KNCV To eliminate TB

TUBERCULOSISFOUNDATION

aighd

New predictive tests for the diagnosis of tuberculosis infection

How should they be evaluated and what evidence is needed for WHO endorsement?

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What is our target condition?

PICO

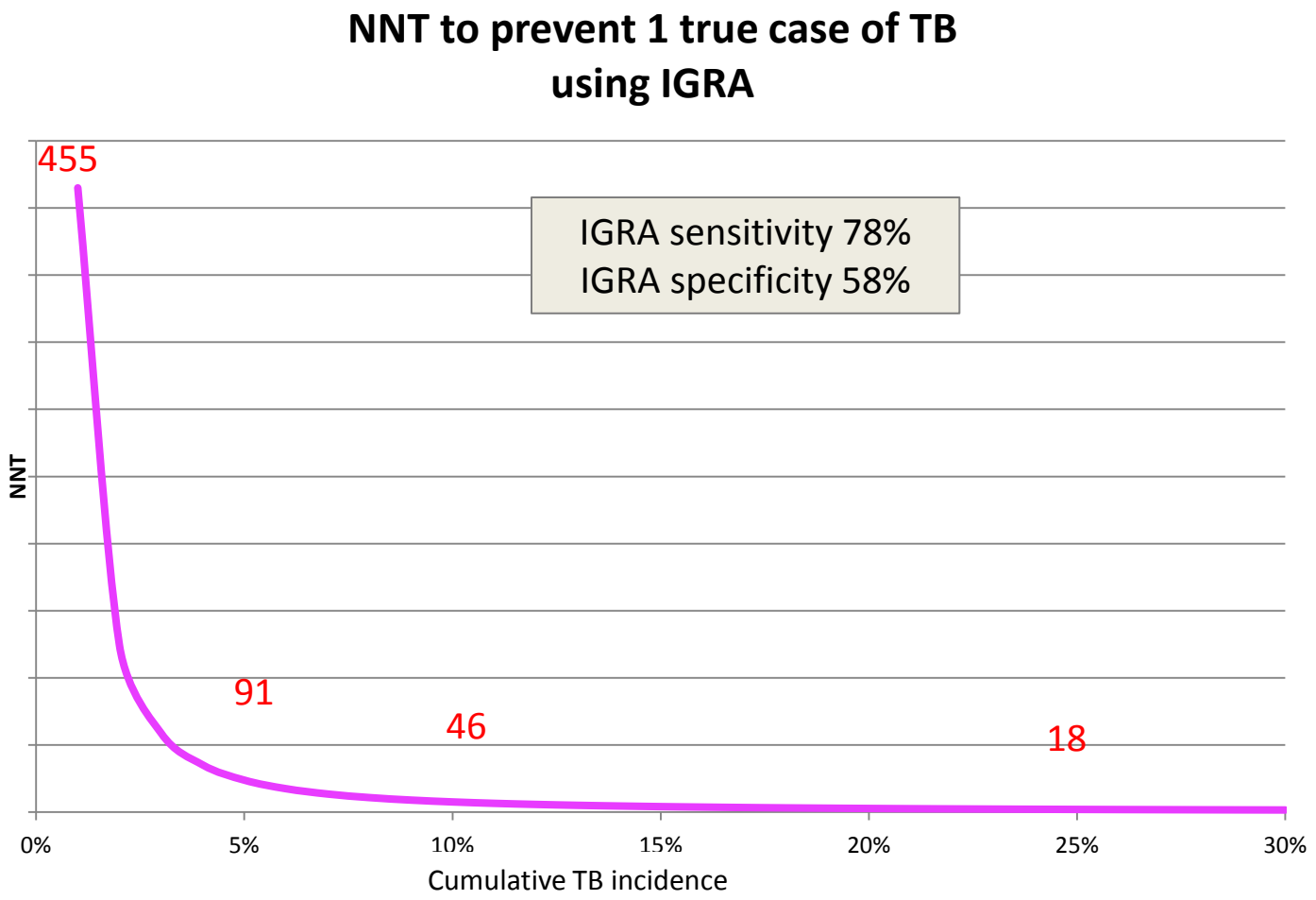
Among persons at high risk of LTBI who are not on tuberculosis preventive therapy, which test(s) alone or in combination with other proxies for LTBI, when positive, *can best identify individuals most at risk of progression*?

⇒ New test has to be better predictor of TB than existing tests

Questions:

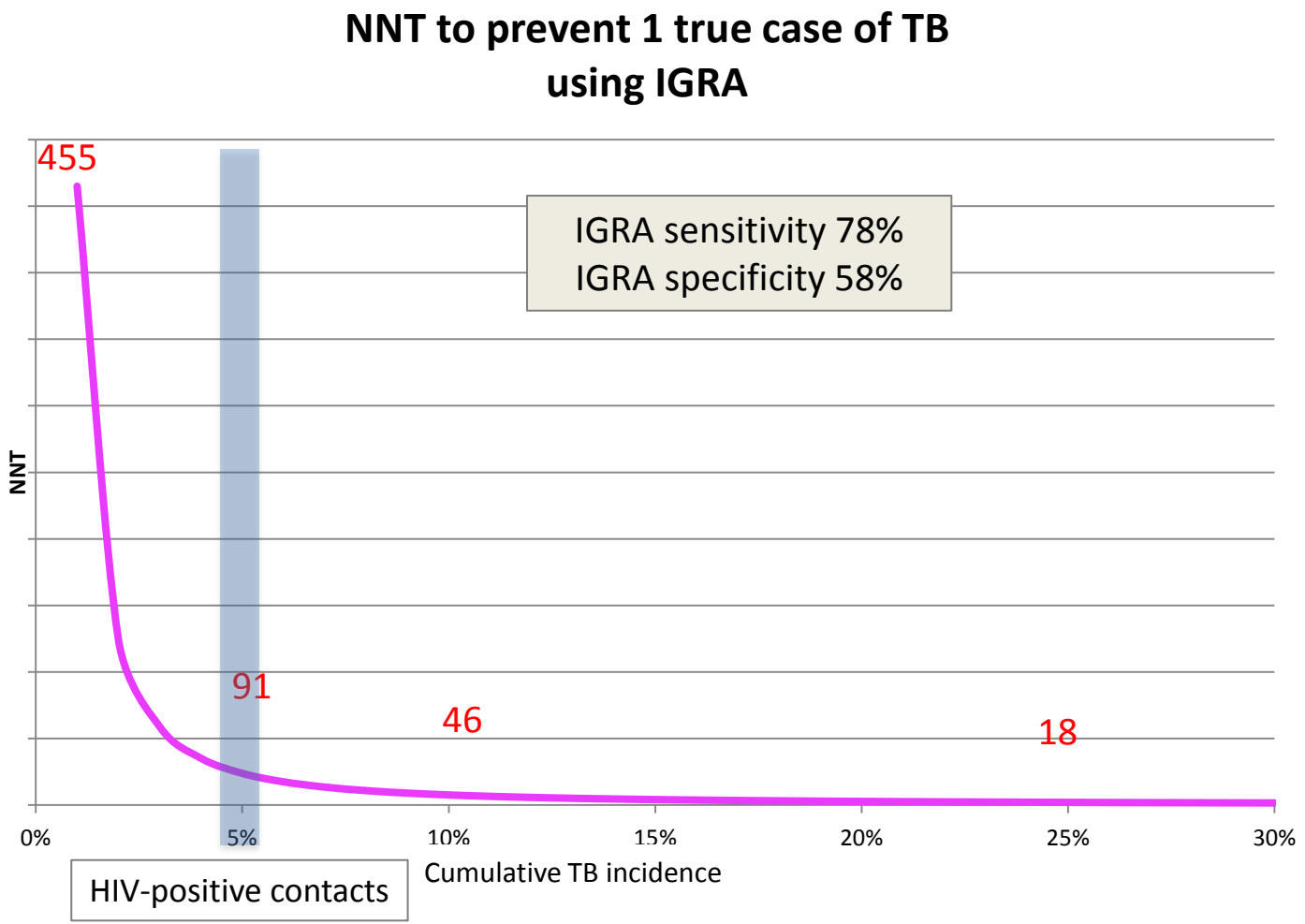
- Why is better prediction important?
- what does "better prediction" mean?

