LTBI conception

definitions and relevance for diagnostic products

Frank Cobelens

Amsterdam Institute for Global Health and Development
Amsterdam, Netherlands

KNCV Tuberculosis Foundation
The Hague, Netherlands

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Content

1. Use of the test and rationale for improvement
2. Changing paradigm: what does/should a test for LTBI measure?
3. mplications for test development, performance, utilization and design
4. Issues for discussion – implications for TPP

Definition of *latent tuberculosis infection*

Use of the test

1. Target preventive treatment

Select for preventive treatment individuals at (high) risk of progression to TB disease

2. Estimate LTBI burden

Measure LTBI prevalence in general population and in at-risk populations

3. Estimate trend of LTBI burden (or: transmission)

Measure recently acquired LTBI in general population and in at-risk populations

4. Treatment monitoring

Test of cure for persons with LTBI receiving treatment

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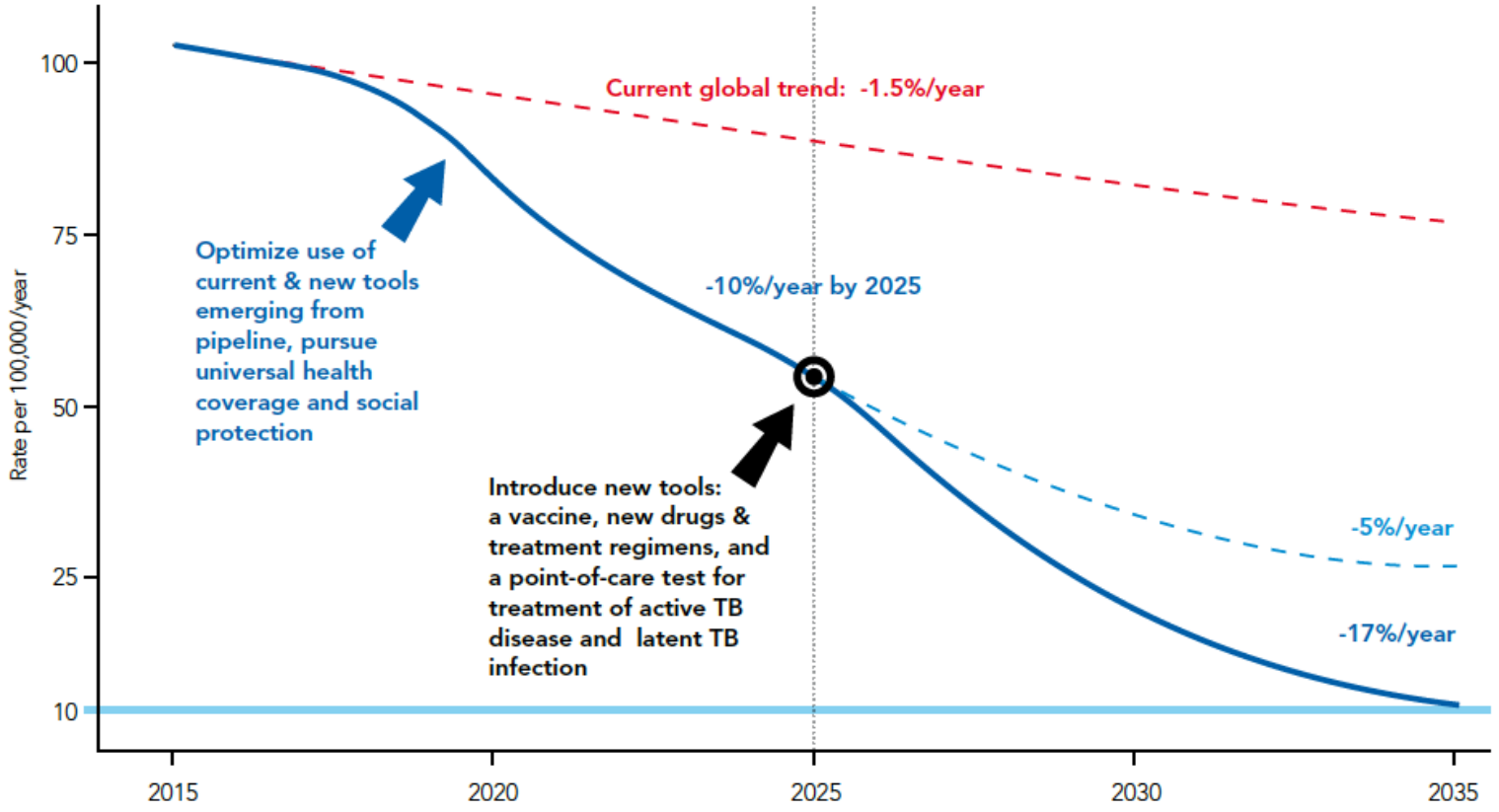
Test of cure for persons with LTBI receiving treatment

Rationale: scale up preventive treatment

WHO aims at global elimination of TB by 2035

Current approaches insufficient – need to expand preventive treatment of latent infection



Preventive treatment

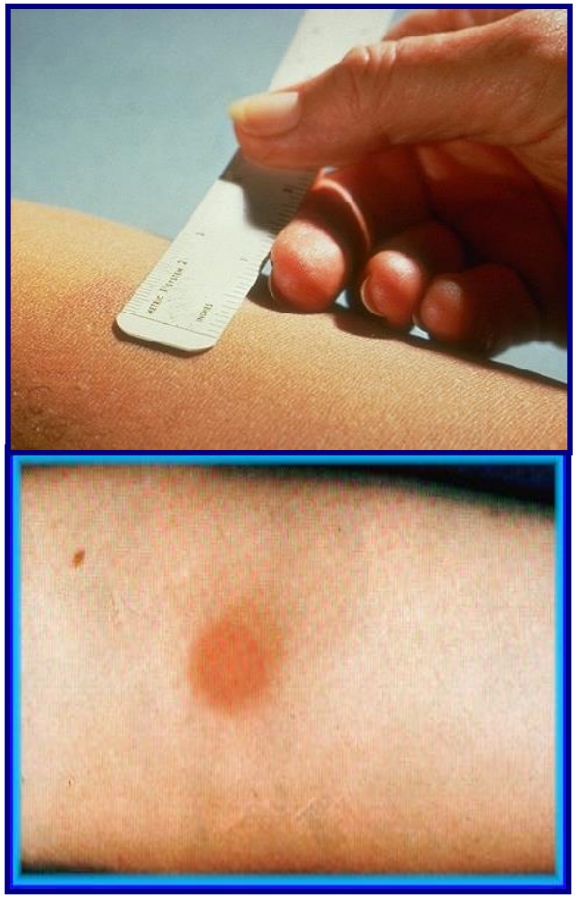
- Various regimens exist, most studies show protective efficacy of 60-80
  - Isoniazid 6-9 months
  - Rifampin-isonazid 3-4 months
  - Rifapentine-isoniazid 3 months

- But there are limitations:
  - Toxicities (e.g. hepatoxicity)
  - Completion & adherence
  - Feasibility
  - Cost
  - Drug resist

- Recommend
  - Globally: hildren exposed to TB
  - Low-incide ce countries: other contacts of TB patients, immigrants?

Utilization restricted partly due to diagnostic limitations

Current diagnostics for LTBI: TST

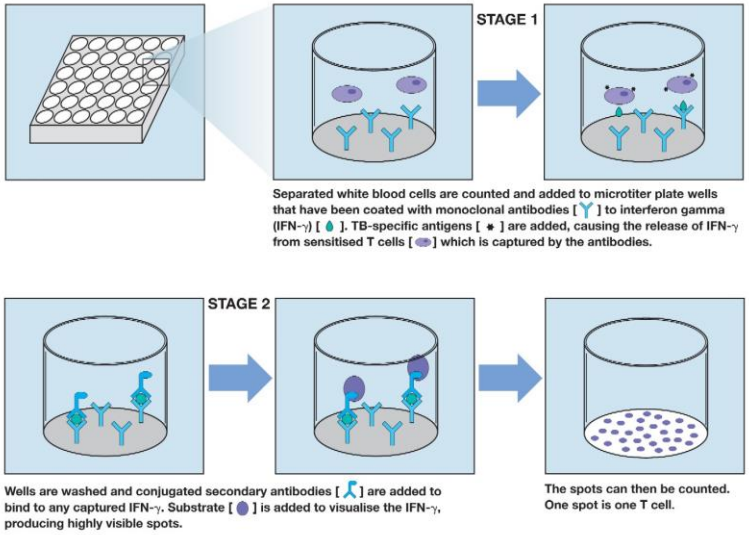


Tuberculin skin test

- 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?

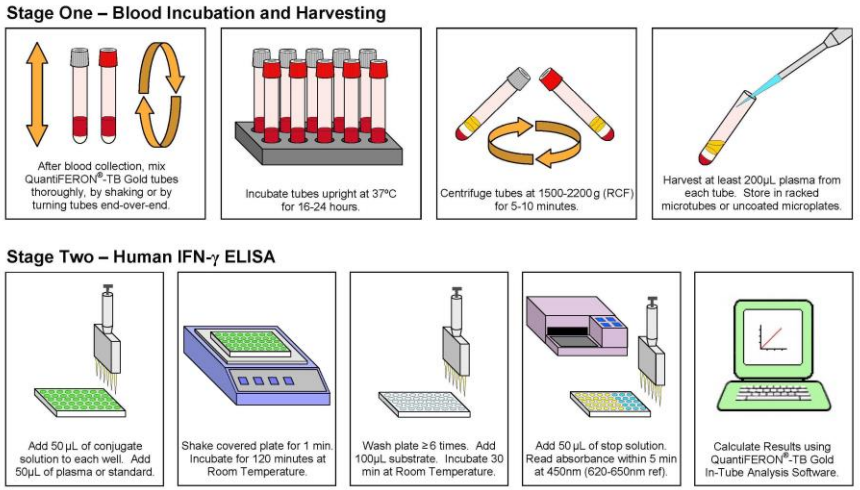
Current diagnostics for LTBI: IGRA

Elispot (TB-Spot)



