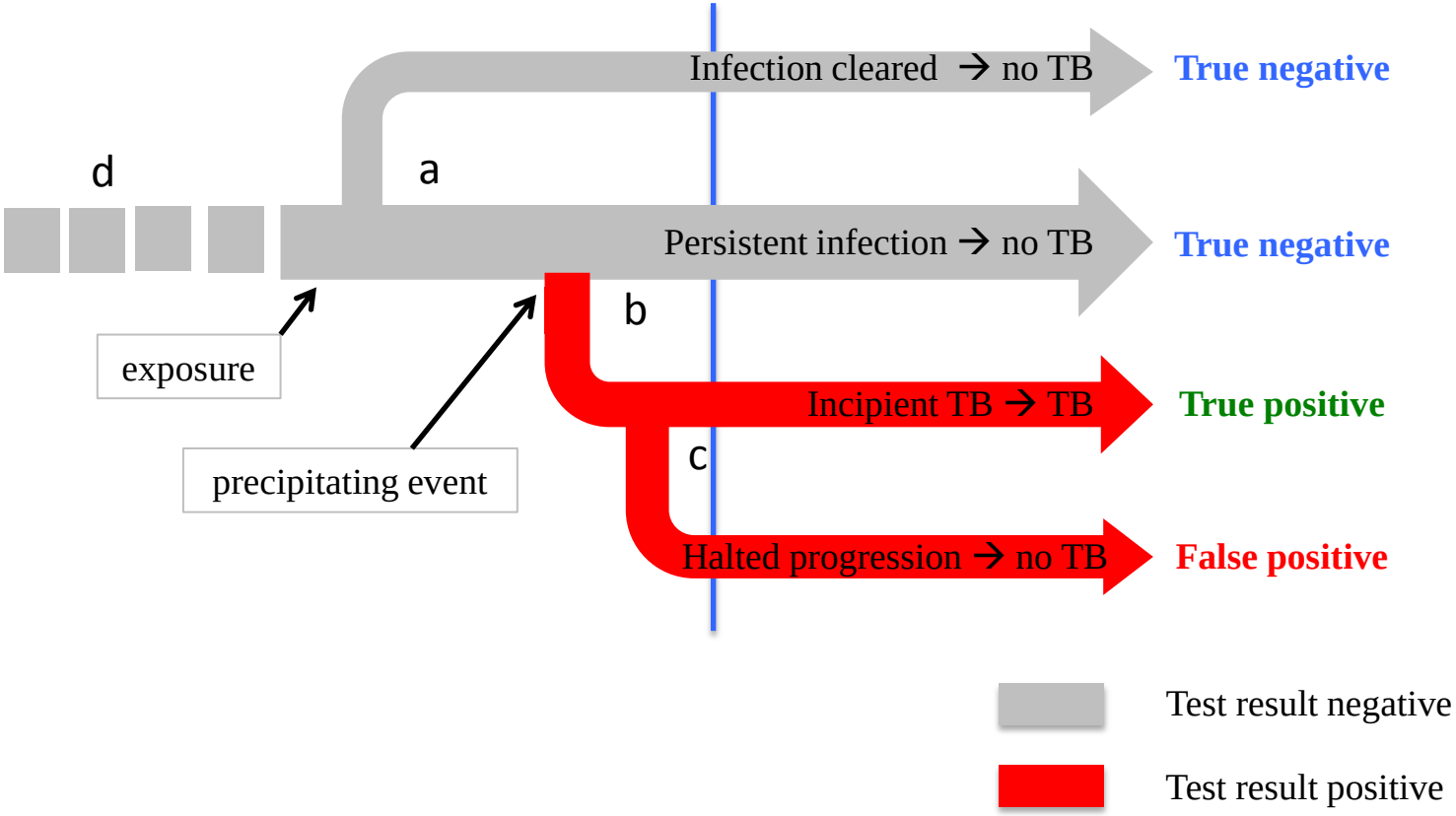


PPV depends on c (probability of spontaneous halting of disease progression)