Number needed to treat



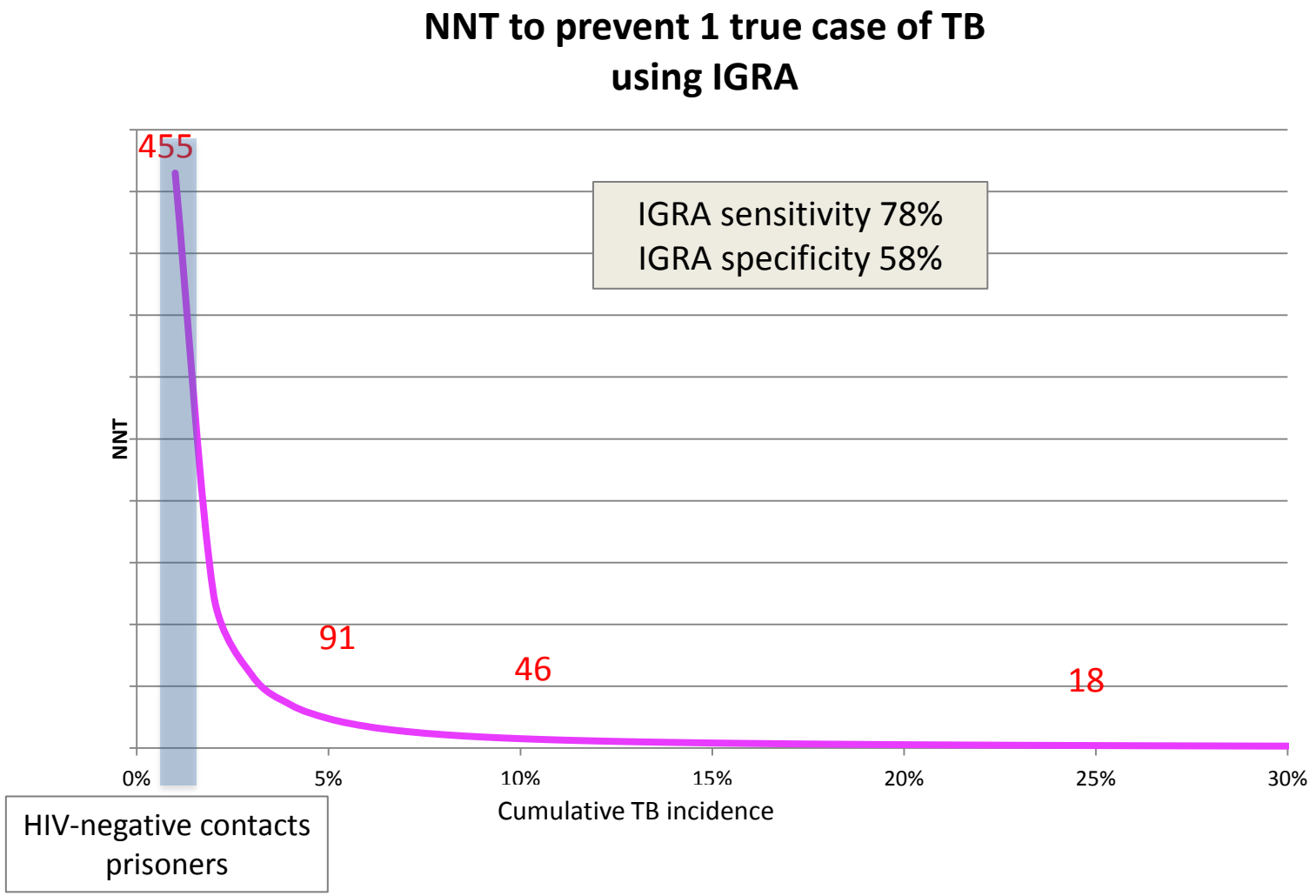
Kik & Cobelens, in prep

Number needed to treat



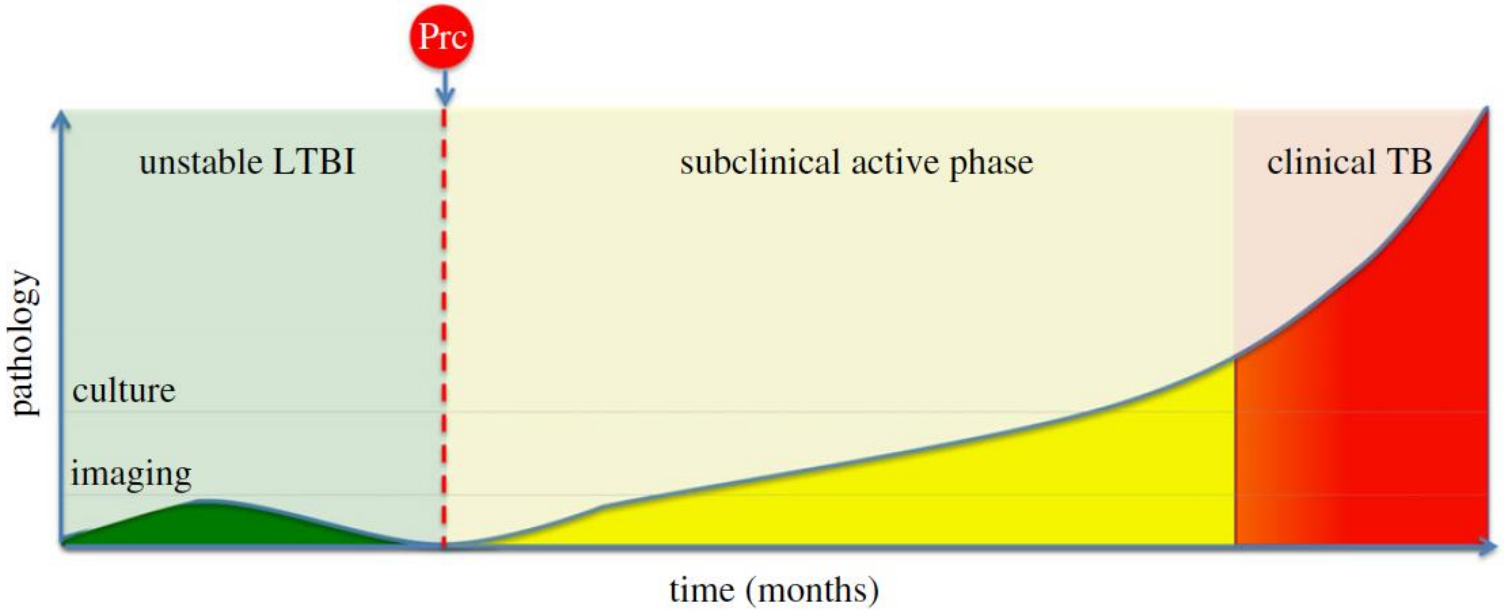
Kik & Cobelens, in prep

Number needed to treat



Kik & Cobelens, in prep

What does better prediction mean?