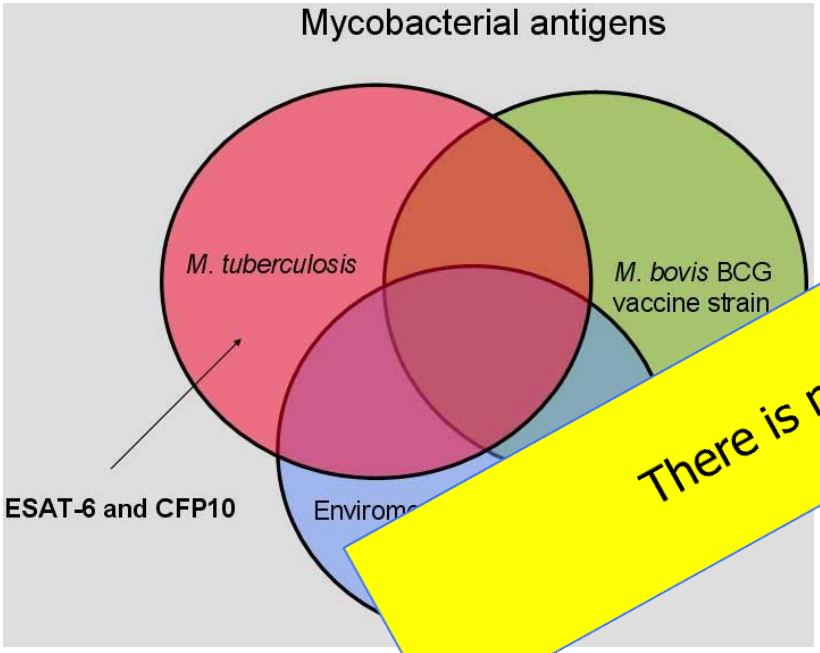
24H incubation with specific antigens
IFNg production by individual T-cells

Whole-blood assay (Quantiferon)



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

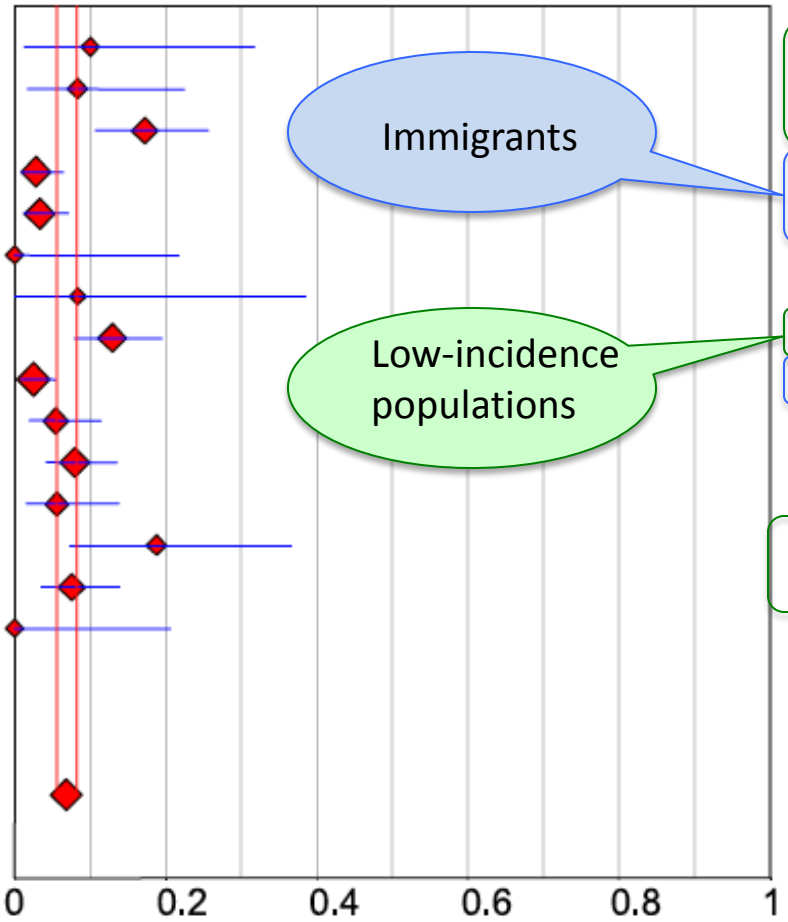
Current diagnostics for LTBI: IGRA



There is no gold standard for LTBI

- Sensitivity as good a… immune suppression (&…
- M…
  - …ss-reaction
- …elates 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)?

IGRA as predictor of TB disease

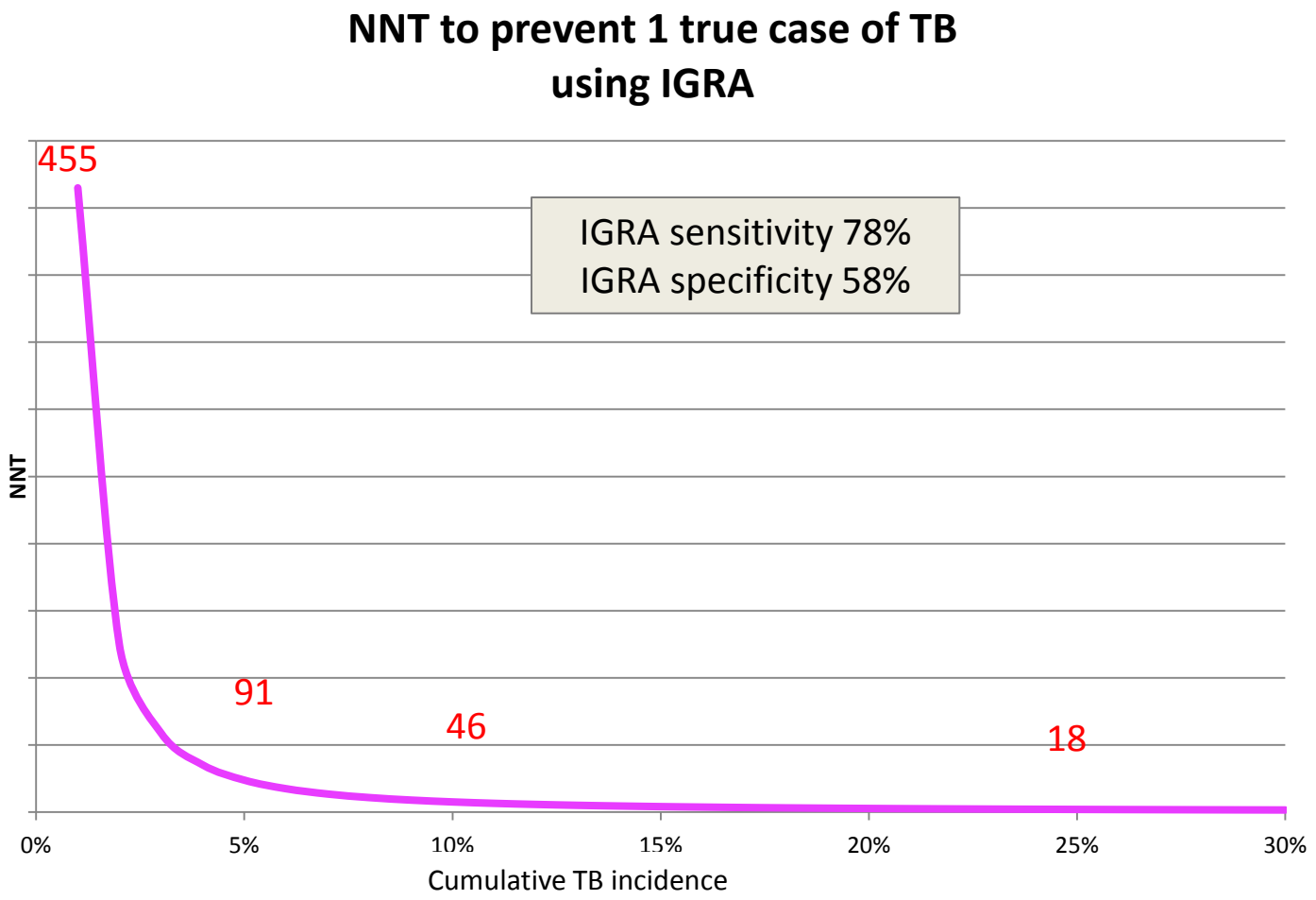


	PPV	(95% CI)	n/N
Clark 2007[36]	0.10	(0.01 – 0.32)	2/20
Aichelburg 2009[24]	0.08	(0.02 – 0.22)	3/36
Haldar 2009[25]	0.17	(0.11 – 0.26)	19/110
Kik 2009[14]	0.03	(0.01 – 0.06)	5/178
Kik 2009[14]	0.03	(0.01 – 0.07)	6/181
Lee 2009[13]	0.00	(0.00 – 0.22)	0/15
Lee 2009[13]	0.08	(0.00 – 0.38)	1/12
Diel 2011[27]	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 %