→ **PPV is largely population independent …**

Cobelens et al. Lancet Resp Med, accepted

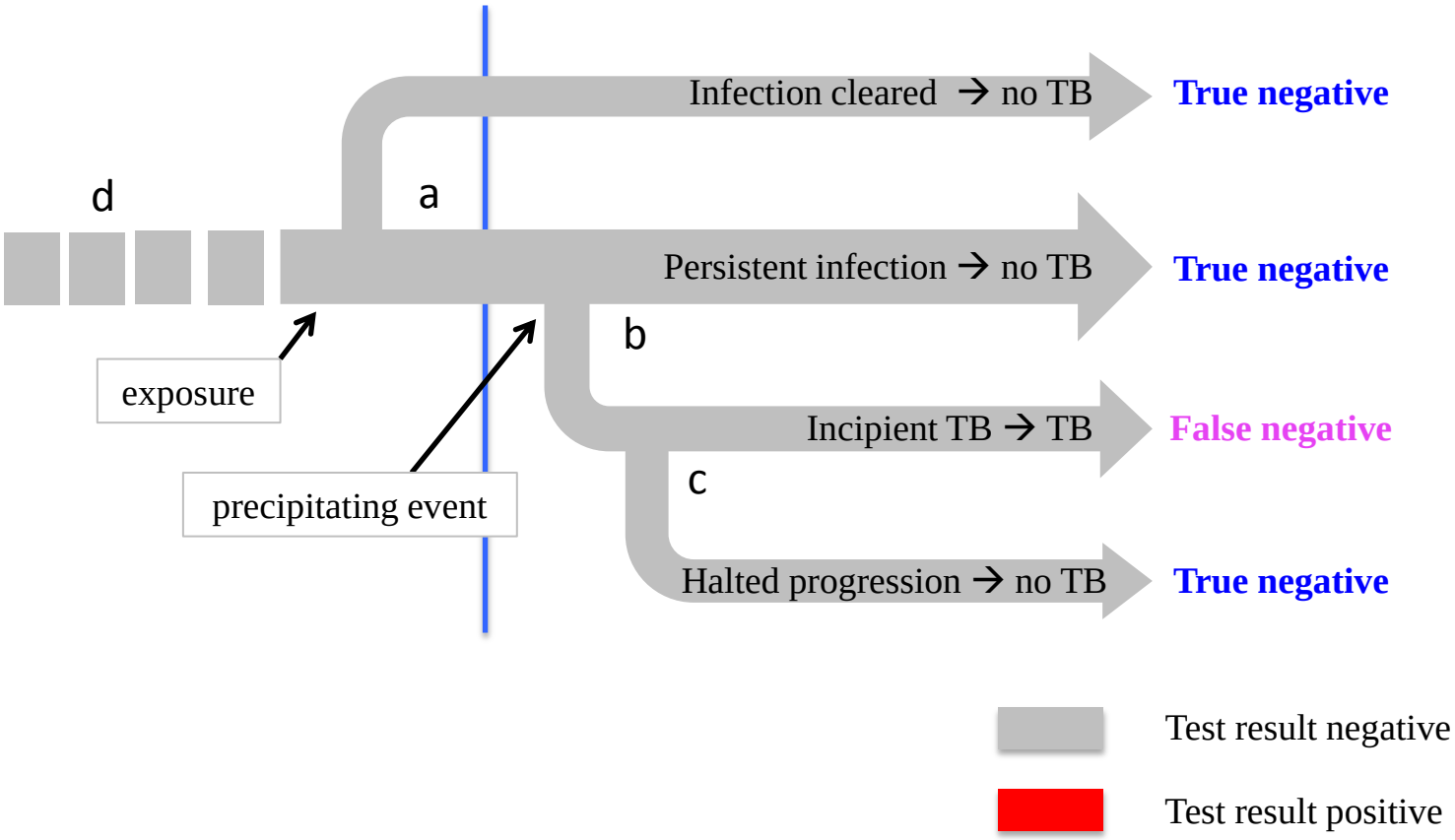
Performance for a test for *incipient TB*