Esmail et al. Phil Trans Roy Soc 2015

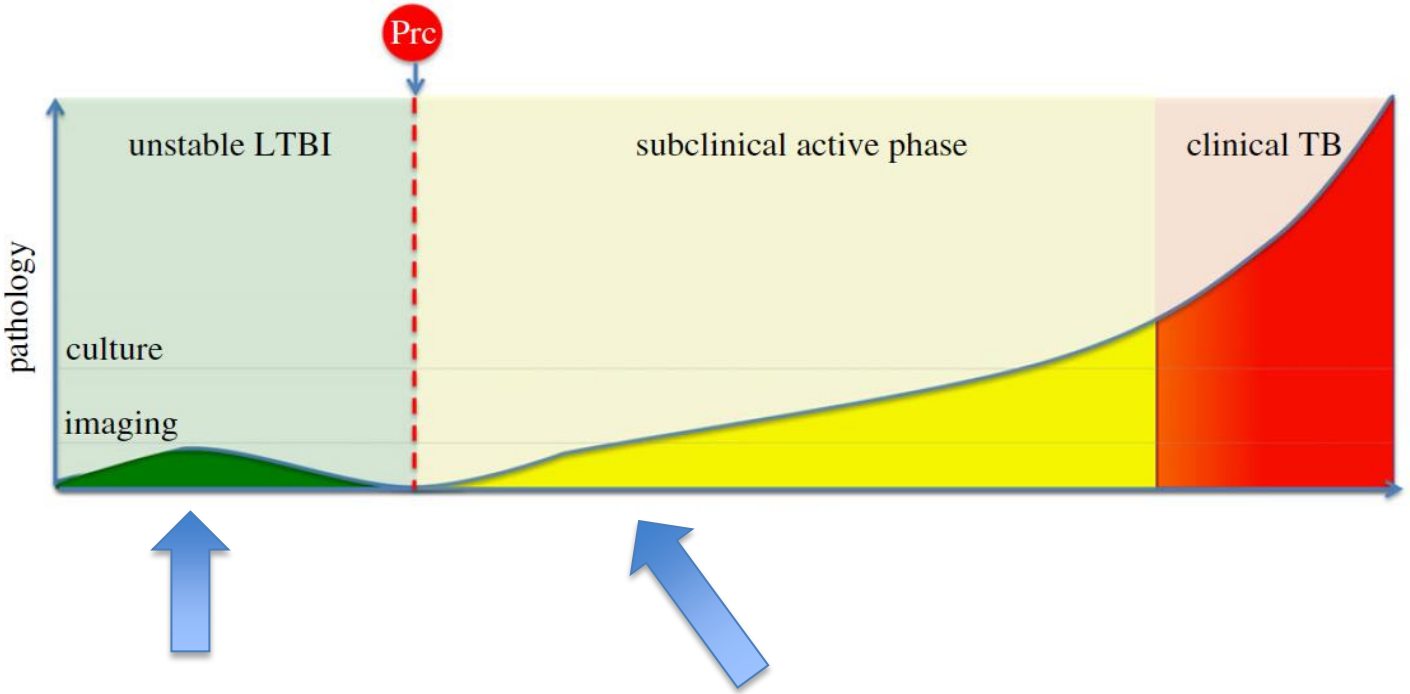
Can we at all predict disease?

We do not know what precipitates TB disease in a latently infected individual

– therefore *beyond existing risk classification* we cannot predict who will and who will not become diseased (i.e. it's a stochastic event)

What does the test measure?

