



Incipient TB assays to support TB Elimination: opportunities and challenges

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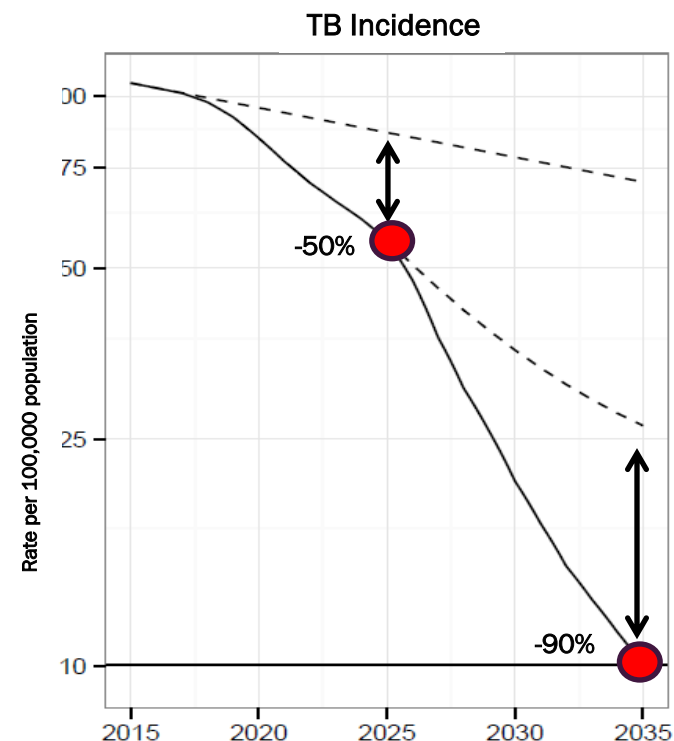
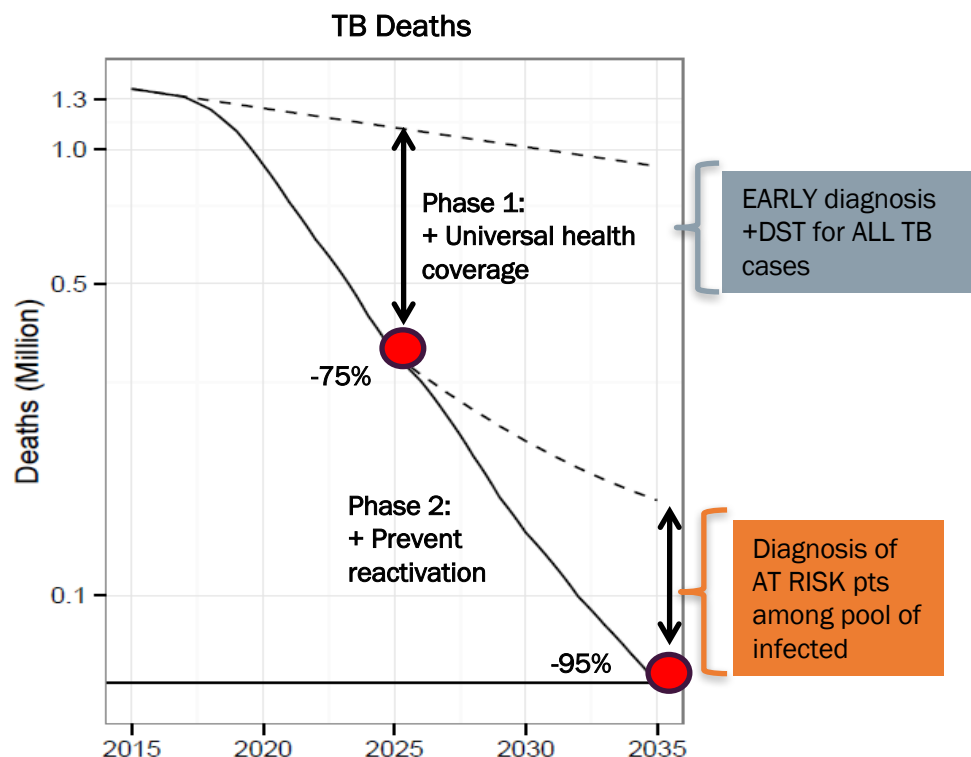
Acknowledgements

- Members of the New Diagnostic Working Group Taskforce on LTBI
- Participants in Technical Expert Consultation
- NDWG
- WHO



EndTB targets will not be achieved

...if we only address active TB



Courtesy of Global TB Program

■ What we have: TST & IGRAs

- Reasonable tests to detect persistent infection
- Poor performance to predict progression

