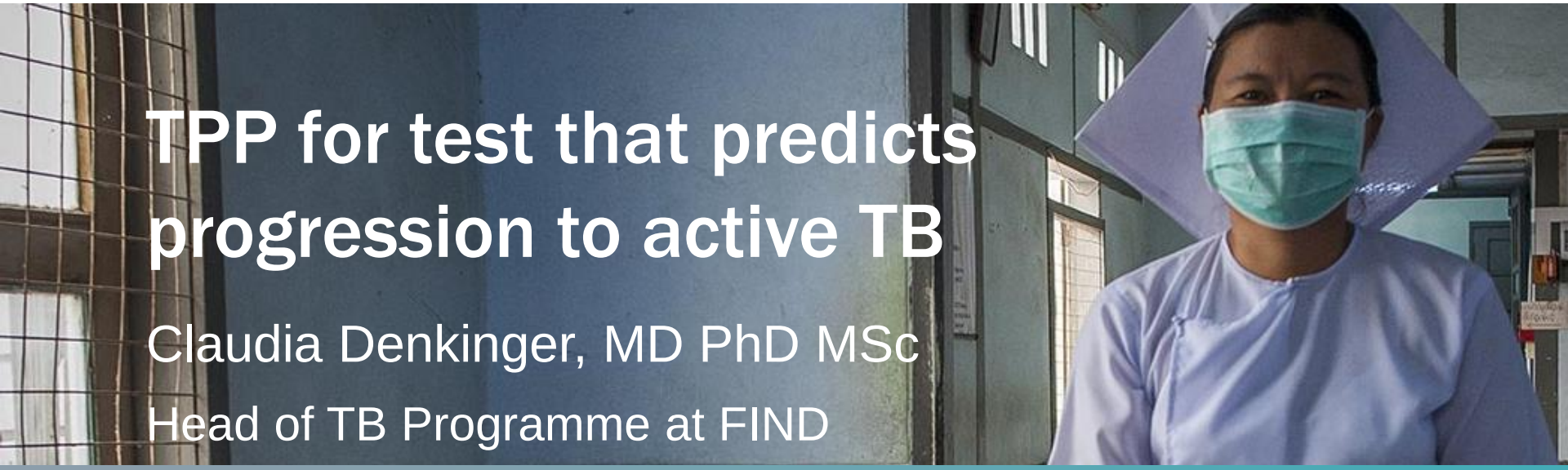
FIND

Because diagnosis matters



TPP for test that predicts progression to active TB

Claudia Denkinger, MD PhD MSc

Head of TB Programme at FIND

3rd December 2015, Union Meeting Cape Town

Target Product Profiles

Stop TB Partnership
New Diagnostics Working Group

- Prioritized TPPs:
  - Point-of-care, non-sputum based test
  - Point-of-care triage test
  - Point-of-care sputum based test for microscopy replacement
  - Point-of-care DST -microscopy center
- Iterative process with input from many stakeholders
- WHO Consensus Meeting
  - Delphi process leading up to the meeting
  - > 75% agreement amongst stakeholders