Conceptually, the test either…

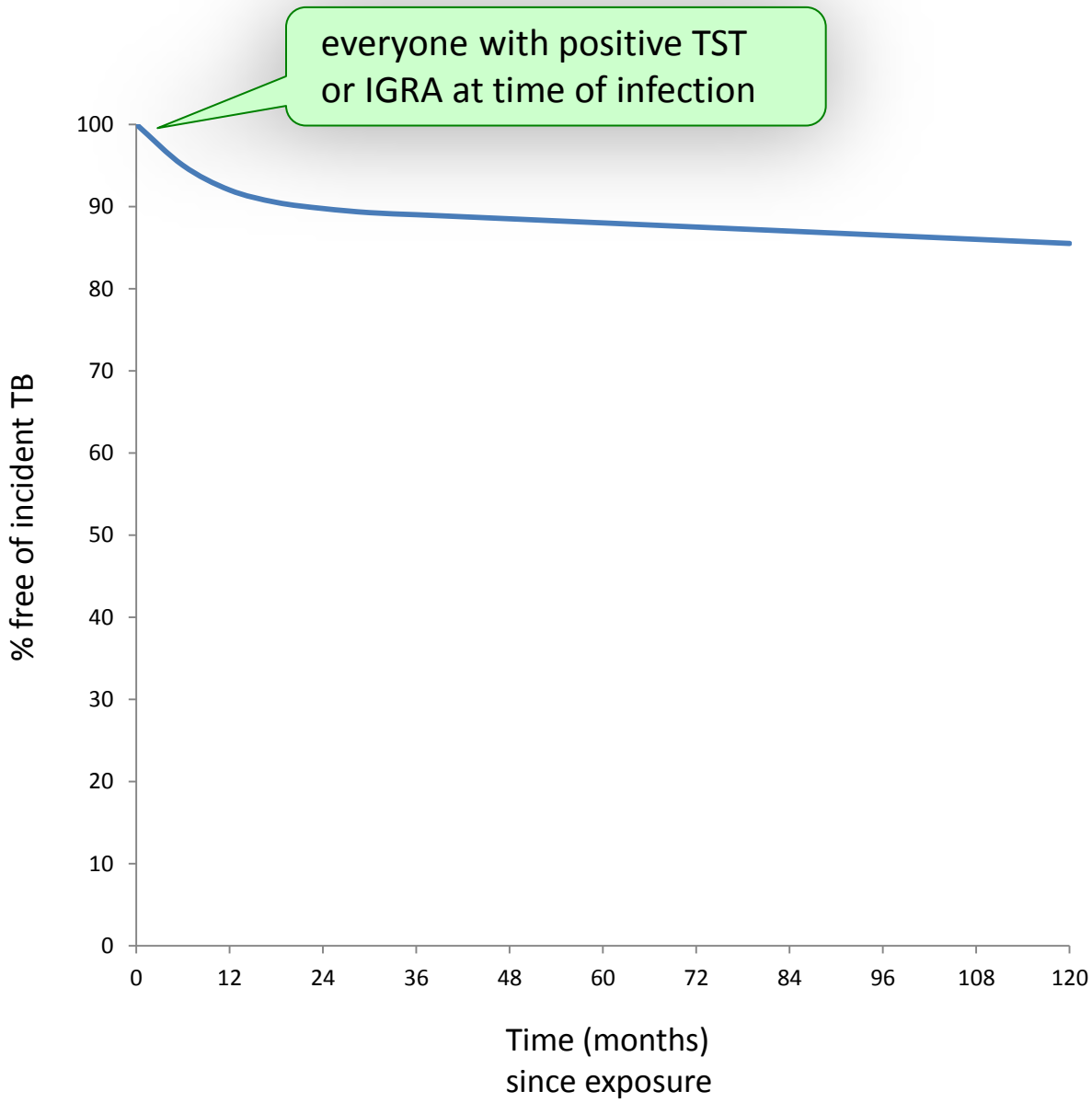


… predicts that disease cannot happen *because there is no persistent infection*

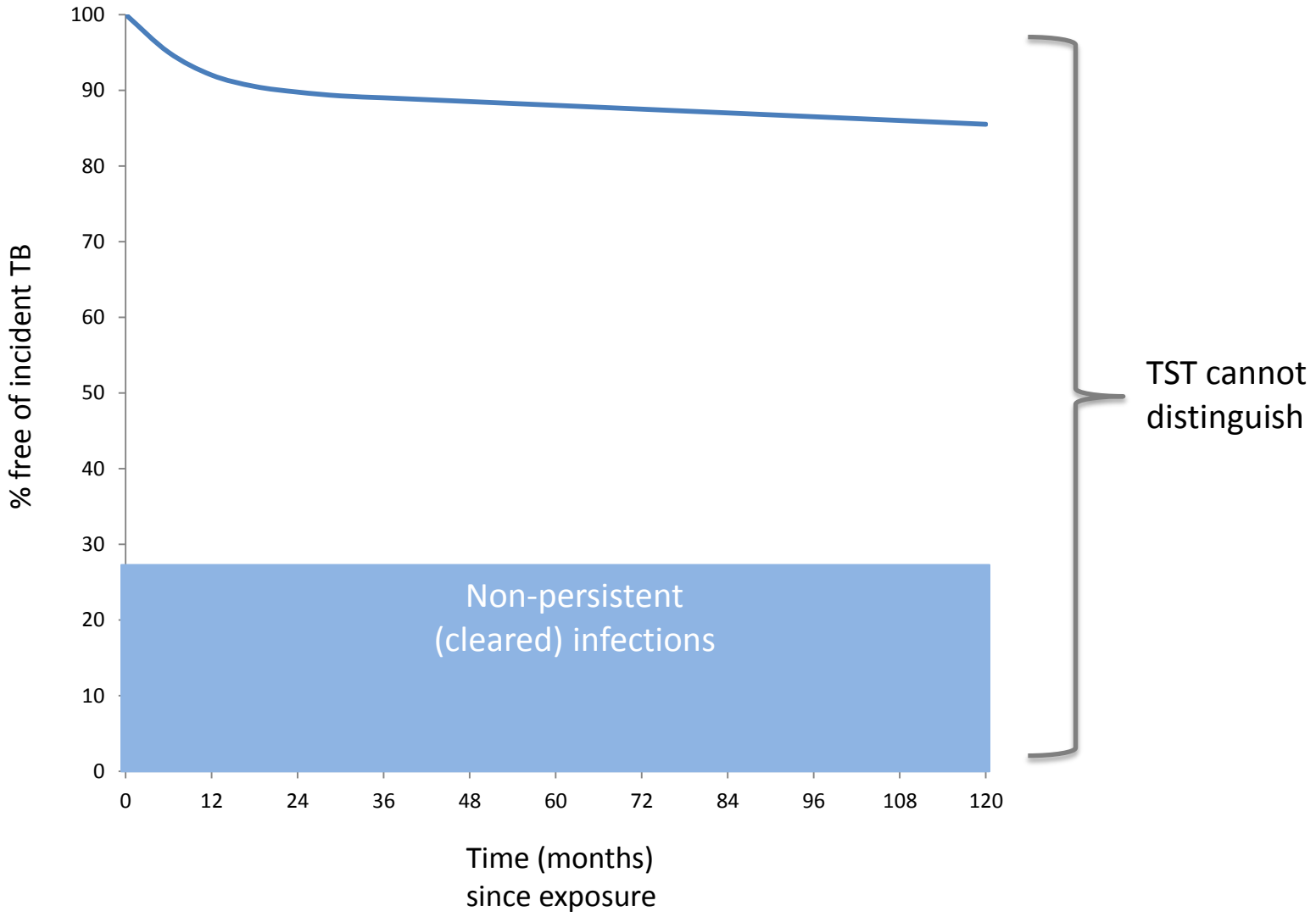
“persistent infection test”

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

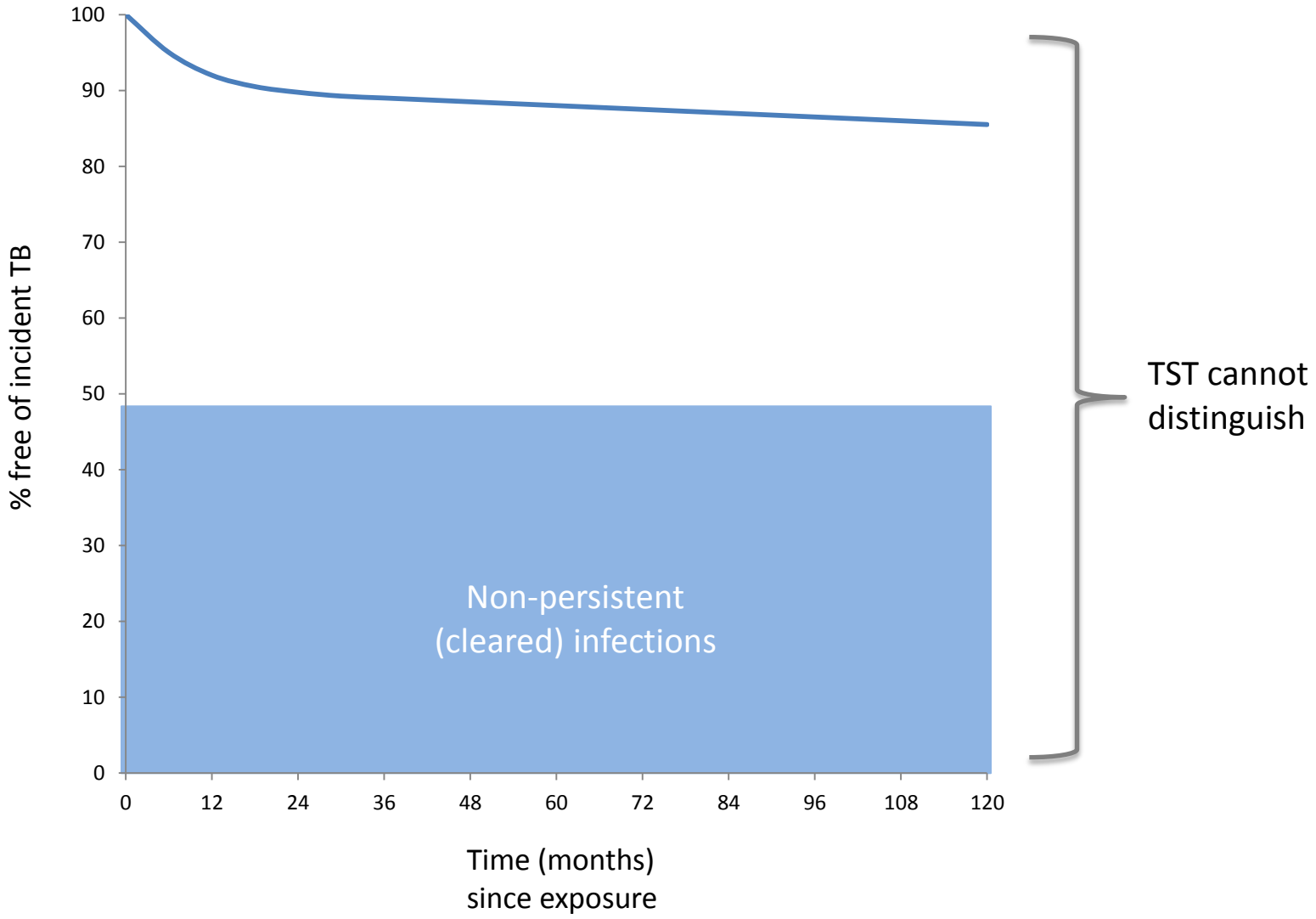
“incipient TB test”


everyone with positive TST
or IGRA at time of infection
100
90
80
70
60
50
40
30
20
10
0
% free of incident TB
0
12
24
36
48
60
72
84
96
108
120
Time (months)
since exposure