… but test is only positive AFTER the precipitating event →

Cobelens et al. Lancet Resp Med, accepted

Performance for a test for *incipient TB*



→ **NPV depends on when test is done**

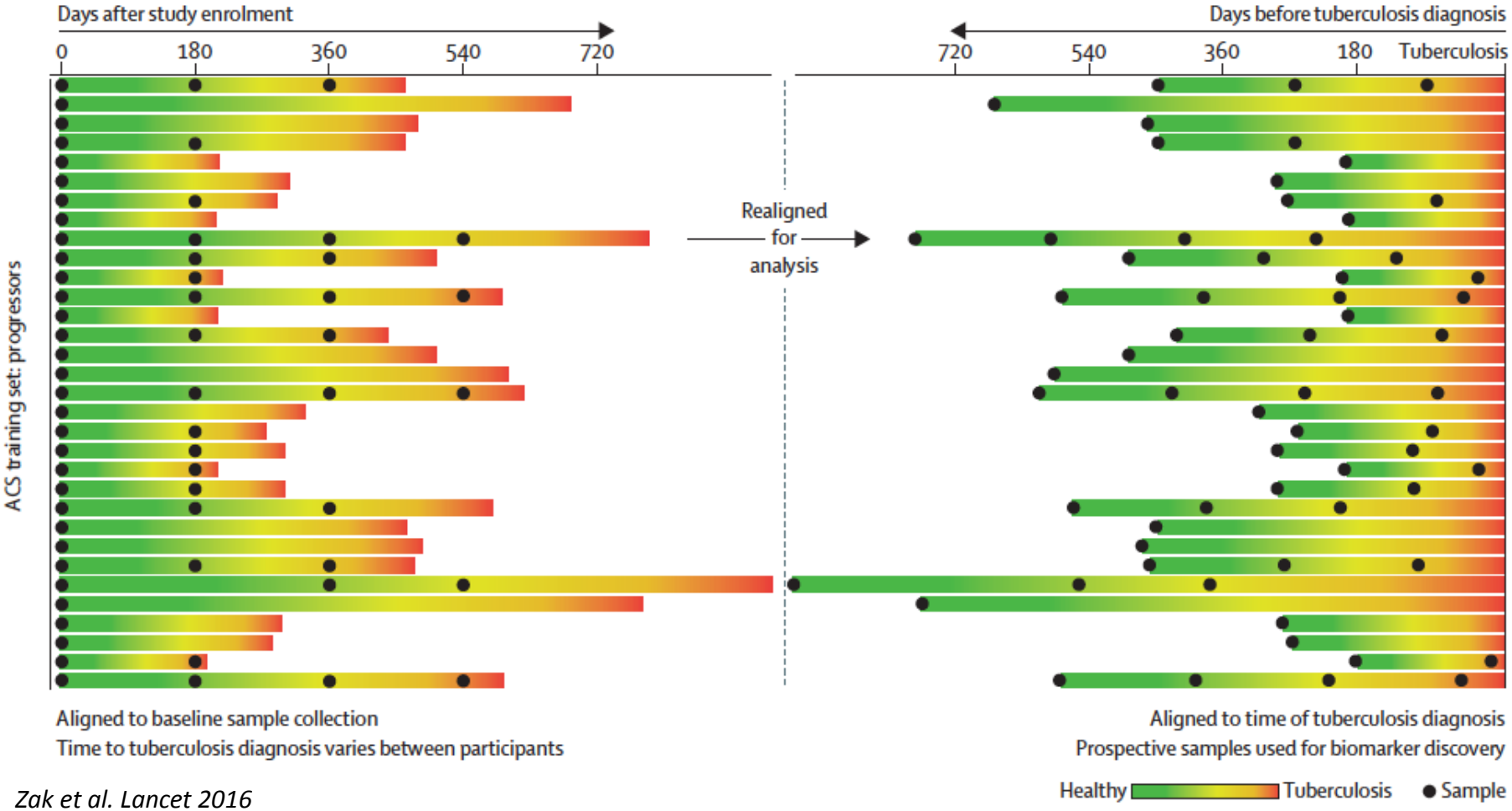
→ NPV will be higher the closer the test is done to the moment TB disease becomes apparent