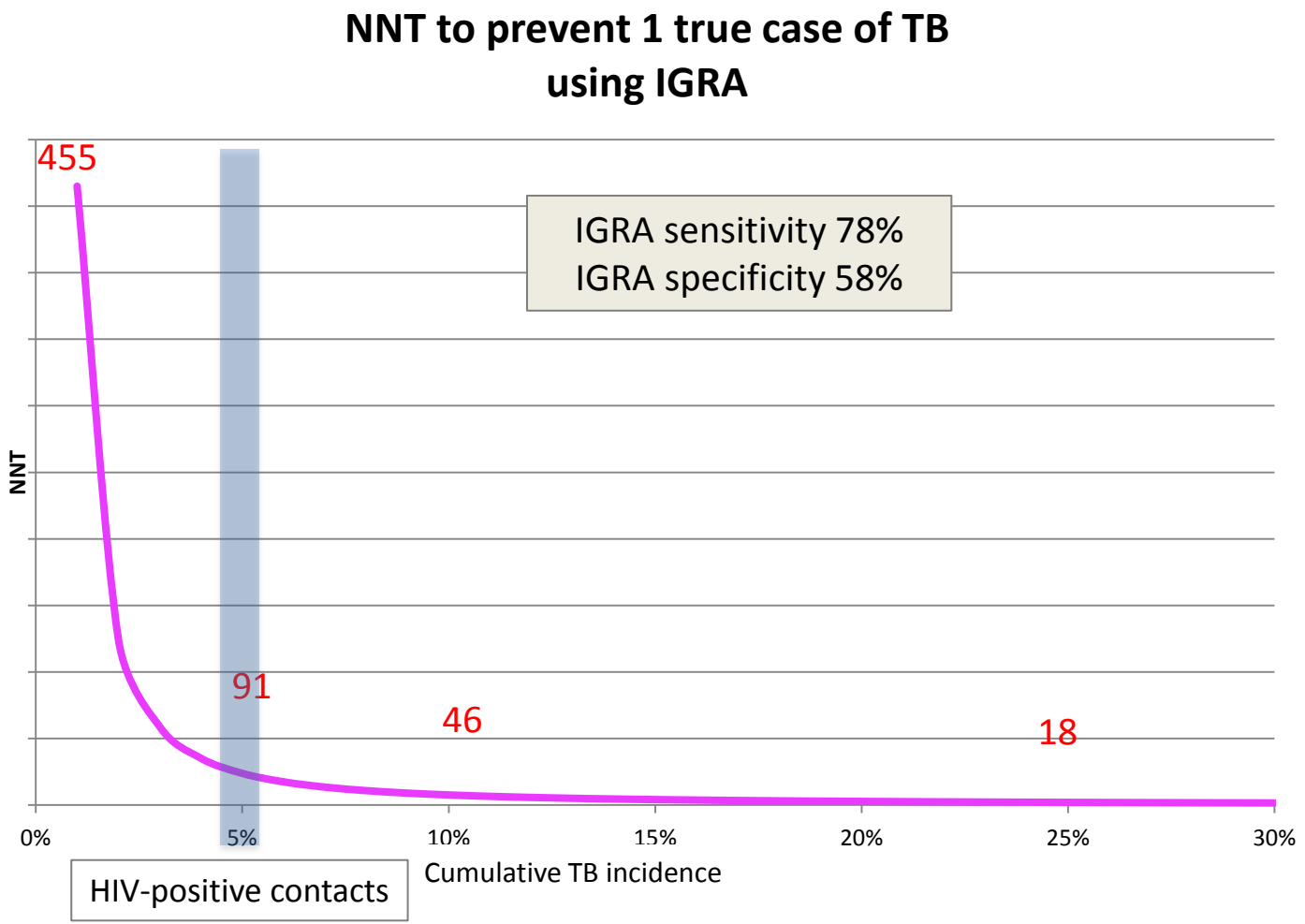
Diel et al. Chest 2012

Number needed to treat



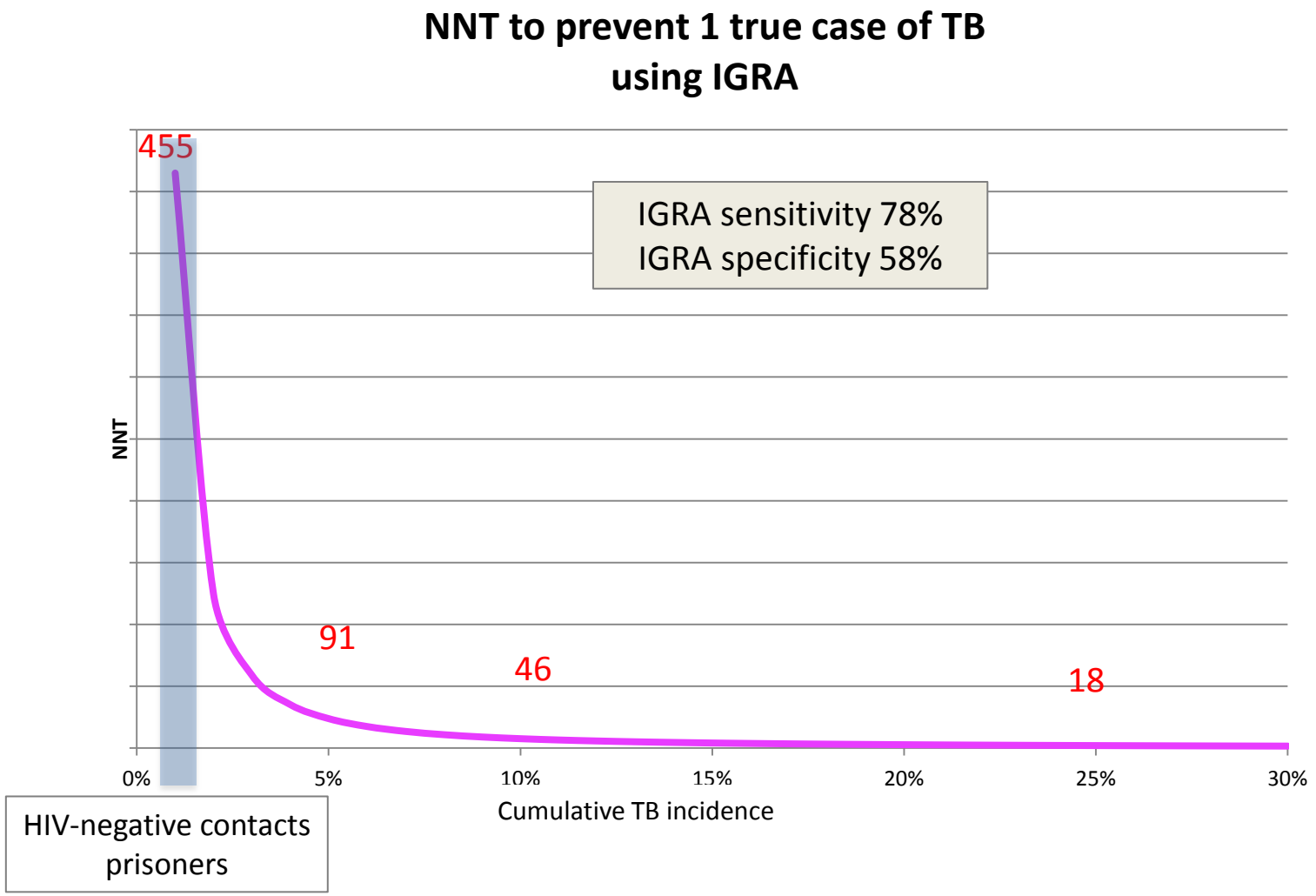
Kik & Cobelens, in prep

Number needed to treat



Kik & Cobelens, in prep

Number needed to treat



Kik & Cobelens, in prep

The need

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

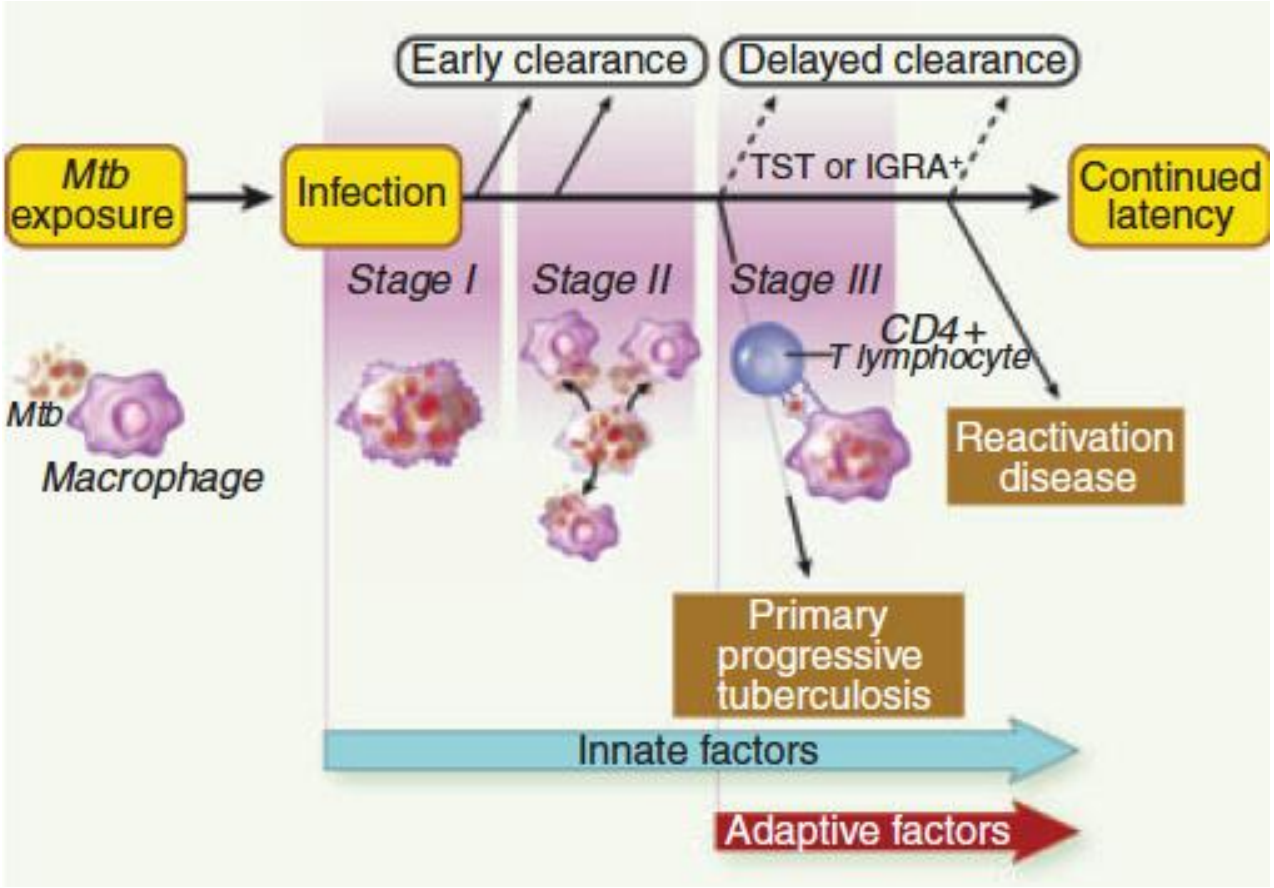
~~*LTBI test*~~

~~*TB risk stratification test*~~

"TB prediction test"

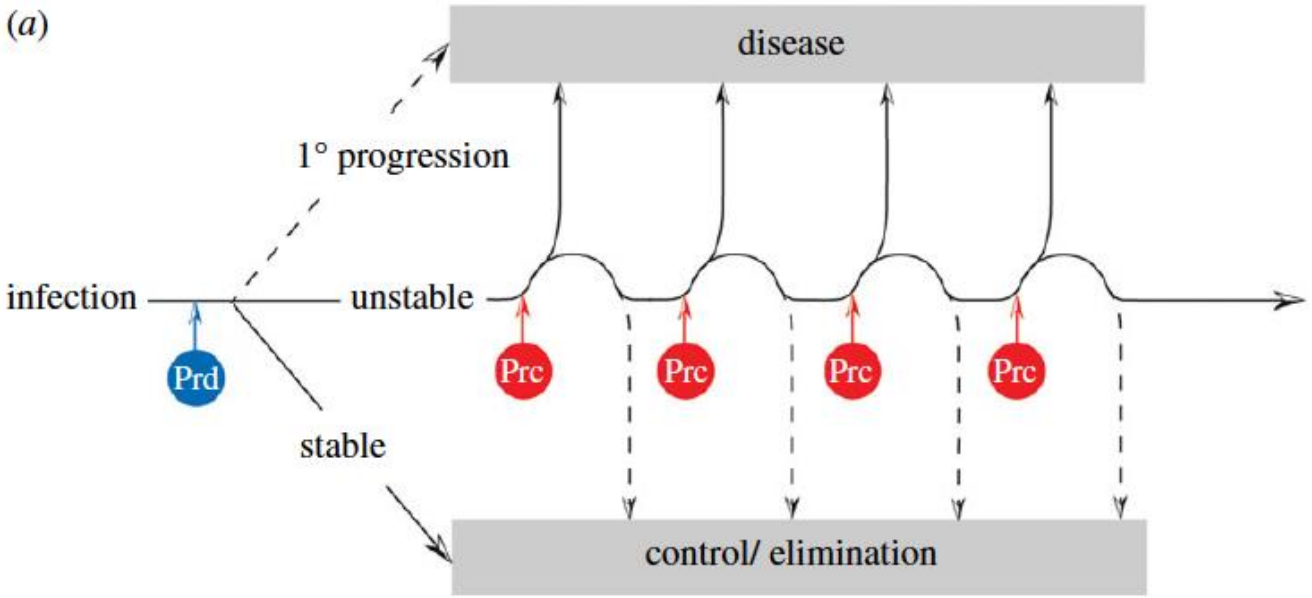
Can high positive predictive values be attained?