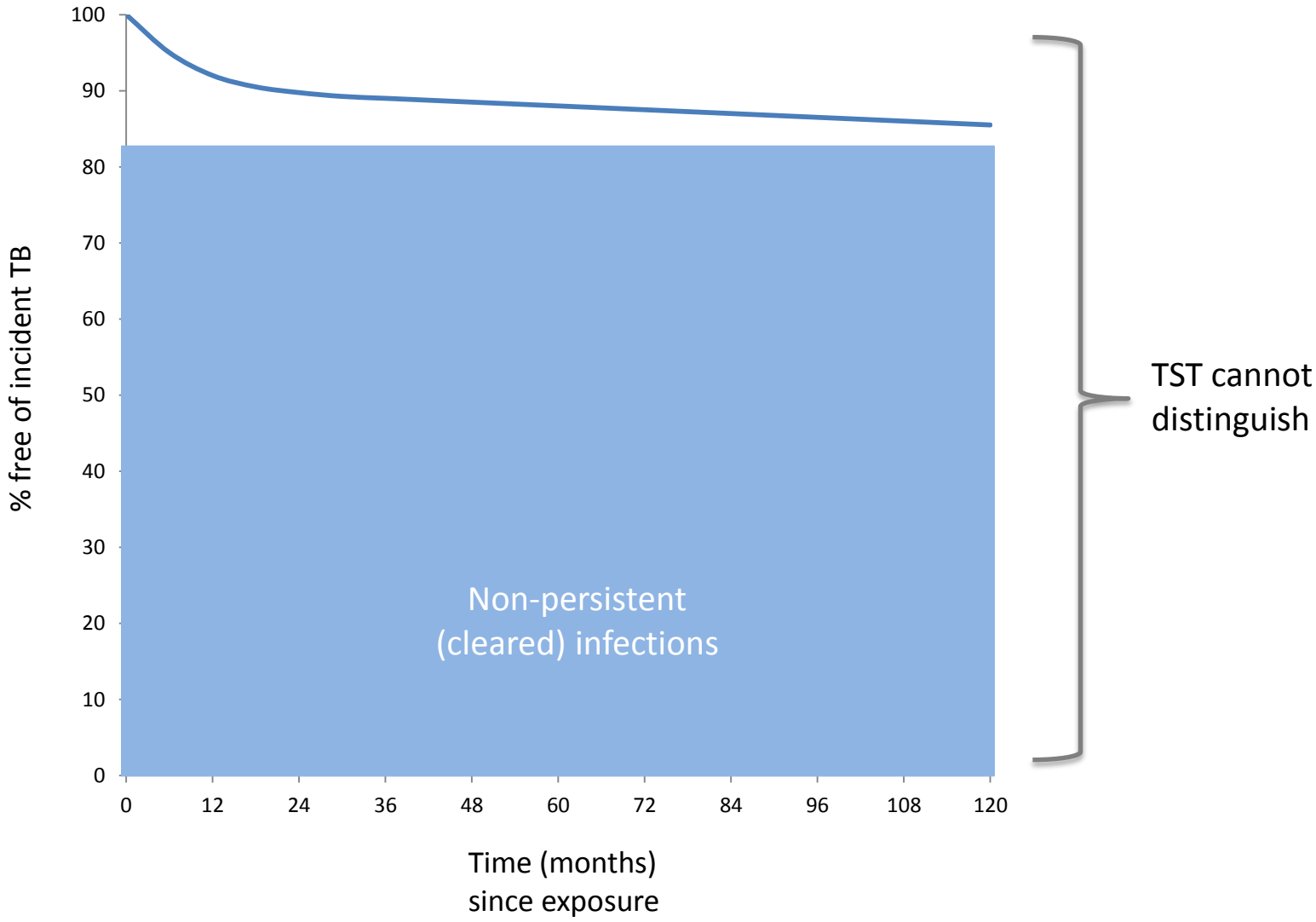
Test for persistent infection



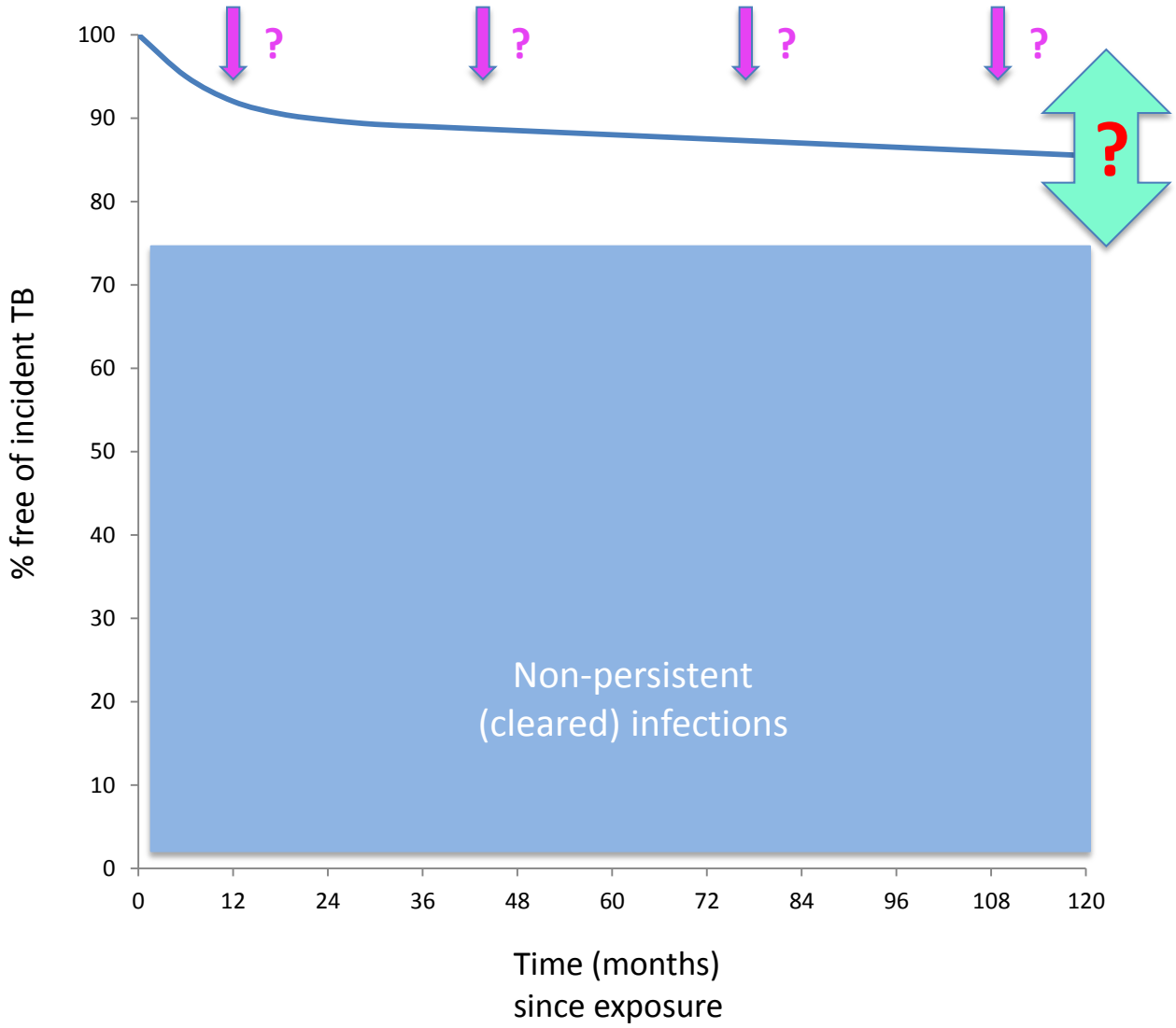
Test for persistent infection



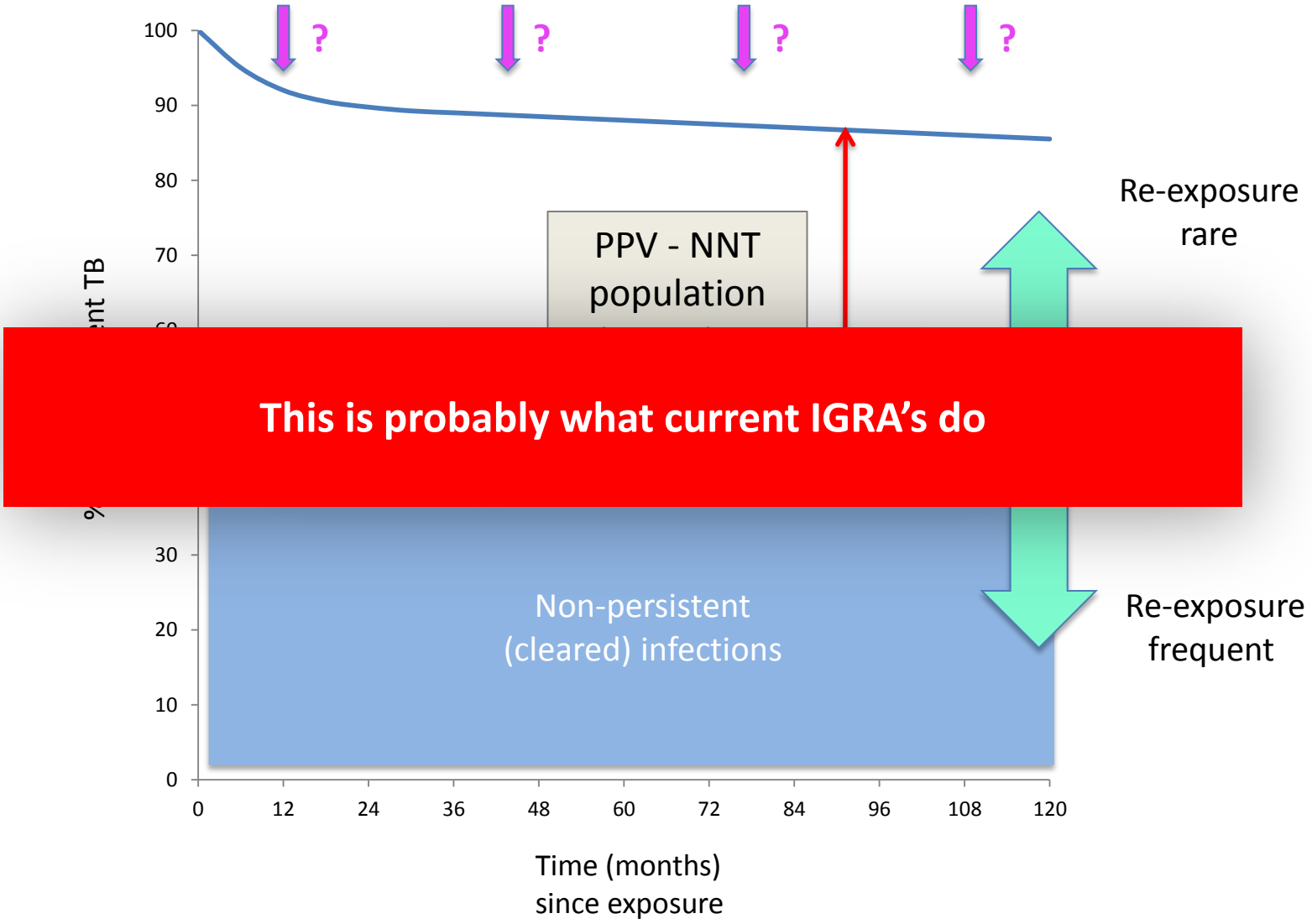
Test for persistent infection



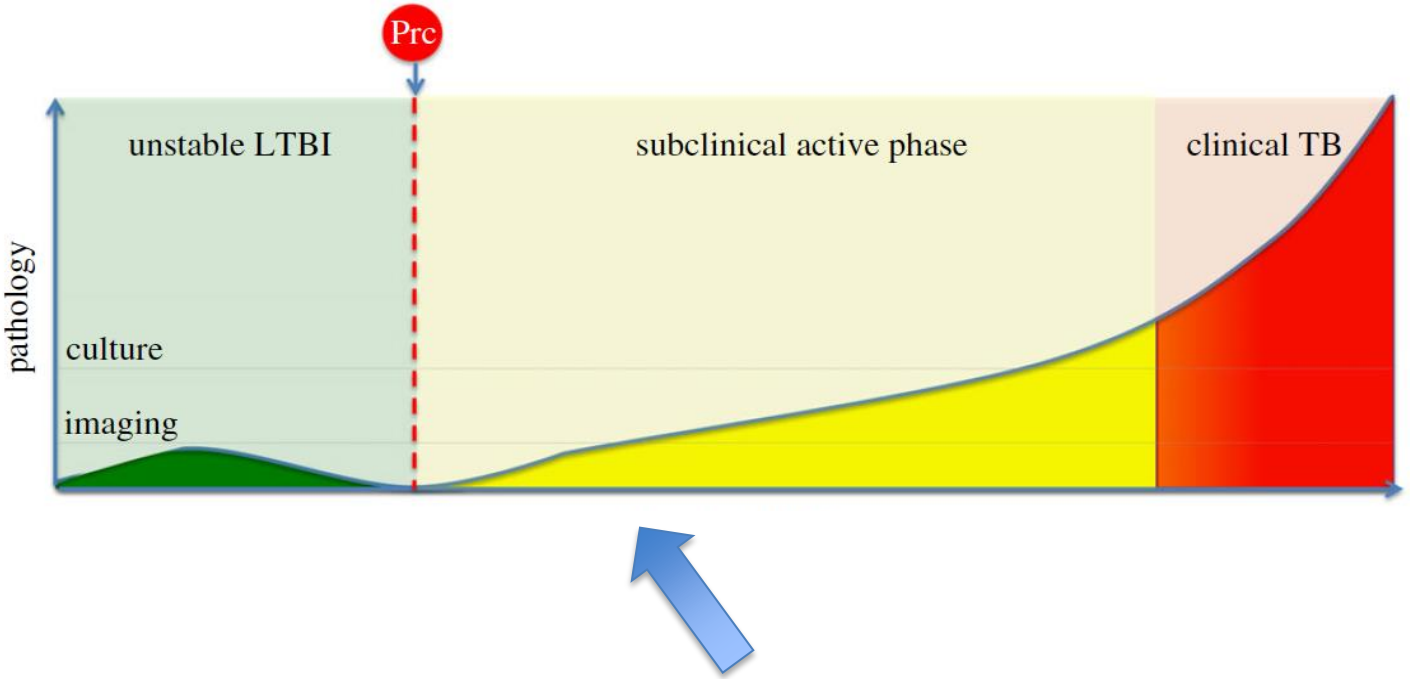
Test for persistent infection



Test for persistent infection



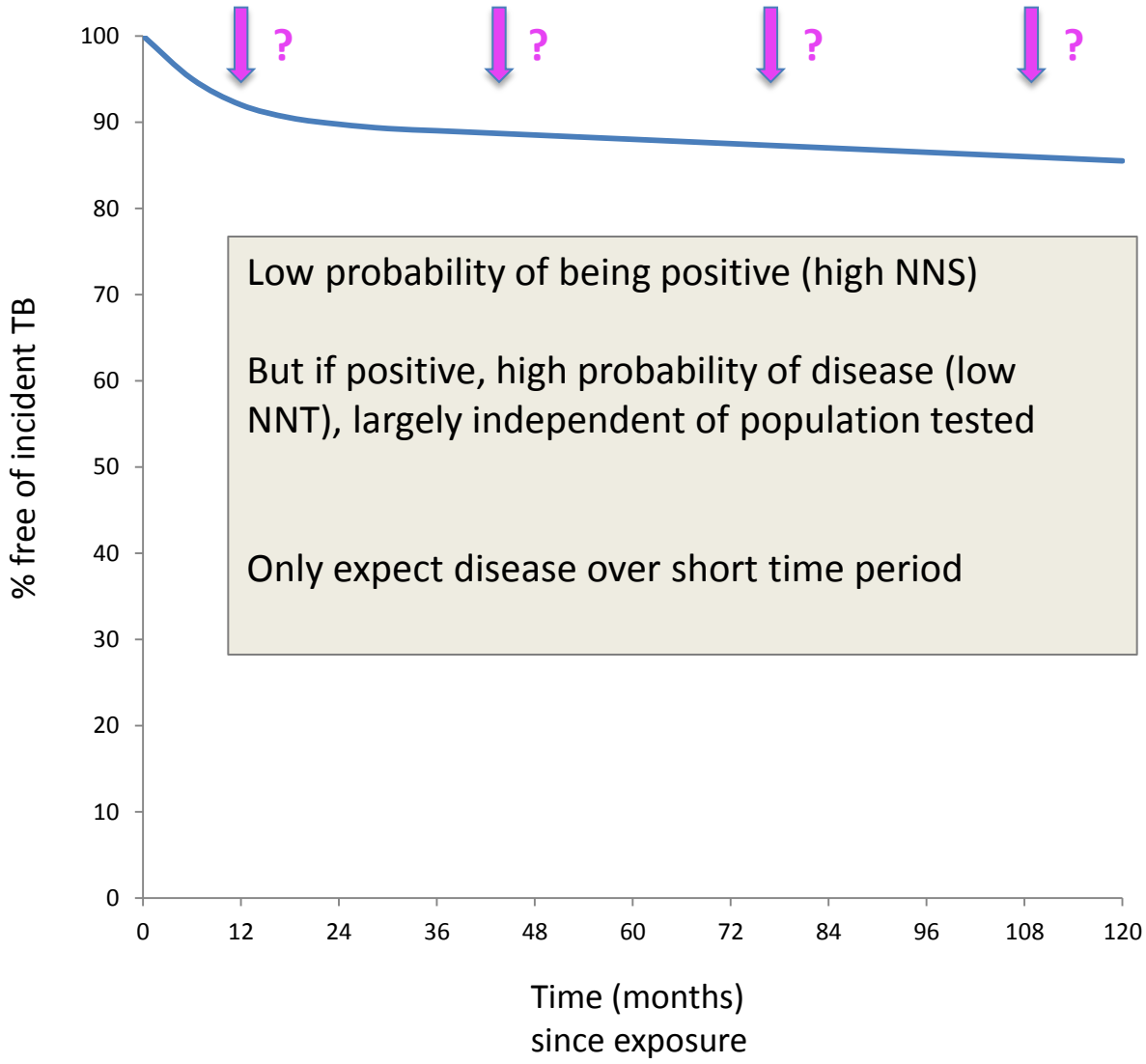
So we need a test that predicts that…



… disease occurs *because it has already started….*

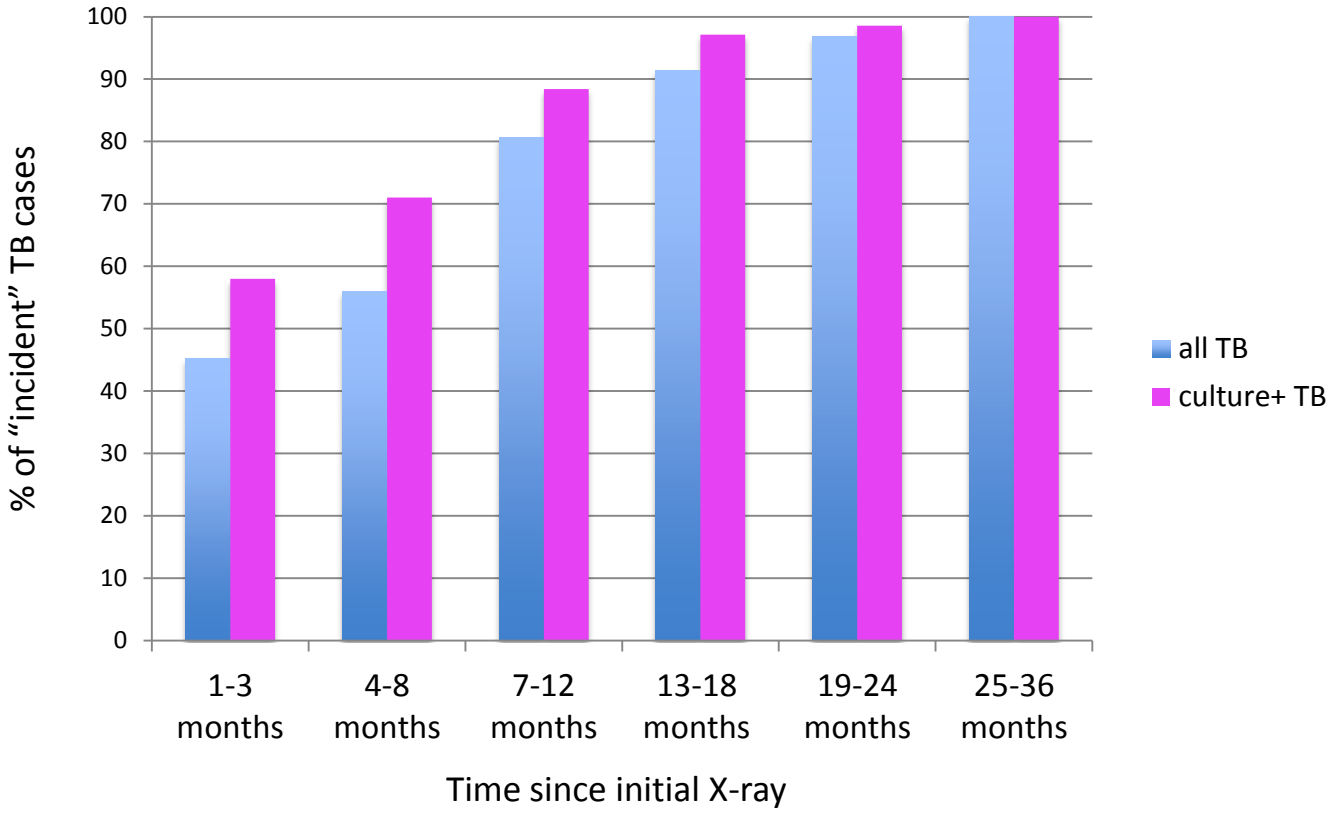
“incipient TB test”

Test for incipient TB



Incipient TB: required length of follow-up

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

A few consequences (1)

For targeting preventive treatment we are not interested in latent TB infection as such, but in predicting disease

→ WHO endorsement must be ultimately based on **prediction of disease**

Some designs used in evaluation of IGRA will be non-informative:

- studies comparing test results with that of IGRA or TST as 'reference' standard (beyond very early stages of test evaluation – candidate selection)
- studies that analyze test results along a M.tb exposure gradient

A few consequences (2)

The new test may identify the same absolute number of persons who develop TB disease as TST or IGRA but with much higher PPV (= **lower number-needed-to-treat**)

→ Comparative studies cannot just have effectiveness endpoints but must also have **cost-benefit endpoints**

Should this be required for WHO endorsement?