Cobelens et al. Lancet Resp Med, accepted

Subclinical TB test: RNA signatures

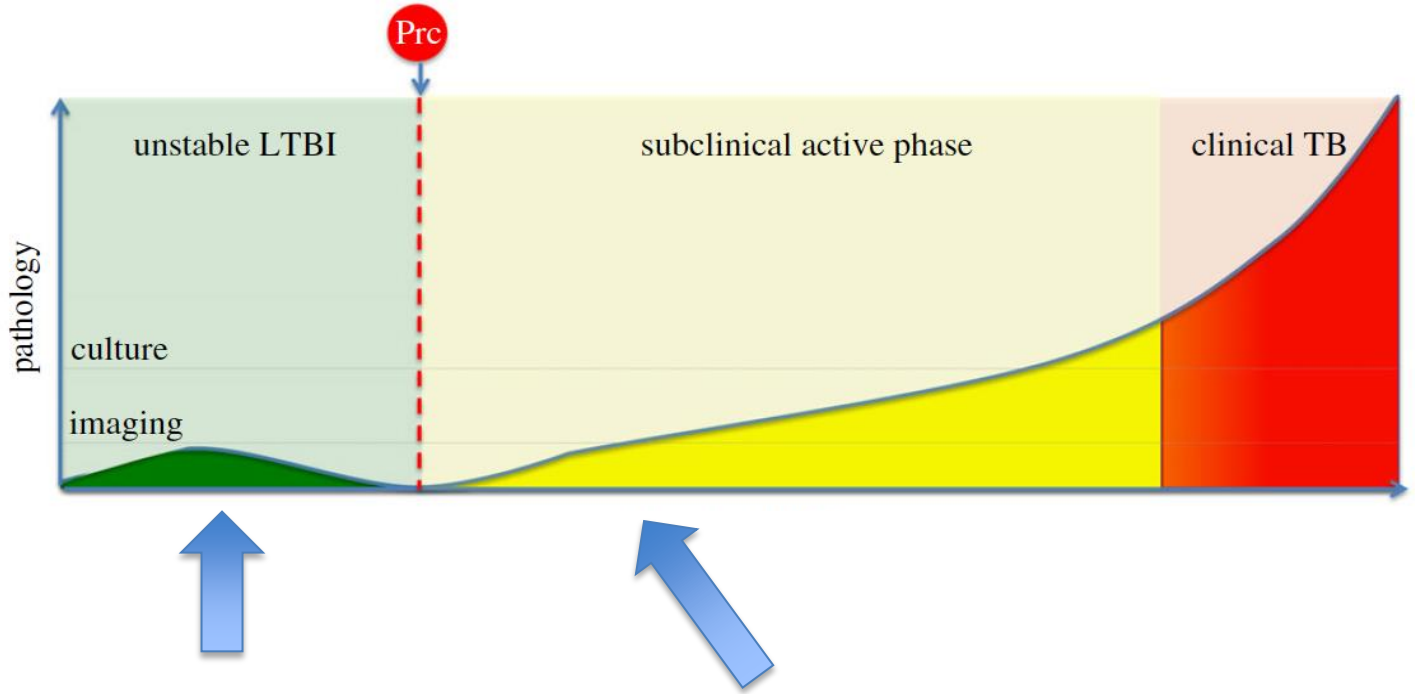
16-gene RNA signature in 6363 South African adolescents follwed for incident TB

Prediction improves as sample was tested closer to the timepoint of TB diagnosis



Zak et al. Lancet 2016

Implications for test utilization



persistent infection test

Rule-out *progression to TB disease*

Incipient TB test

Rule-in *progression to TB disease*

Implications for test utilization

When to rule out, when to rule in?

Rule out (= persistent infection test)

- **High probability of progression**, in particular to severe TB disease (e.g. HIV infection, pre-TNFalpha blocking, infants)
- Irrespective of recent exposure

Rule in (= incipient TB test)

- **Recent exposure** (e.g. contacts, high transmission settings)
- Irrespective of probability of progression

→ potential for mass test & treat campaigns!

Implications for test design

Incipient TB test

- Rule in test with potential and intended use at large scale
- Low number-needed-to-treat, but high number-needed-to-test
- May need to be repeated within individuals

→ Important for test to be low-cost

"**Risk signatures**" may in fact be combinations of persistent infection and incipient TB tests

Conclusions

We need a **TB prediction test**

Positive predictive values for current tests are too low → numbers needed to treat too high

A high PPV prediction test probably identifies **incipient TB** rather than persistent infection