LTBI: changing paradigm



Verrall et al. Immunology 2014

LTBI: changing paradigm

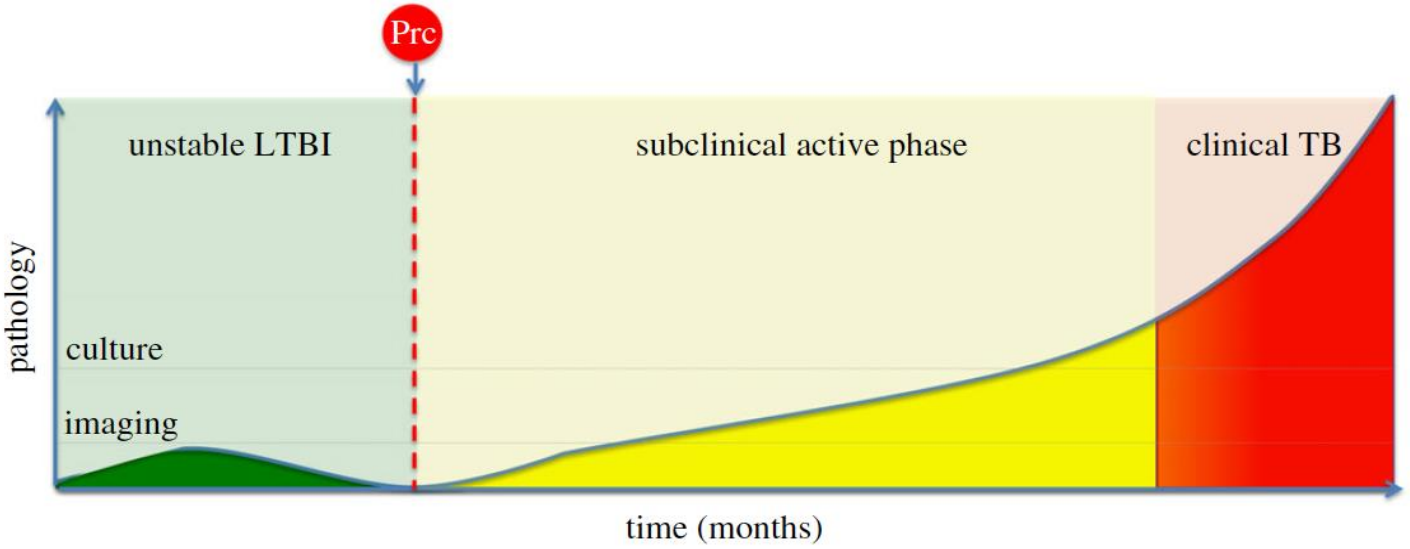


possible predisposing factors
HIV
malnutrition
diabetes
alcoholism
pro/anti inflammatory imbalance

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

Esmail et al. Phil Trans Roy Soc 2015

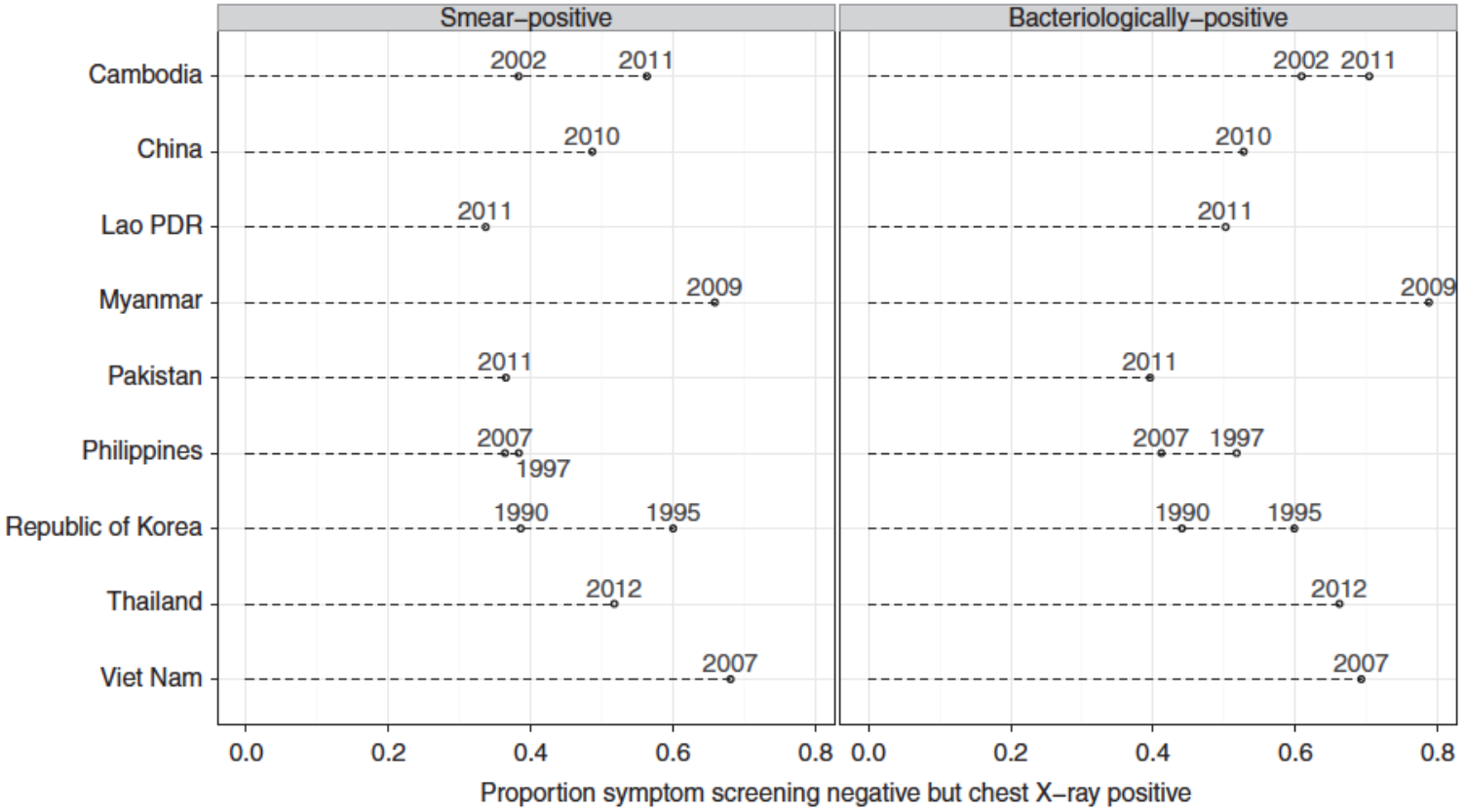
LTBI: changing paradigm



Esmail et al. Phil Trans Roy Soc 2015

Subclinical active phase

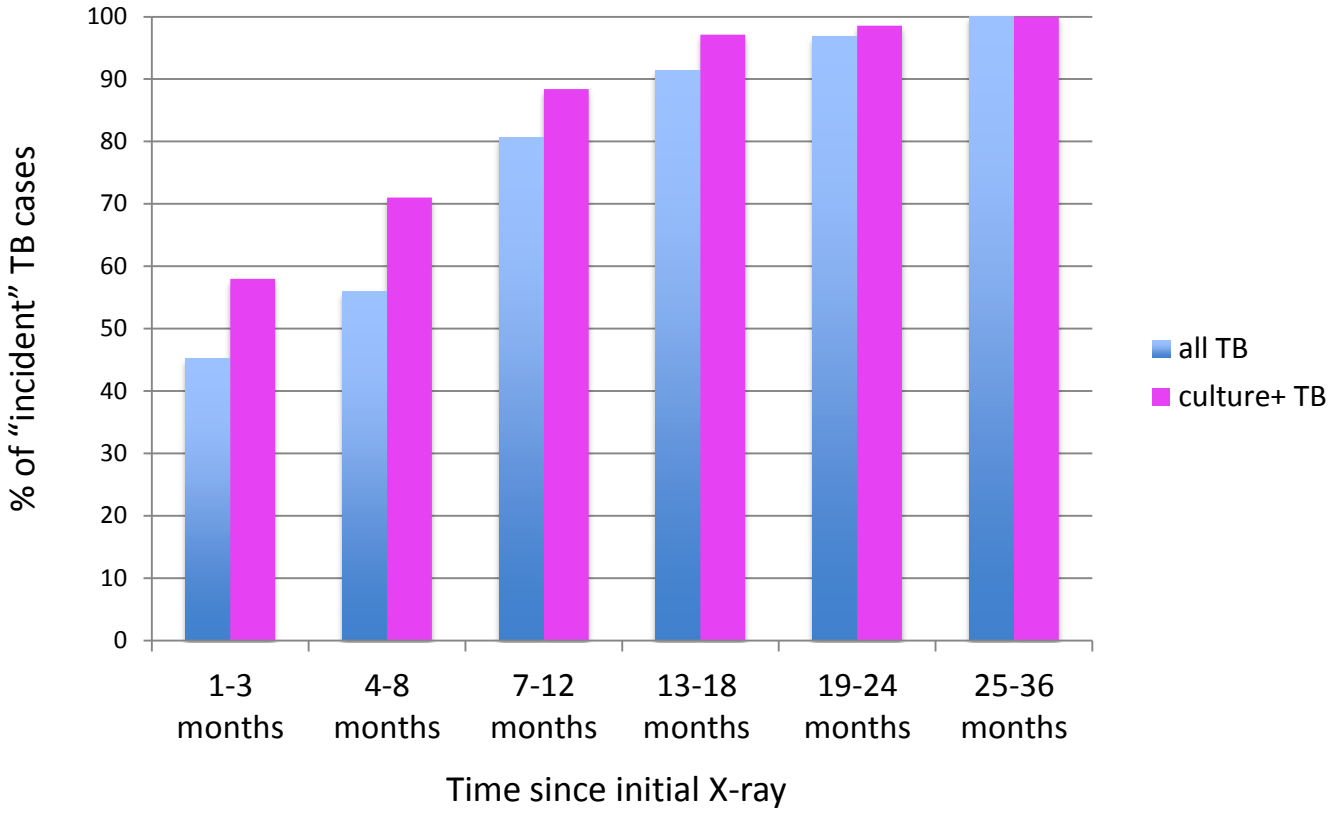
Overview of national TB prevalence survey conducted in Asia, 1990-2012
Proportion of all detected prevalent TB cases that did not report cough