■ What we want: tests that better predict progression

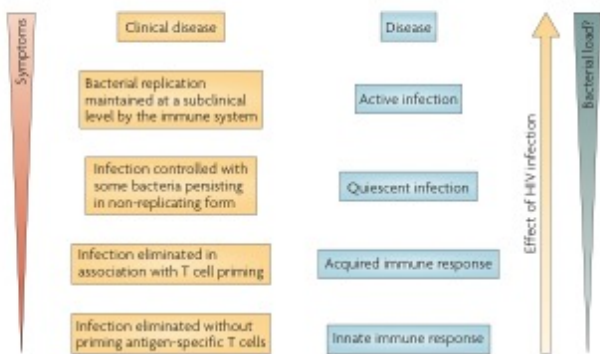


Opportunities

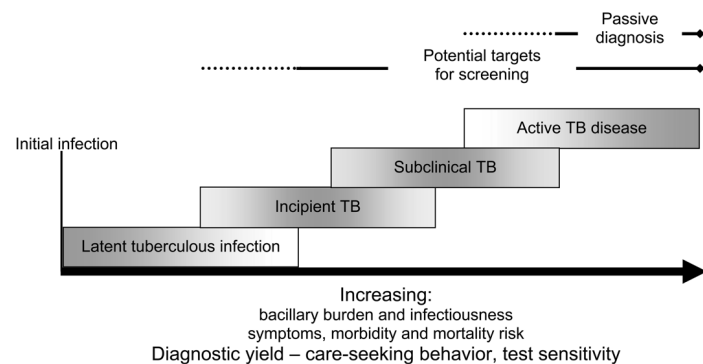


The spectrum of TB

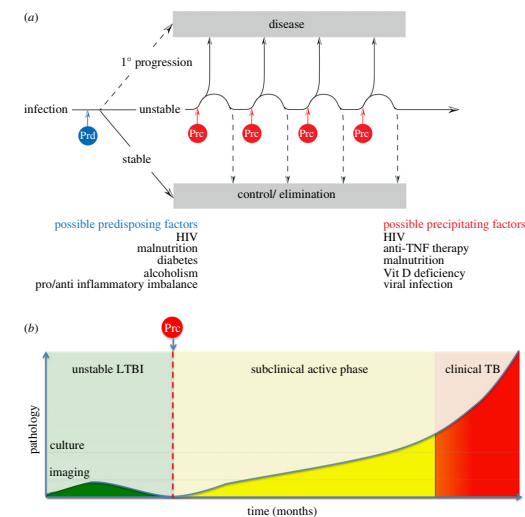
Re-conceptualising TB natural history



Barry, 2009



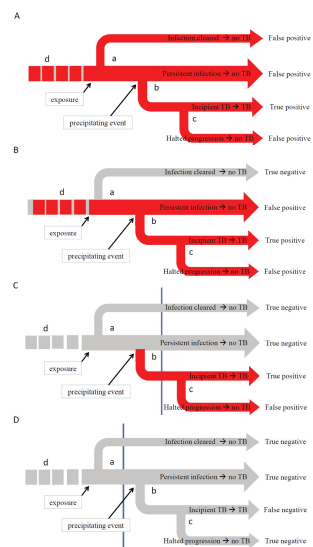
Golub, 2013



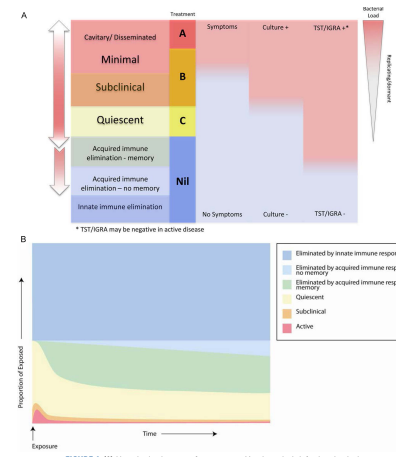
Esmail, 2014

Phase of <i>M. tuberculosis</i> infection	Support	Test					
		TST/IGRA	<i>M. tuberculosis</i> culture	COR signature (mRNA, 16-gene)	T-cell activation	Ag-specific CD8 T-cells	M/L ratio
Active clinical TB disease	+	+	+	+	+	+	↑
Subclinical TB disease	-	+	+	+	+	?	↑
Incipient TB disease	-	+	-	+	+/-	?	↑
<i>M. tuberculosis</i> infection	-	+	-	-	-	-	↓
Cleared infection	-	+/-	-	-	-	-	↓
No infection	-	-	-	-	-	-	↓