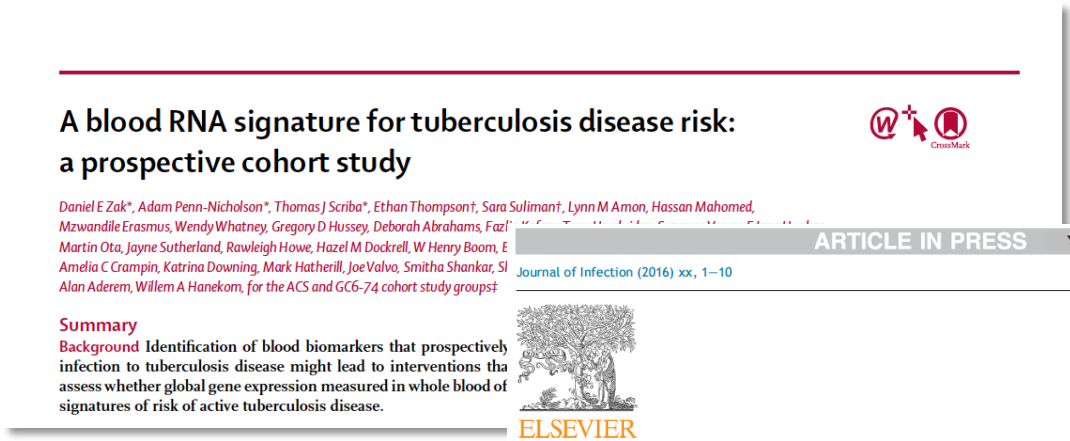
A test for incipient TB will be a test for **ruling in** 'likely progression to TB disease' in recently exposed individuals

An inexpensive and easy-to-use test for incipient TB could open opportunities for mass test & treat campaigns

Acknowledgements

Sandra Kik
Hanif Esmail
Alberto Matteelli
Daniela Cirillo
Christian Lienhardt
Alessandra Varga

Potential candidates for incipient disease tests

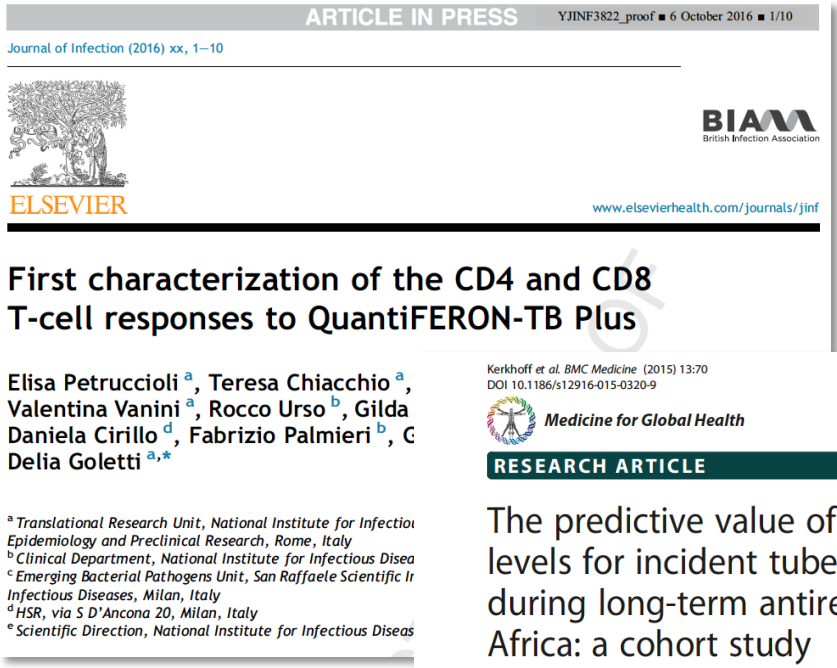


A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Daniel E Zak*, Adam Penn-Nicholson*, Thomas J Scriba*, Ethan Thompson†, Sara Sulimant, Lynn M Amon, Hassan Mahomed, Mzwandile Erasmus, Wendy Whatney, Gregory D Hussey, Deborah Abrahams, Fazl
Martin Ota, Jayne Sutherland, Rawleigh Howe, Hazel M Dockrell, W Henry Boom, E
Amelia C Crampin, Katrina Downing, Mark Hatherill, Joe Valvo, Smitha Shankar, Sl
Alan Aderem, Willem A Hanekom, for the ACS and GC6-74 cohort study groups‡

Summary

Background Identification of blood biomarkers that prospectively
infection to tuberculosis disease might lead to interventions tha
assess whether global gene expression measured in whole blood of
signatures of risk of active tuberculosis disease.