Onozaki et al. TMIH 2015

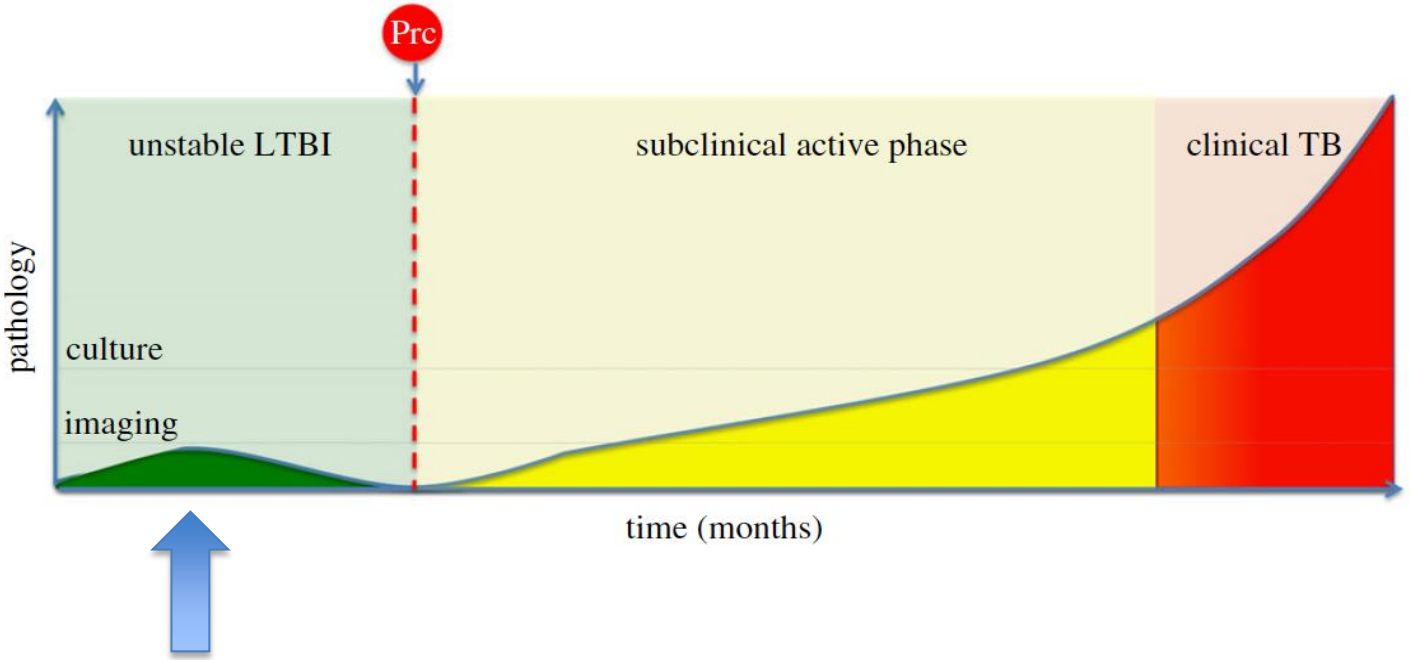
Subclinical active phase

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

LTBI: changing paradigm

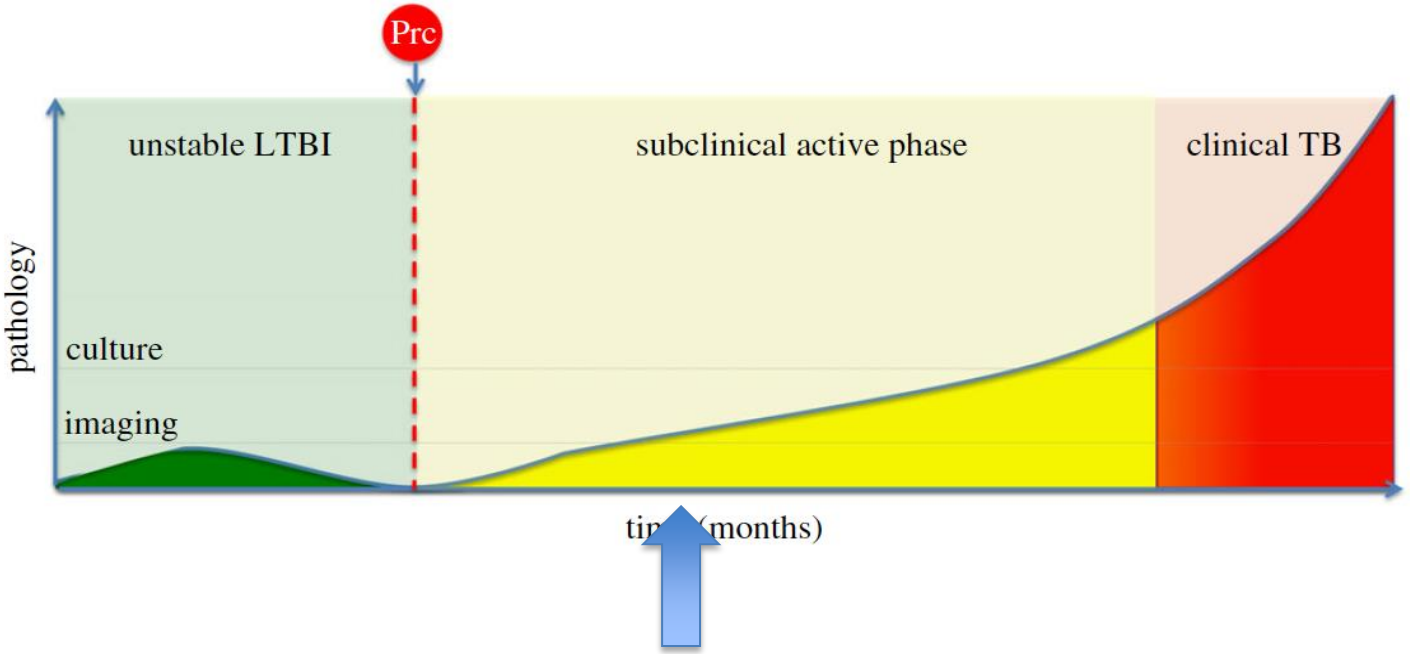


In this stage we cannot predict if and when a precipitating event will occur
→ *beyond existing risk classification* we cannot predict who will become diseased

→ **PPVs will be relatively low**

Esmail et al. Phil Trans Roy Soc 2015

LTBI: changing paradigm



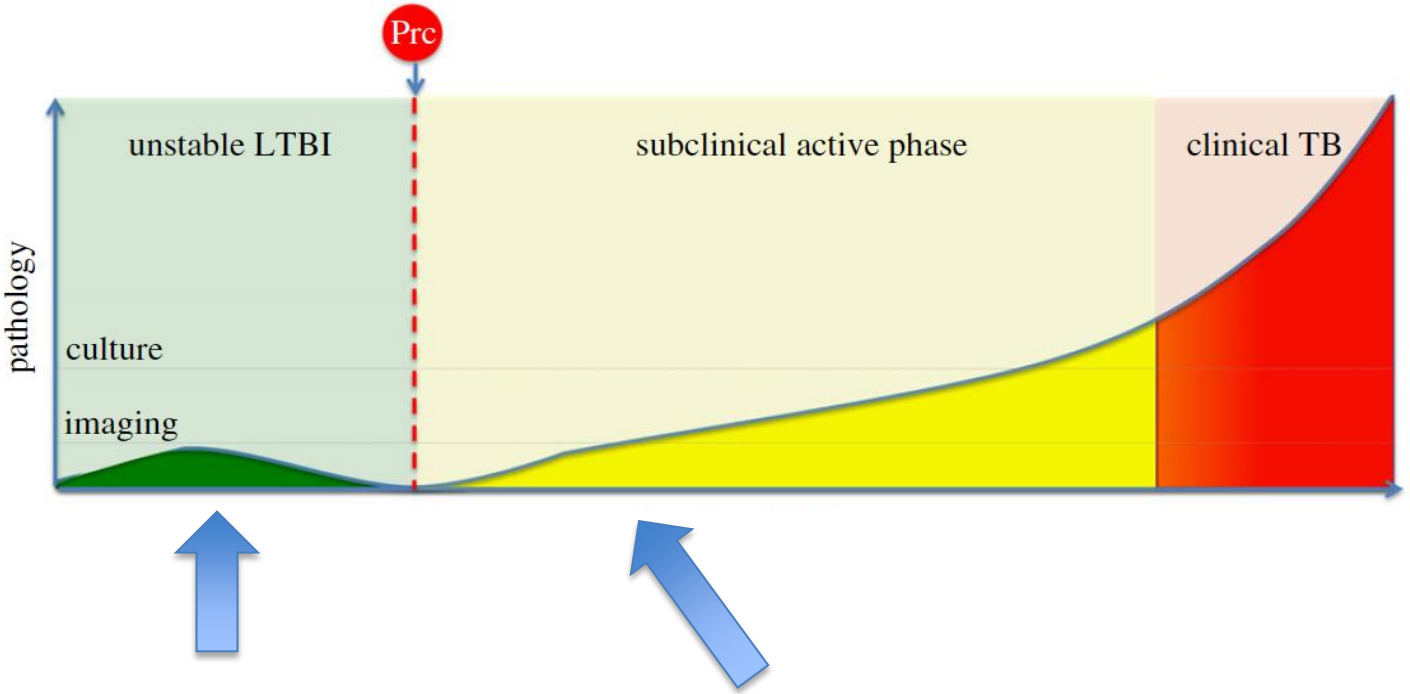
In this stage we there is active bacterial multiplication with high probability of leading to TB disease

→ **PPVs can be relatively high**

Esmail et al. Phil Trans Roy Soc 2015

What does the test measure?