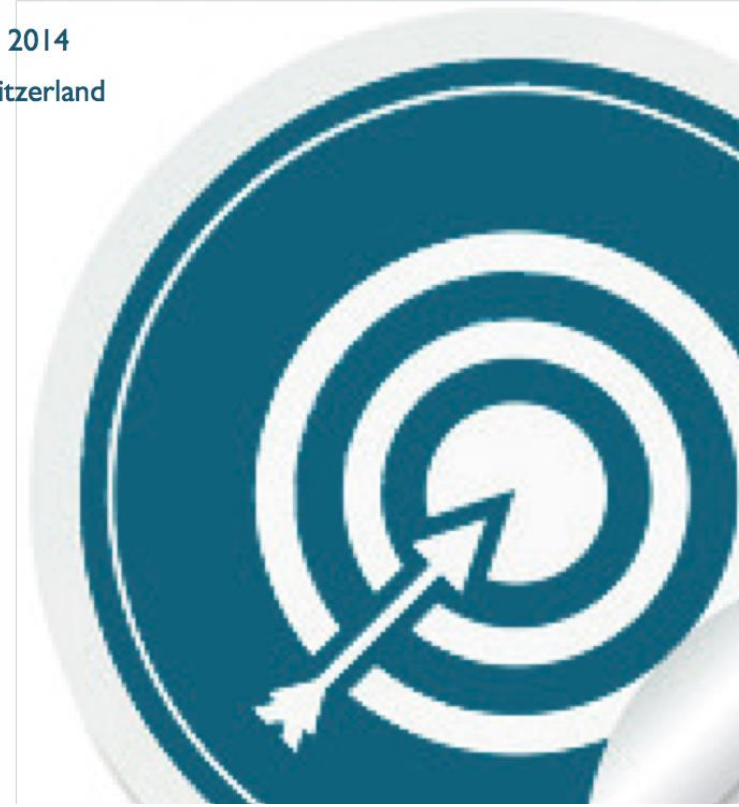
Meeting Report

High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting

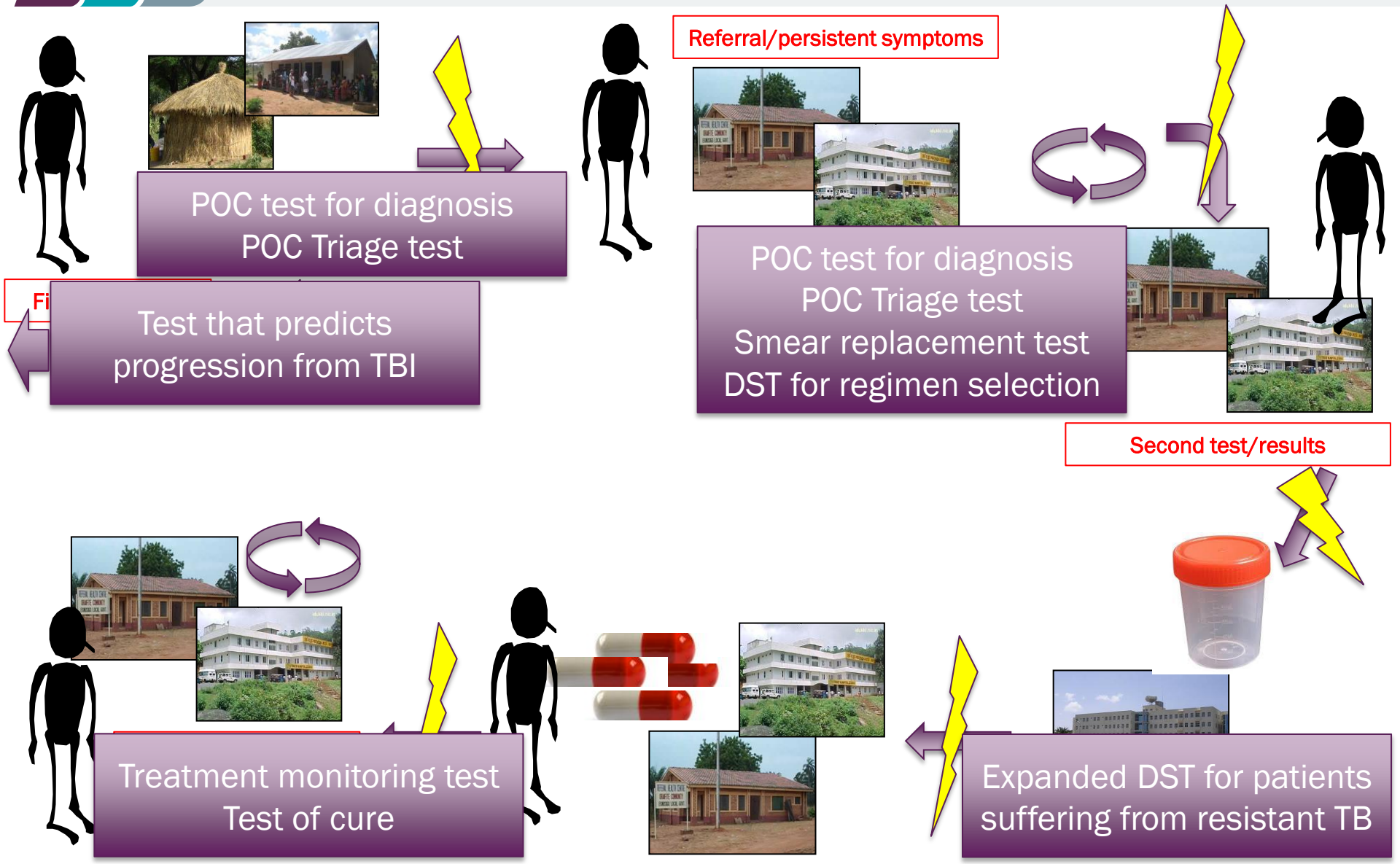
http://apps.who.int/iris/bitstream/10665/135617/1/WHO_HTM_TB_2014.18_eng.pdf?ua=1