Evaluation phases

1. Analytical evaluation:

evaluation of different subsets of well characterized (banked) samples

2. Clinical evaluation:

evaluate the test in the intended target population

in a controlled setting with high quality standards

(compare the results of the new test against a reference standard)

3. Evaluation for (public) health impact:

evaluate the test under routine conditions

for impact on patient-important or health system-important outcomes

(comparison against a reference standard not necessary)

Also important: reproducibility, conversion/reversions, field robustness, feasibility, accepatbility etc. But I will not address them here

1. Analytical evaluation

Key questions:

1. Is the test **positive** in persons with **active TB**? (at beginning of therapy)
2. Is the test **negative** in persons **never exposed** to M.tb?

3. Is the test **positive** in persons who **develop active TB** over 18-24 months?
4. Is the test **negative** in persons who remain **without active TB** over same period?

Design:

Analysis of well-characterized banked specimens

Limitations:

- Various, but this phase is primarily meant to select promising candidate assays for further development and evaluation

2. Clinical evaluation

Key questions:

1. Is the test **positive** in persons who **develop active TB** over 18-24 months?
2. Is the test **negative** in persons who remain **without active TB** oversame period?

Design:

Follow-up studies of persons at high risk of developing TB

Various sub-populations, including people living with HIV, people with diabetes, malnutrition, children, elderly

Options:

1. Cohort designs
2. Nested case-control designs
3. Case-base (case-cohort) designs

Cohort designs

Follow tested individuals actively over up to 24 months

Active ascertainment of incident TB, stratified by test result

Requirements:

Minimal cohort attrition

- Will be related to length of follow-up

Blinded TB case ascertainment with regard to test result

Re-infection rate should not be very high

- Re-infection reduces relative risk if occurred randomly

Cohort designs - issues

Large sample size needed

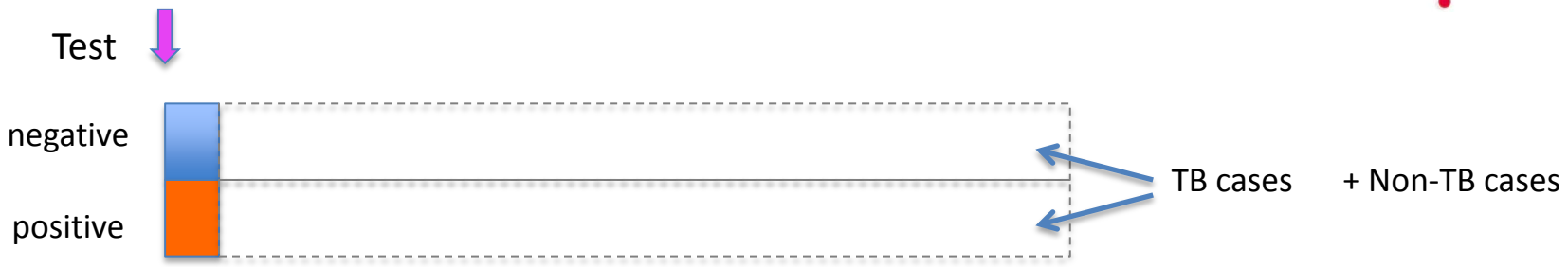
- depends on expected TB incidence and length of follow-up
  → identify high risk study populations

Follow-up for relapse after TB treatment as a cohort design model

TB ascertainment should be culture-confirmed

- leads to unbiased relative risk, but increases sample size

Nested case-control design



Follow tested individuals passively over defined period (passive cohort)

Passive ascertainment of incident TB

Test status among incident TB cases compared to that of random subset of non-TB cases

Allows for larger sample sizes

Requirements:

Probability of being included as a TB case should be independent of test result

Blinded TB case ascertainment with regard to test result

Re-infection rate should not be very high

Case-control designs - issues

Some TB cases will be missed

- the cases in the analysis are assumed to be a random subset of all cases accrued in the cohort --> potential for selection bias

Record linkage may lead to misclassification

TB ascertainment should be culture-confirmed

- may be more difficult with passive follow-up

Do not test all at t=0 but store specimens only

2. Evaluation of health impact

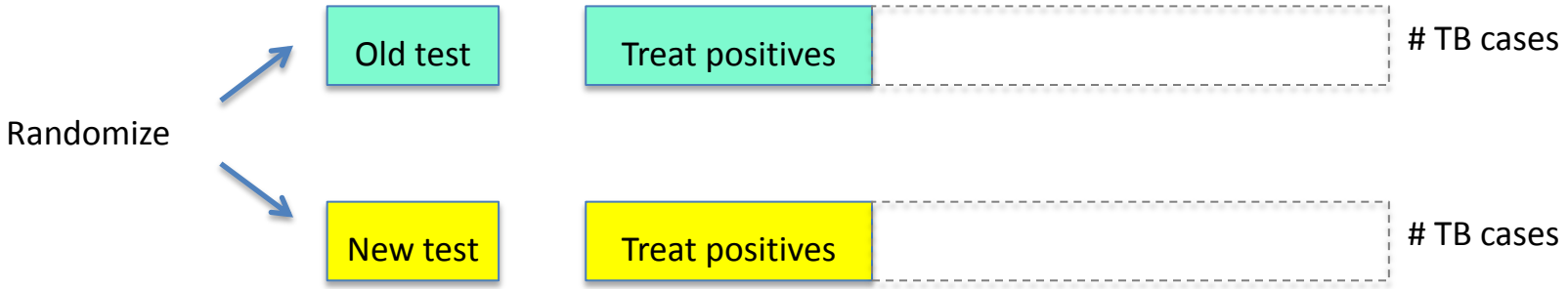
Key questions:

1. Does the test when used in routine settings **improve health outcomes**?
2. Does the test when used in routine settings **improve cost-effectiveness**?

Design:

Comparative designs, ideally randomized trial (individual/group)

Comparative designs (trials)



In each arm follow individuals actively over time (treated + non-treated)

Active ascertainment of incident TB, stratified by arm

Determine:

- Incidence ratio and difference for TB
- Incidence ratio and difference for adverse events from preventive treatment
- Difference in number-needed-to-treat
- Cost-effectiveness

Conclusions

What we're looking for is a test for incipient TB

This requires a different evaluation approach than used for IGRA thus far

Endorsement should ultimately be based on predictive power (of incident TB)

→ follow-up studies

Cohort studies with relatively short follow-up are needed for clinical evaluation

Nested case-control studies may be useful alternative

Randomized trials are ideally done to show impact on patient/health system-important outcomes

For such trails, number-needed-to-treat, adverse events and cost-effectiveness are important endpoints

Thank you