Conceptually, the test either…



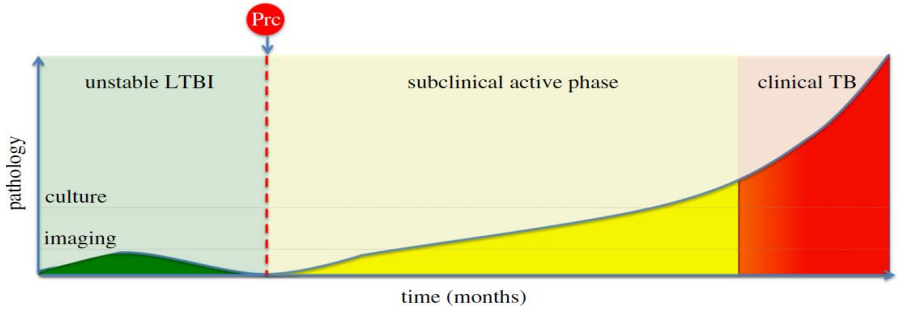
… predicts that disease cannot happen *because there is no persistent infection*

"persistent infection test"

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

"incipient/subclinical TB test"

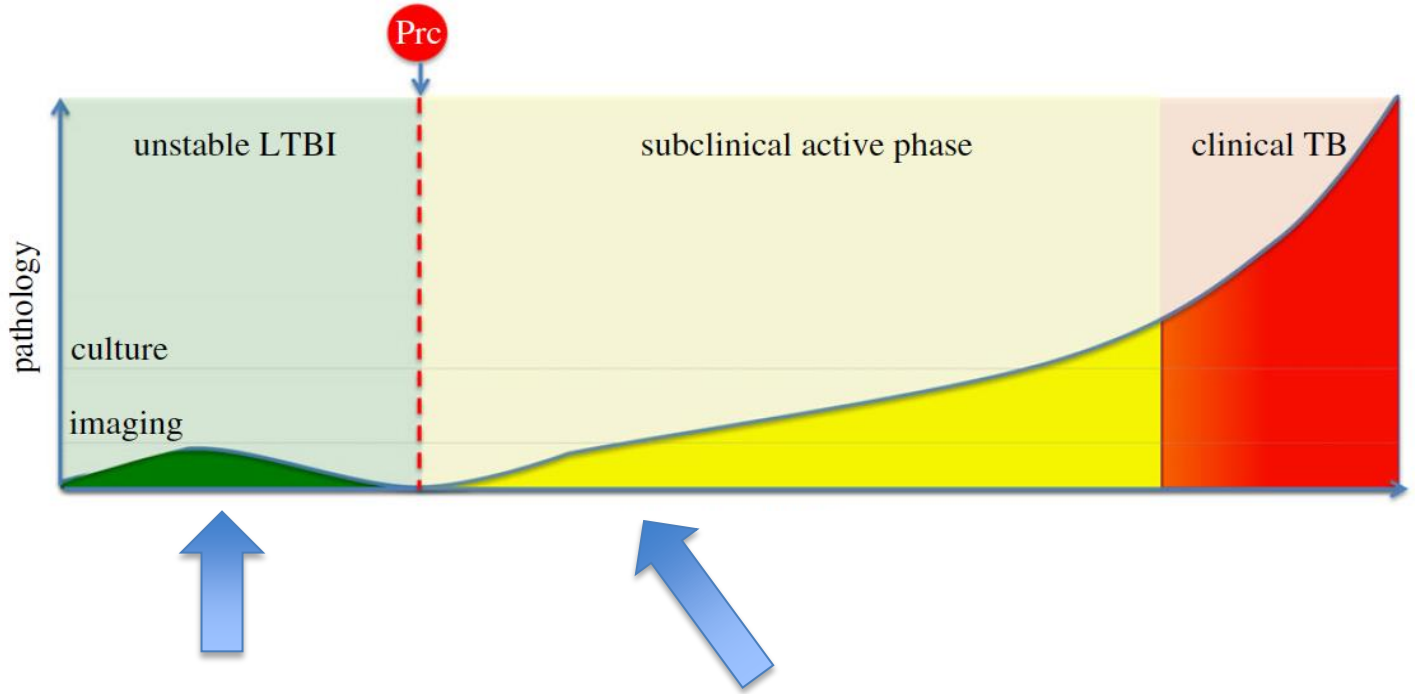
So what…?



This dichotomy matters because it has implications for:

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

Implications for test development



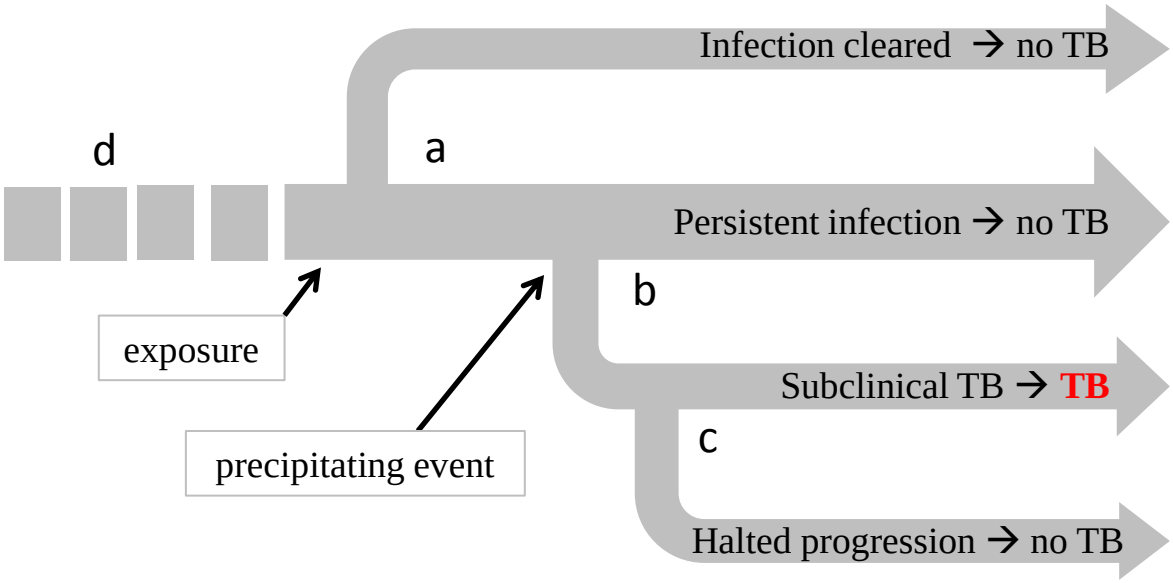
“persistent infection test”

CD4 response
Other?

“incipient/subclinical TB test”

bacterial multiplication?
inflammatory response?
CD8 response?
Other?

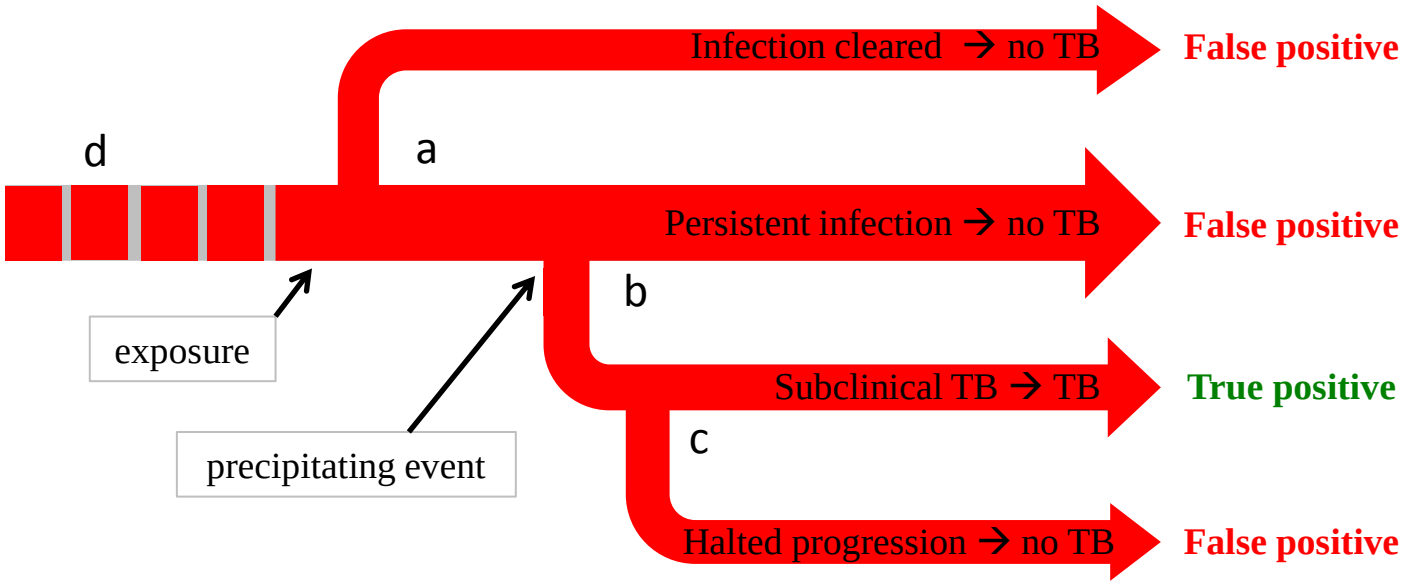
Implications for test performance



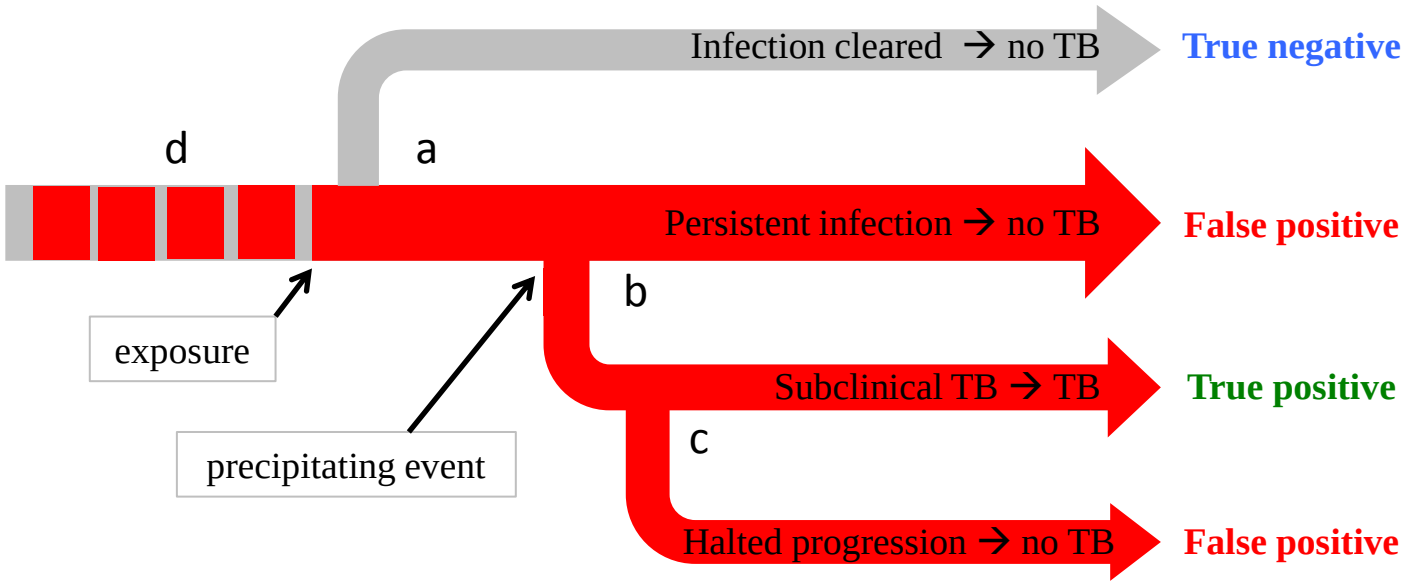
a probability that infection is cleared
b probability that infection leads to subclinical/incipient TB
c probability that subclinical/incipient TB leads to TB disease
d probability that infection existed before the (recent) exposure

PPV = true positives out of all positives

Performance for anamnestic response (TST?)