28–29 April 2014

Geneva, Switzerland



Diagnostic cascade – the patient perspective



Process for TPP development

Step 1
- Drafted TPP by FIND and reviewed with experts

Step 2
- Meeting May 2015 with experts organized by NDWG, WHO and FIND > revised document

Step 3
- Survey with a larger stakeholder group also leveraging the WHO LTBI taskforce

Step 4
- Final review in stakeholder meeting prior to finalization

Tests we have available

- IGRAs, skin tests (TST, C-Tb, Diaskintest)
- Available data suggest that the majority (>95%) of those with a positive IGRA or TST result (one time testing) will never develop TB (IRR of ~2 over TST or IGRA negative patients)
- Lack the capacity to differentiate between recent and remote infection
- Not useful in monitoring response or cure with preventive therapy for LTBI

What are we looking for in LTBI tests?

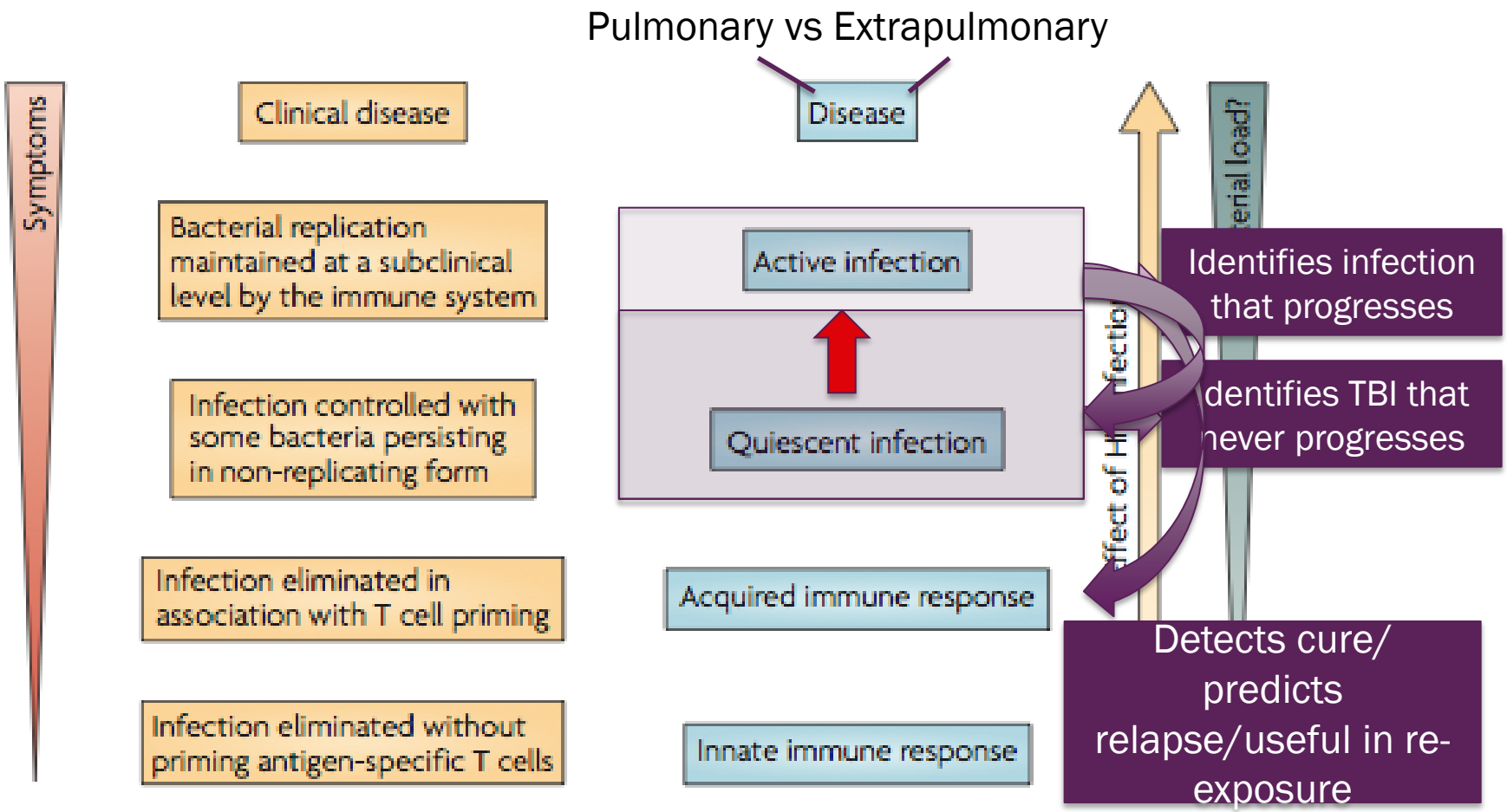
Individual patient diagnosis

- A test that diagnosis infection with better predictive value of who will progress to active disease (but differentiates from active TB)
- A test of cure that allows to say who received sufficient therapy/ predicts relapse at the end of therapy
- A test that is able to detect re-exposure after treatment was taken

Epidemiology/ Research

- A test for surveillance of who is infected and can inform burden of disease in the absence of therapy
- Identify recent transmission

Test for TB infection



Barry Nature Reviews 2009

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- A test for surveillance of who is infected and can inform burden of disease in the absence of therapy
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Definitions – clinical and research

TB infection:

- Any person with a positive test for TB infection (TST≥5mm, positive IGRA according to manufacturer's instructions)
- Without microbiological, radiological, or clinical evidence of active TB.

Subclinical TB disease (for research purposes)

- Asymptomatic patients with evidence of TB on radiographic and/or microbiological examination or with development of TB within 2 months of initial evaluation.
- Two forms of subclinical TB are conceivable:
  - disease is early and still contained (mostly immunocompetent patients) or
  - disease is early but not contained however the patient is unable to mount an inflammatory response that would result in symptoms (mainly immunocompromised patients).
- A subset of patients with subclinical disease (primarily immunocompetent patients) will not progress to active disease.

TB disease:

- Symptomatic patients
- With compatible clinical and/or radiology and/or histology for TB and a positive microbiological test and started TB treatment (confirmed TB),
- or with compatible clinical and/or radiology and/or histology for TB and started TB treatment (clinical TB).

Definitions – clinical and research

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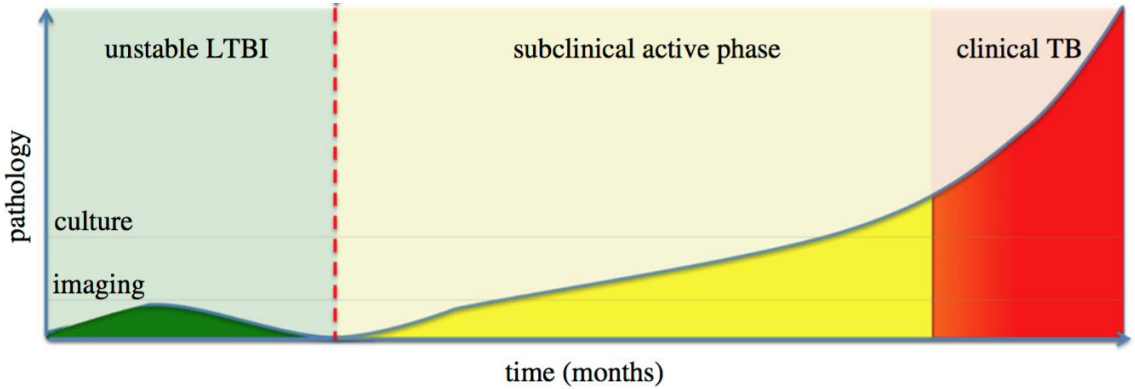
TB diseas

- Symptoma
- With comp started TB
- or with co TB).



biological test and

atment (clinical

Esmail 2014

Scope of the test

Who do we want to test?

- People at risk of TBI and at risk for progression
- People where active TB has been ruled out

Use cases:

- High-prevalence settings in patients with high risk of progression to active TB (e.g. HIV, recent exposure)
- Low-medium prevalence settings aiming for elimination

Do we need a point-of-care test?