ARTICLE IN PRESS YJINF3822_proof ■ 6 October 2016 ■ 1/10

Journal of Infection (2016) xx, 1–10

ELSEVIER

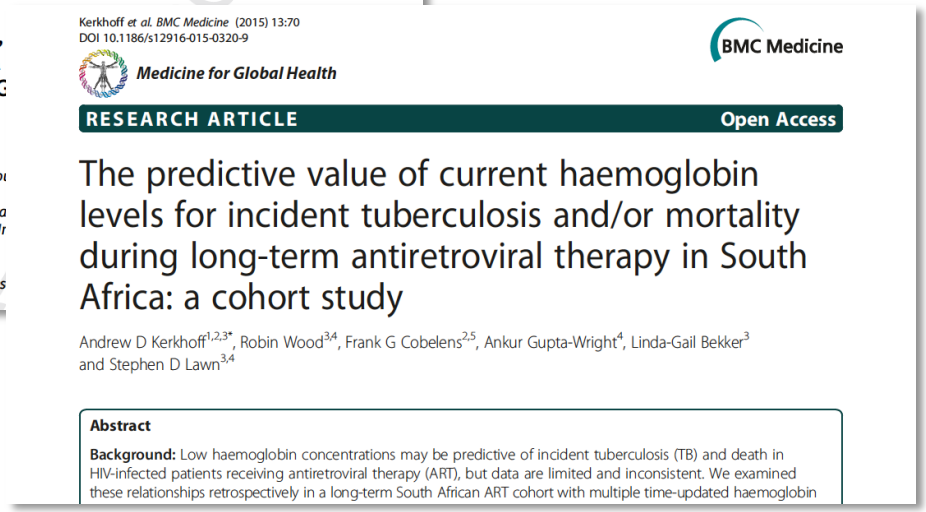
BIAM British Infection Association

www.elsevierhealth.com/journals/jinf

First characterization of the CD4 and CD8 T-cell responses to QuantiFERON-TB Plus

Elisa Petruccioli [a], Teresa Chiacchio [a], Valentina Vanini [a], Rocco Urso [b], Gilda Daniela Cirillo [d], Fabrizio Palmieri [b], G Delia Goletti [a,*]

[a] Translational Research Unit, National Institute for Infectiou Epidemiology and Preclinical Research, Rome, Italy
[b] Clinical Department, National Institute for Infectious Disea
[c] Emerging Bacterial Pathogens Unit, San Raffaele Scientific I Infectious Diseases, Milan, Italy
[d] HSR, via S D'Ancona 20, Milan, Italy
[e] Scientific Direction, National Institute for Infectious Diseas



Kerkhoff et al. BMC Medicine (2015) 13:70
DOI 10.1186/s12916-015-0320-9

BMC Medicine

Medicine for Global Health

RESEARCH ARTICLE Open Access

The predictive value of current haemoglobin levels for incident tuberculosis and/or mortality during long-term antiretroviral therapy in South Africa: a cohort study