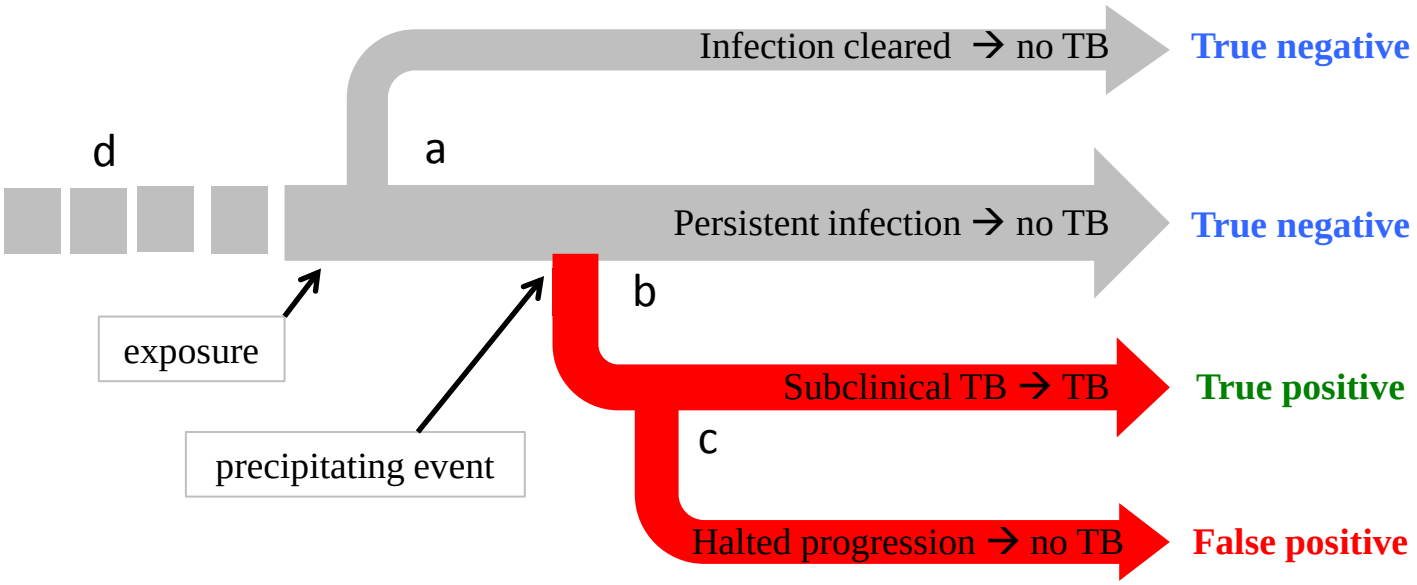
Performance for a test for persistent infection



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

→ **PPV is population dependent (IGRA)**

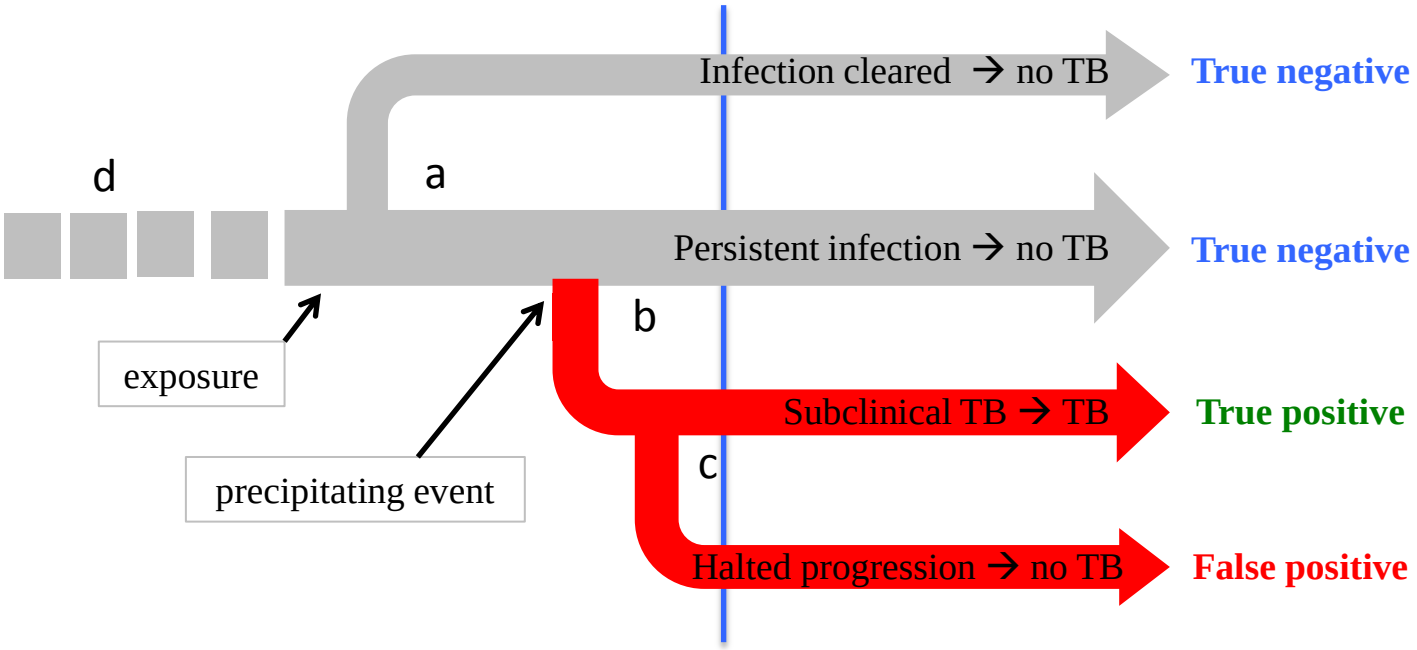
Performance for a test for subclinical TB



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

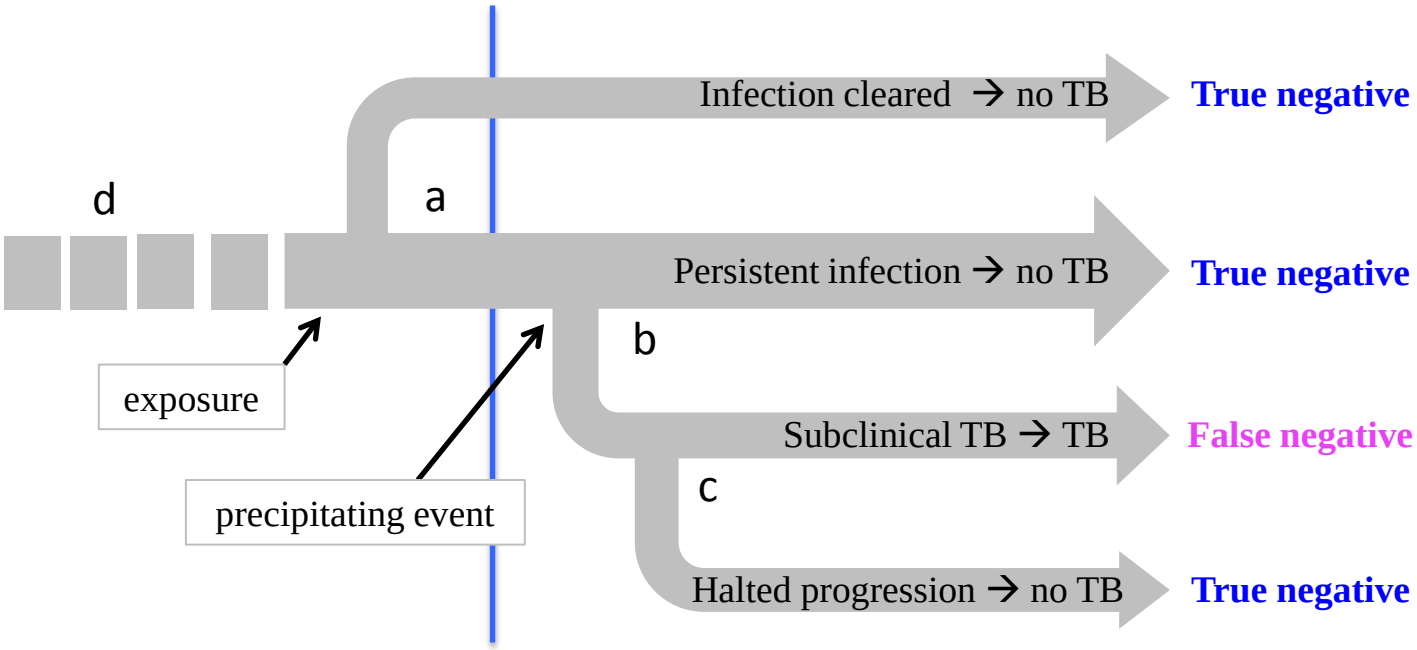
→ **PPV is largely population independent …**