- No immediate clinical decision necessary

Scope of Test

Characteristic	Optimal	Minimal
Goal of test/ Intended use	Biomarker-based test that can be used to **predict risk of progression** to active TB from TB infection (TBI) within the next 2 years, with the ability to **rule out active TB**. Ideally the test result should **decrease or revert to negative** with treatment and thus allow an assessment of treatment success or cure and consequentially also reinfection.	Biomarker-based test that can be used to predict risk of progression to active TB from TB infection within the next 2 years. As this test may also be positive in patients with active TB, identification of these individuals needs to be done by a highly sensitive test
Target user of the test	Health care workers with no or minimal laboratory training e.g. nurses	Health care workers with laboratory training e.g. skilled laboratory technicians
Setting	Health post	Referral facilities with some laboratory facilities

Diagnostic performance – How good is good enough?

Characteristic	Optimal	Minimal
Diagnostic sensitivity for progression to active TB	≥90% sensitivity	≥75% sensitivity
Diagnostic specificity for risk of progression to active TB	≥90% sensitivity	≥75% specificity
Diagnostic specificity for TBI (able to differentiate from active TB)	>97%	NA (expected to be positive in active TB)

2-step approach to determining performance targets

Premise: risk/benefit-profile is key, thus PPV and NNT useful metrics for the determination of performance targets

- PPV captures patient perspective (If test+, how likely am I to have disease?)
- NNT captures clinician/PH perspective (If treating all test+, how many do I need to treat to prevent one case?)

[Of course PPV and NNT are closely linked to one another]

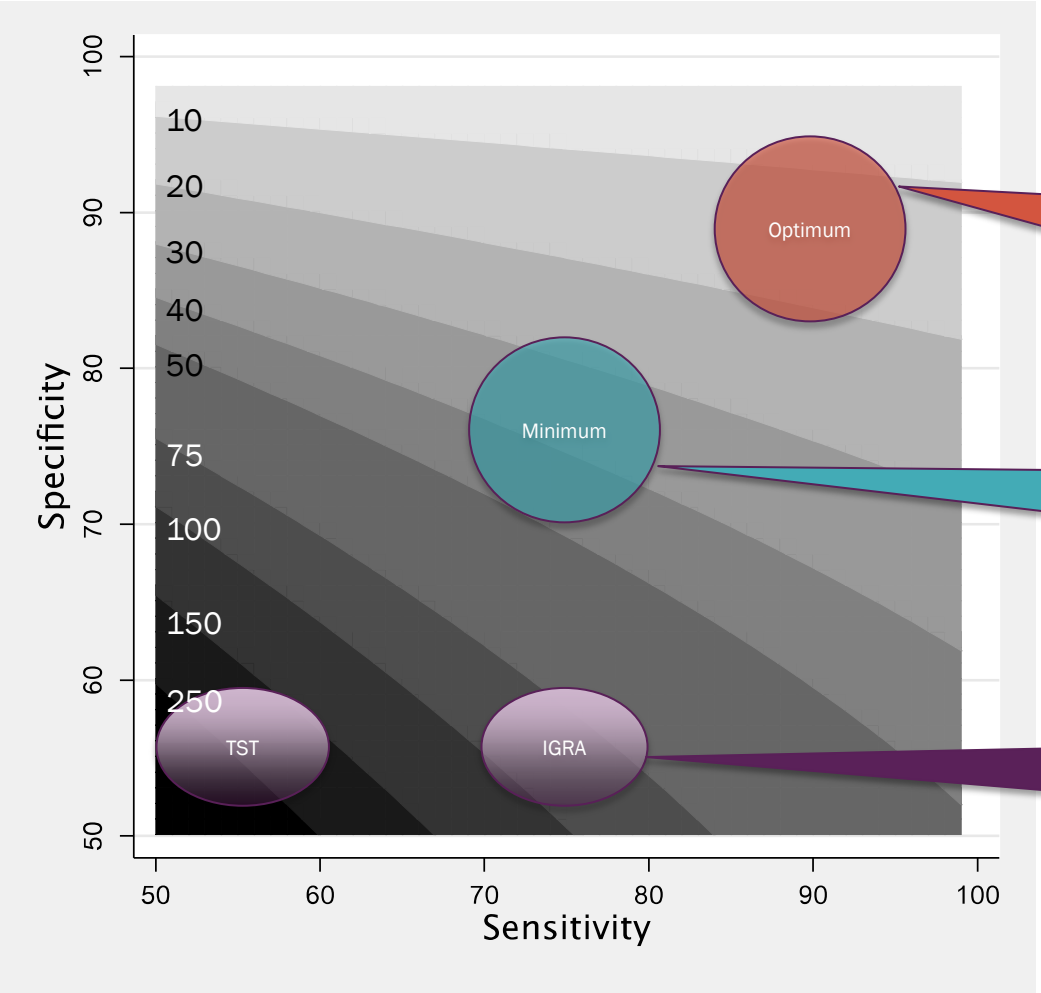
Step 1. Clarify what values of PPV and NNT are currently found acceptable to patients/clinicians/policy makers