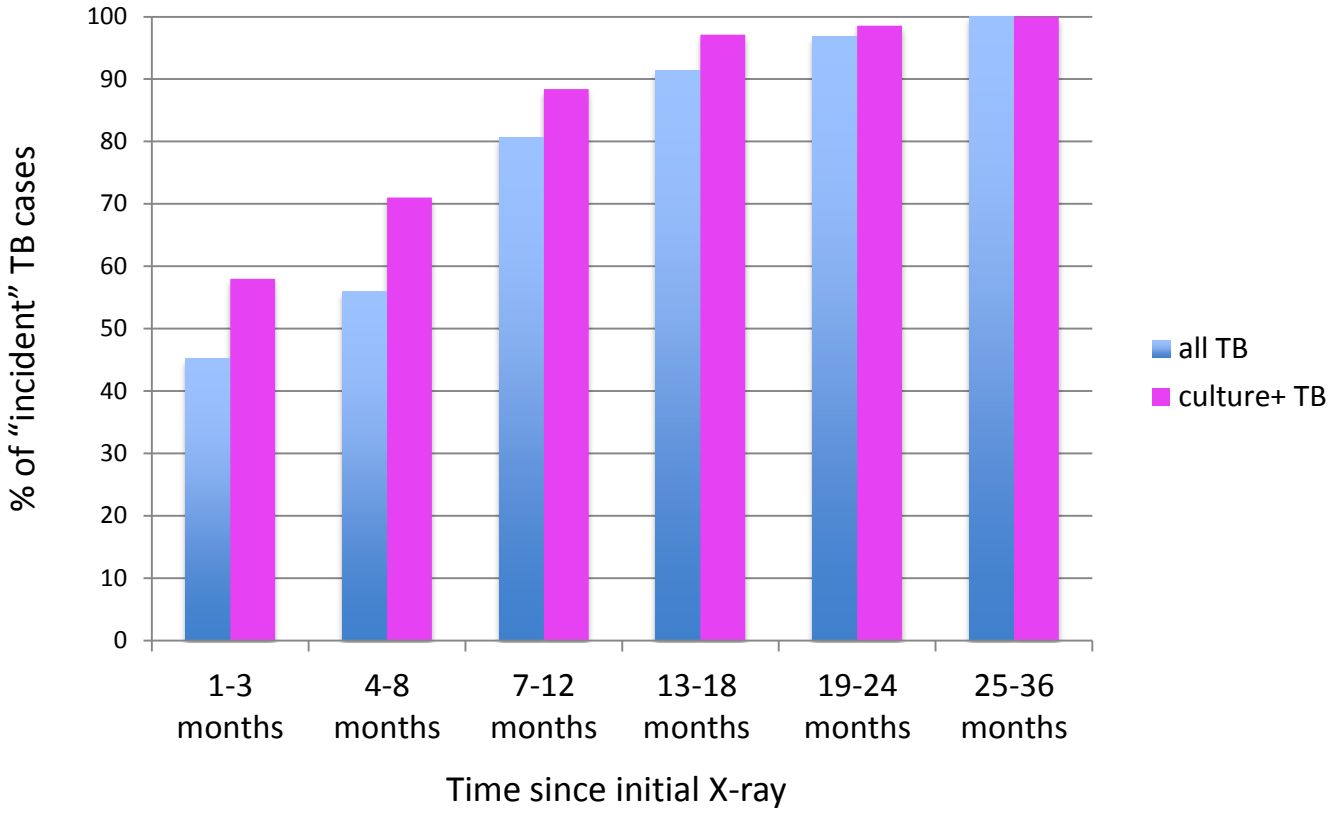
Andrew D Kerkhoff[1,2,3*], Robin Wood[3,4], Frank G Cobelens[2,5], Ankur Gupta-Wright[4], Linda-Gail Bekker[3] and Stephen D Lawn[3,4]

Abstract

Background: Low haemoglobin concentrations may be predictive of incident tuberculosis (TB) and death in HIV-infected patients receiving antiretroviral therapy (ART), but data are limited and inconsistent. We examined these relationships retrospectively in a long-term South African ART cohort with multiple time-updated haemoglobin

Subclinical active phase

176 Chinese patients with abnormal X-rays but 5 negative cultures
Followed up for TB for 36 months: 93 TB cases (69 culture-confirmed)