Performance for a test for subclinical TB



… but test is only positive AFTER the precipitating event →

Performance for a test for subclinical TB



… but test is only positive AFTER the precipitating event →

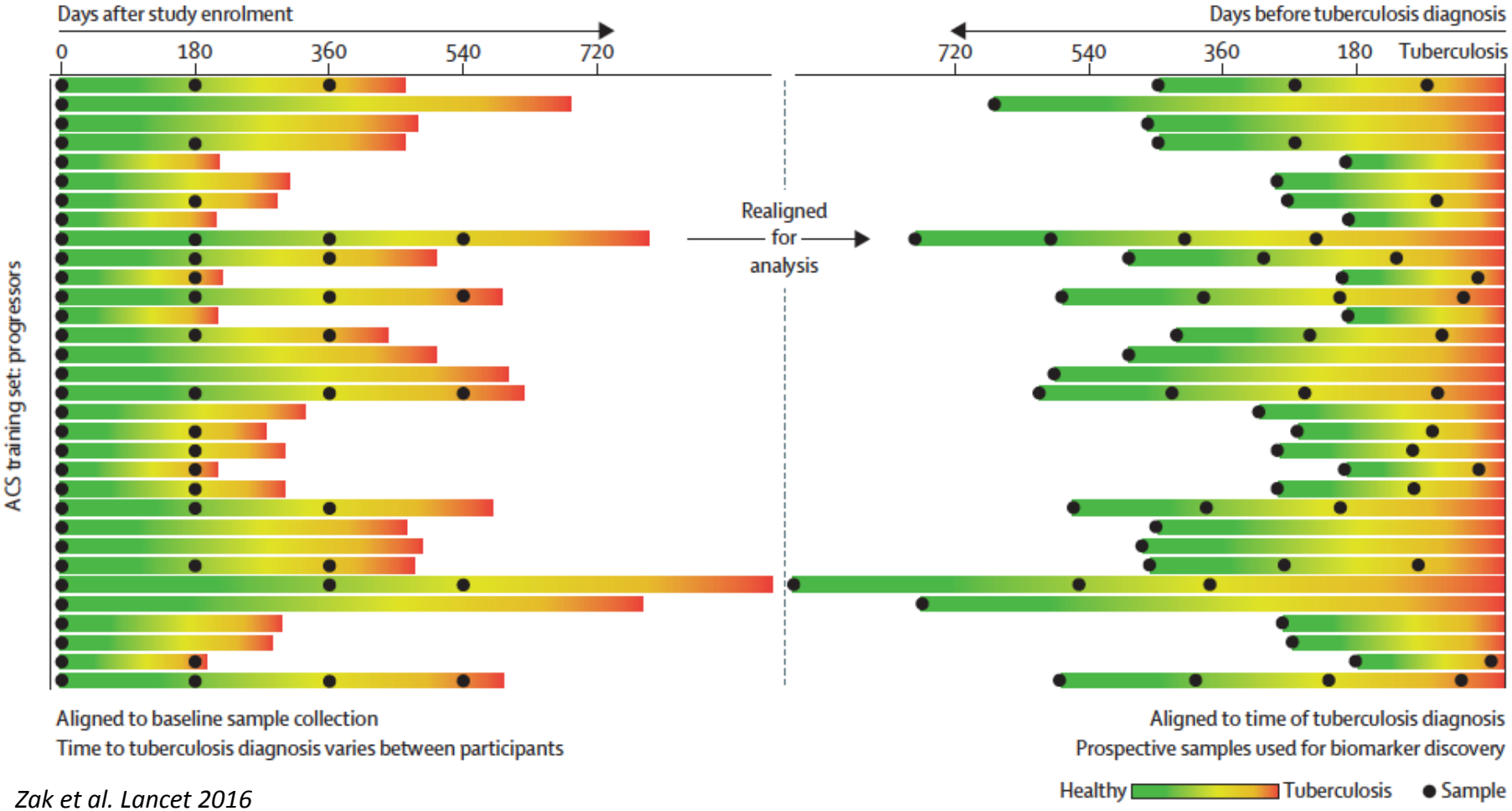
→ NPV depends on when test is done

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

Subclinical TB test: RNA signatures

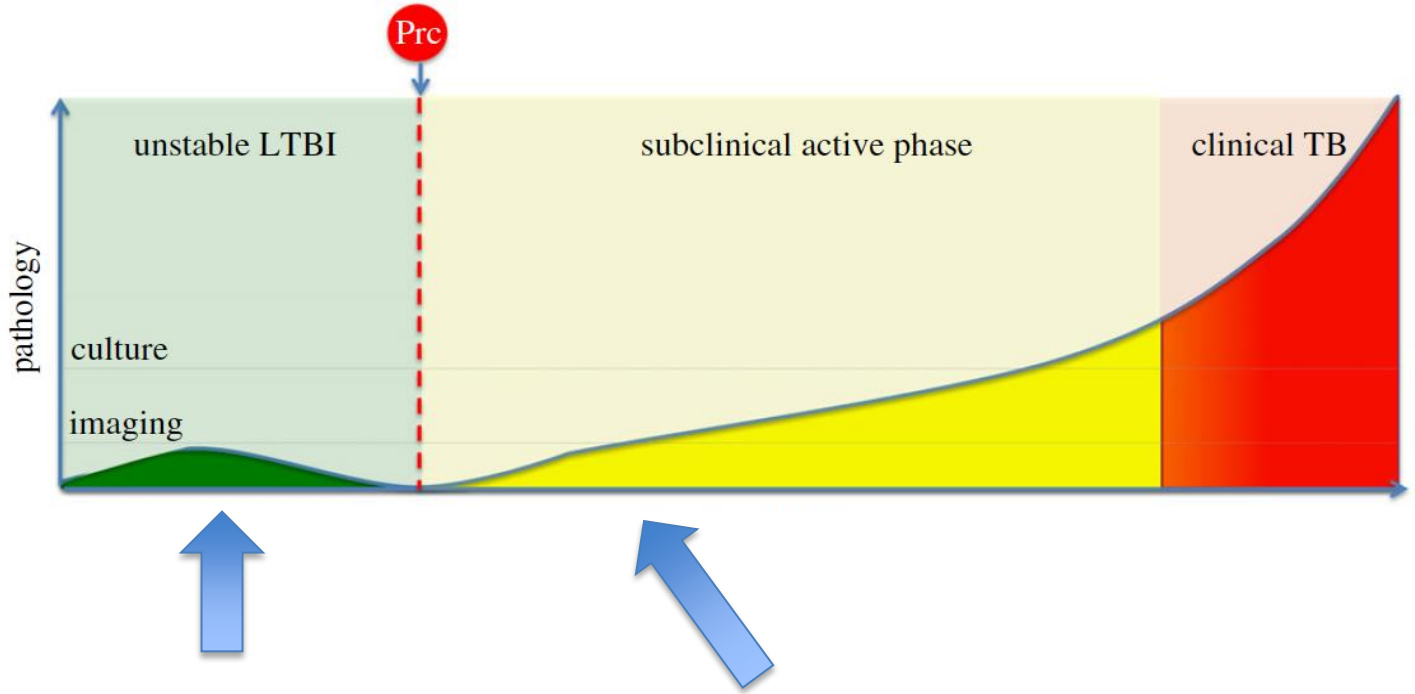
16-gene RNA signature in 6363 South African adolescents follwed for incident TB

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/subclinical TB test

Rule-in *progression to TB disease*

Implications for test utilization

1. When to rule out, when to rule in?
   - **Rule out**:
     - **High probability of progression**, in particular to severe TB disease (e.g. HIV infection, pre-TNFalpha blocking, infants)
     - Irrespective of recent exposure
   - **Rule in:**
     - **Recent exposure** (e.g. contacts, high transmission settings)
     - Irrespective of probability of progression

2. **Incipient/subclinical TB:** test may need to be repeated

3. Positive test: check for active TB
   - **Incipient/subclinical TB:** can we safely treat with a single drug (e.g. isoniazid)?

4. **Test reversion** after successful preventive treatment
   - Expected of Incipient/subclinical TB test
   - Also of test for persistent TB?

     does preventive treatment eradicate persisters?

Implications for test design

Incipient/subclinical 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

A single biomarker that will show high sensitivity AND high specificity is not likely to exist

→ opportunities for **combining** persistent TB and incipient/subclinical TB markers in single assay

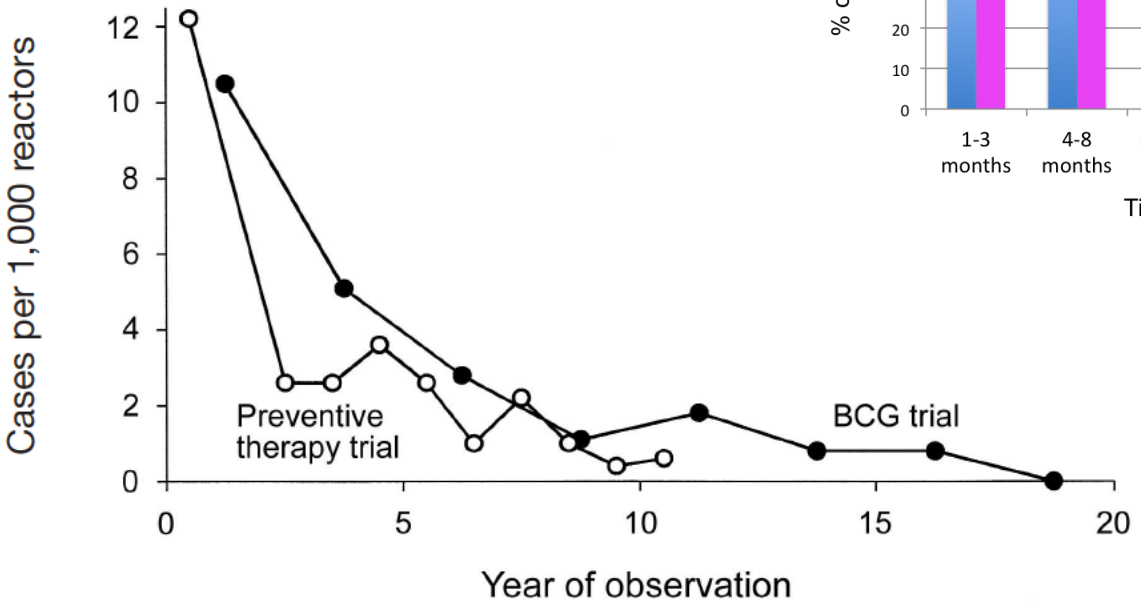
→ "**risk signatures**" may be such combinations

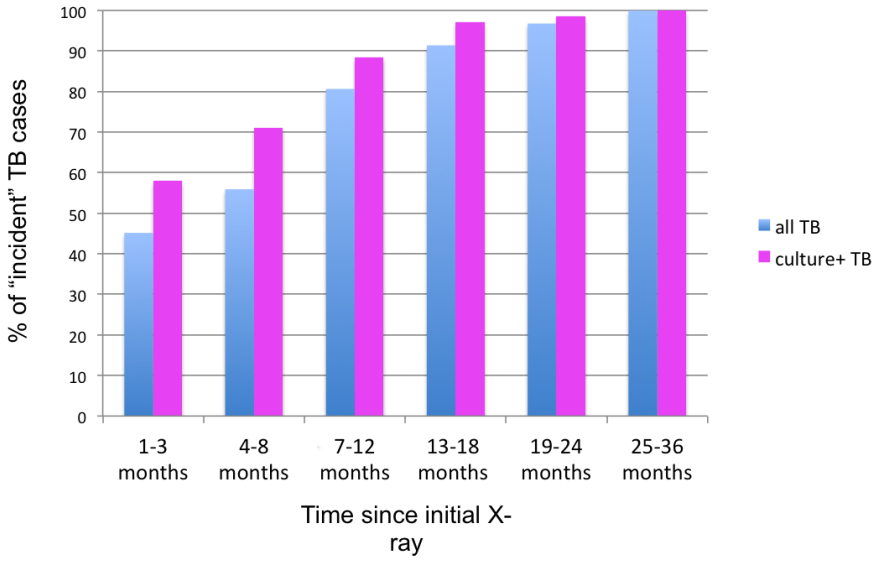
Issues for discussion – implications for TPP

- Do we believe all this?
- How do we deal in the TPP with the issue of rule out versus rule in?
- What is the time period for which the required NPV and PPV should be attained?
- Should the test be able to differentiate from active TB?
- Should the test have a (semi)quantitative read-out?
  - E.g. to indicate whether full-course treatment is needed or only preventive treatment?
- Should we require reversion to negative after successful preventive treatment?

Time period

TST+ individuals





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GRAZIE !