- Based on tests and groups for whom IPT is currently recommended by WHO
- Estimate PPV/NNT in those groups

Step 2. Assess what combinations of sensitivity/specificity are compatible with acceptable values of PPV and NNT

- Look at contours of PPV/NNT across combinations of Se/Sp
- Investigate differences between key subgroups

‘Number Needed to Treat’ according to Sens/Spec for risk of progression



Optimum
- NNT: ~13

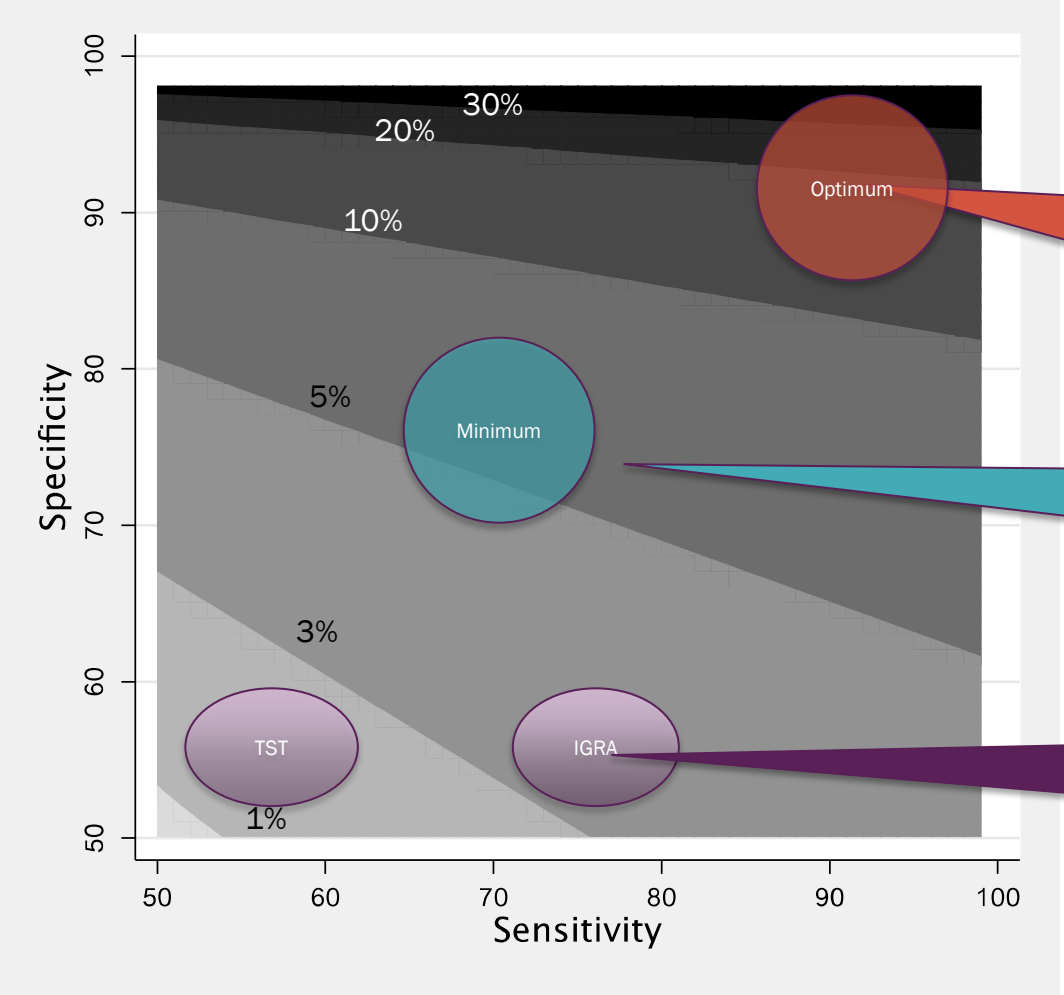
Minimum
- NNT: ~40

TST / IGRA
- NNT: ~250 / ~85

2-year cumulative incidence: 2%
Effectiveness of IPT: 50%

TST/IGRA estimates based on WHO review

‘Positive Predictive Value’ according to Sens/Spec for risk of progression



Optimum
- PPV: ~16%

Minimum
- PPV: ~6%