Hongkong Chest Service. Am Rev Resp Dis 1981

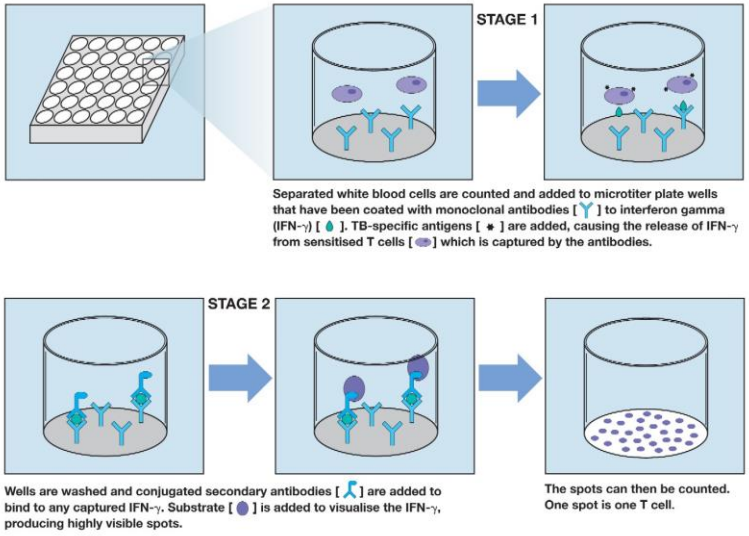
Current diagnostics for LTBI: TST

Tuberculin skin test

- Read after 48-96 H
- Inter/intra-observer variability
- Sensitivity reduced with immune suppression
- Cross-reactions → poor specificity
  - BCG vaccination
  - Non-tuberculous mycobacteria
- Remains positive for decades
  → Anamnestic response?

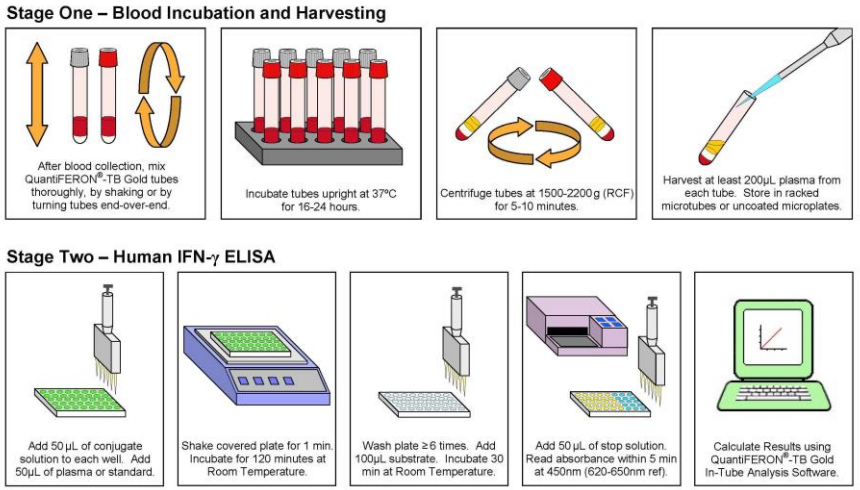
Current diagnostics for LTBI: IGRA

Elispot



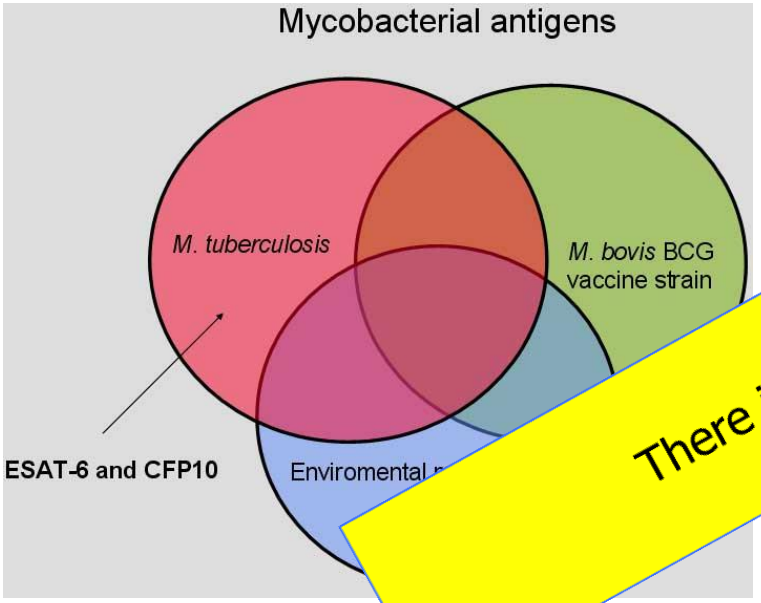
24H incubation with specific antigens
IFNg production by individual T-cells

Whole-blood assay



24H incubation with specific antigens
IFNg measured by ELISA (supernatant)

Current diagnostics for LTBI: IGRA



- Sensitivity as good as TST … etter in immune suppression …
- More spe… → … BCG … eactions with NTM
- …te better with TB exposure than TST … in low-incidence settings but not in high-incidence settings
- What do IGRA measure?
  - Anamnestic response?
  - Recent exposure (→ high risk for disease)?
  - Ongoing antigenic stimulation (persistence)?

There is no gold standard for LTBI