TST / IGRA
- PPV: ~2% / ~3%

2-year cumulative incidence: 2%
Effectiveness of IPT: 50%

TST/IGRA estimates based on WHO review

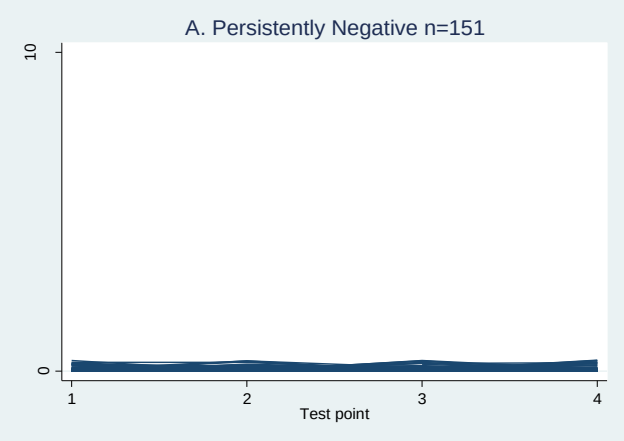
Reproducibility

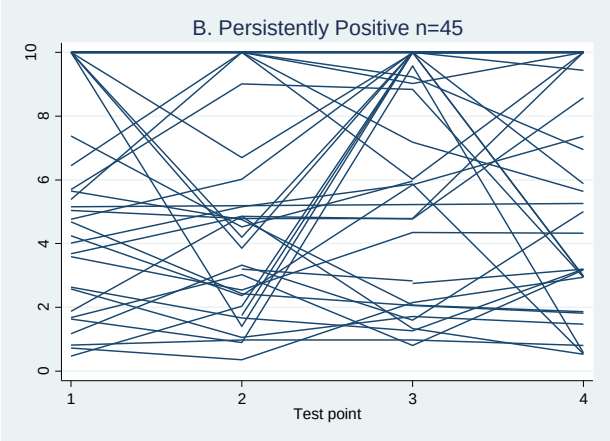
- If quantitative outcomes of a test are measurable
- Reproducibility: Inter-assay CV =< 10.0% at high and low extremes of the assay

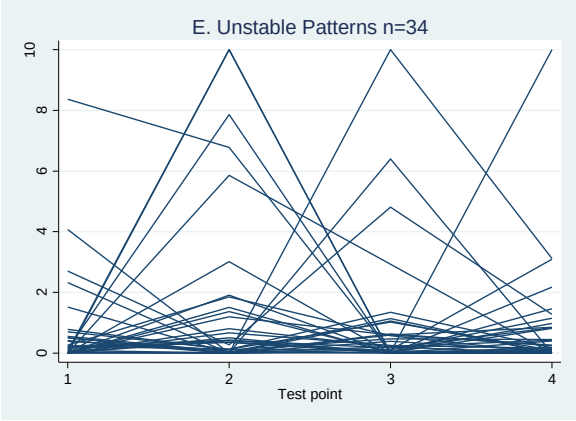
Reproducibility of Interferon Gamma (IFN-γ) Release Assays

A Systematic Review

Saloua Tagmouti[1], Madeline Slater[2], Andrea Benedetti[3,4], Sandra V. Kik[3,4], Niaz Banaei[5], Adithya Cattamanchi[6], John Metcalfe[6], David Dowdy[7], Richard van Zyl Smit[8], Nandini Dendukuri[9], Madhukar Pai[3,4], and Claudia Denkinger[3,10]

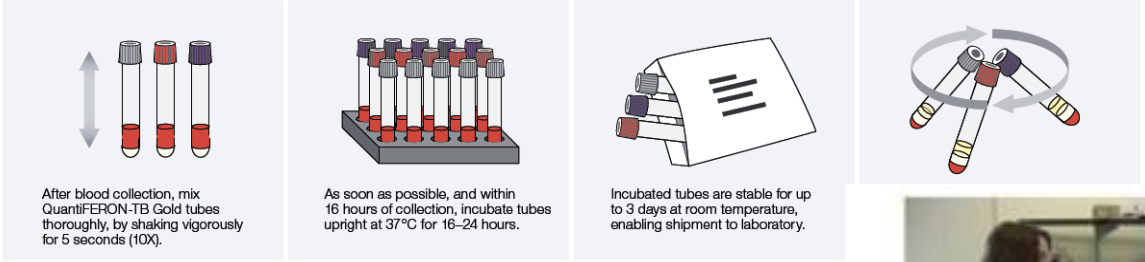




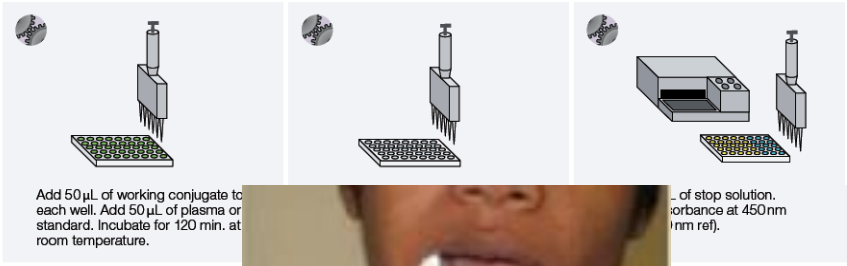


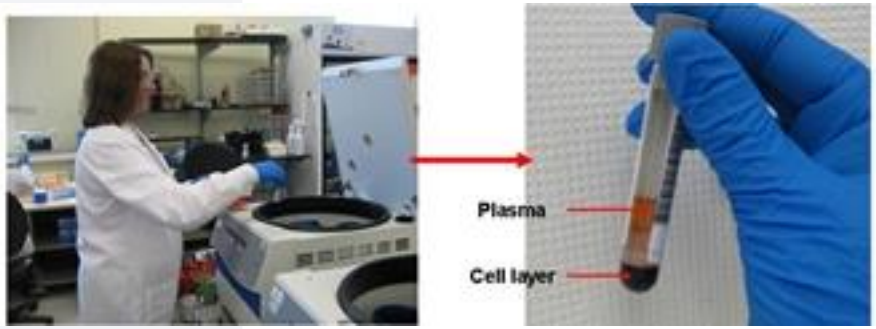
Operational characteristics

Part 1. Blood Incubation



Part 2. Human IFN-γ ELISA





Can we aim for a test with better predictive value in a first step (at the cost of IGRAs currently) and then improve complexity at a later step?

Selected operational characteristics

Characteristic	Optimal	Minimal
No. of steps to be performed by operator	< 2, no timed steps	< 10, 1-2 timed steps
Volume measurements	None	Measuring device provided with kit
Sample preparation	None or fully integrated	Allows for centrifugation/ incubation
Time to results	< 24 hours	2-5 days
Operating Temperature	Between 5 and 50° C, 90% humidity	Between 5 and 30° C, 70% humidity
Reagents	Self-contained within test kit	Up to 2 external reagent, reconstitution not required
Instrumentation	No instrument	Preferably instrument free. If instrument: Small, portable or hand-held instrument (<1kg) that can operate on battery or solar in places with interrupted power supply
Internal Quality control	Included positive control	
Power requirements	Ideally instrument free test; all equipment with rechargeable battery lasting up to 8 hours	110-220 V AC current; UPS for power failures
Electronics and software	None	Integrated
Training	<1 day dedicated training for non-laboratory trained health personnel	3-7 days dedicated training for a laboratory trained health personnel

What can a test cost?

- Considering performance characteristics of the test
- Considering package of test and treat (% completion; success rates of therapy)
- Consider how often a test needs to be performed
- Cost-effectiveness studies: several have demonstrated cost-effectiveness for IGRAs but variable quality and input parameters

How Methodologic Differences Affect Results of Economic Analyses: A Systematic Review of Interferon Gamma Release Assays for the Diagnosis of LTBI

Olivia Oxlade[1], Marcia Pinto[2], Anete Trajman[3], Dick Menzies[4]*

1 Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America, **2** Department of Research, Fernandes Figueira Institute, FIOCRUZ, Rio de Janeiro, Brazil, **3** Gama Filho University, Rio de Janeiro, Brazil and McGill University, Montreal, Canada, **4** Respiratory Epidemiology & Clinical Research Unit, Montreal Chest Institute, McGill University, Montreal, Canada

- Affordability considering priority setting in countries

thank you/merci/danke/gracias/obrigado

Thank you to:

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- Samuel Schumacher
- Daniela Cirillo

Members of expert group