Petruccioli, 2016



Cobelens, 2016



Scriba, 2017



TPP and framework for evaluation

For tests predicting progression from tuberculosis infection to active disease

Consensus Meeting Report

Development of a Target Product Profile (TPP) and a framework for evaluation for a test for predicting progression from tuberculosis infection to active disease

2017

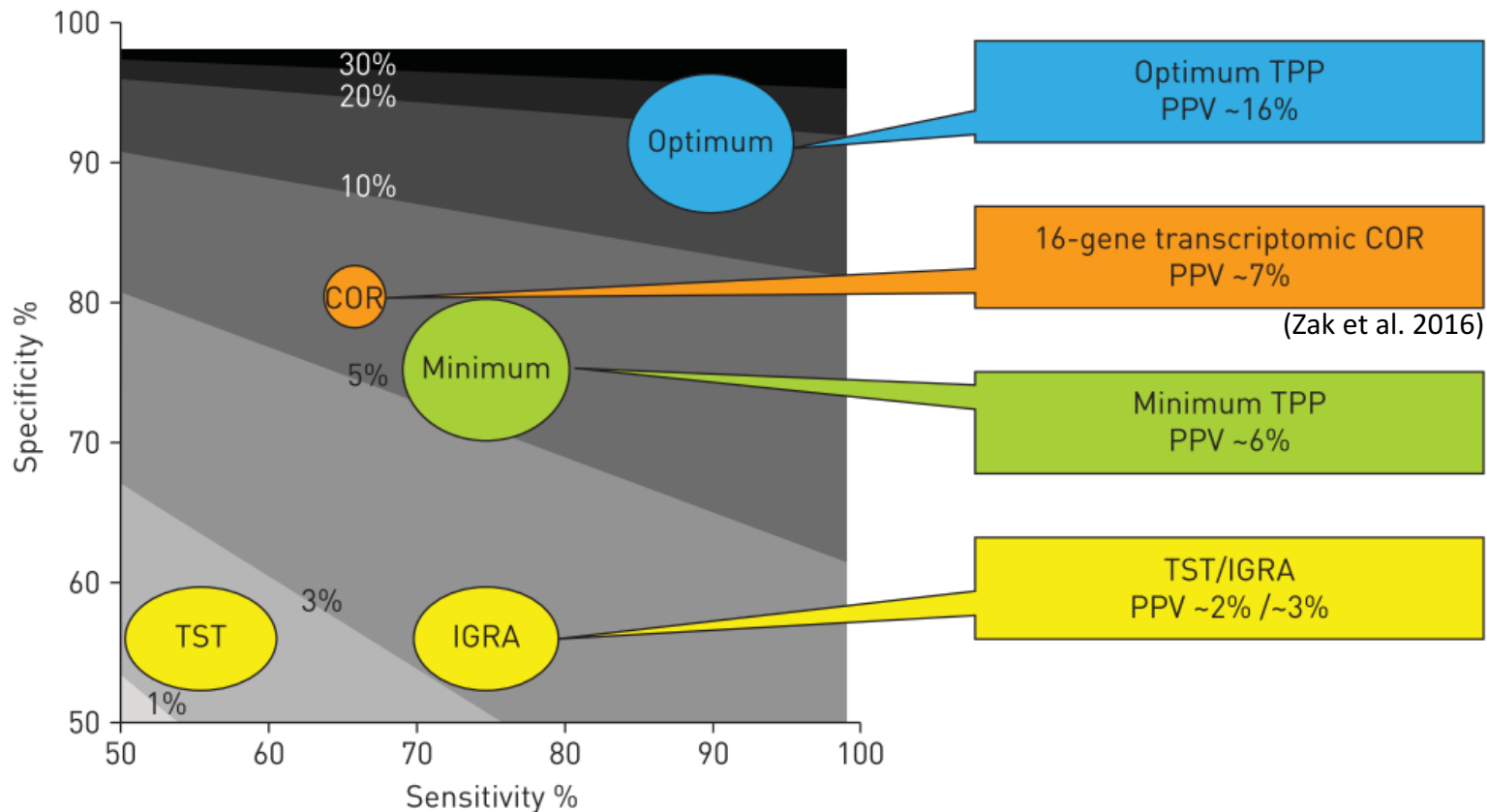


- Result of expert consultation process led by the NDWG, WHO, FIND and AIGHD
- Contains guidance to inform test manufacturers, researchers and research funders to support development of novel tests
- Three parts of report
 1. Description of evolving concept of TB infection
 2. TPP for a test of progression
 3. Guidance on study design



TPP Performance targets

Recent RNA work aligns with new concepts and holds promise for getting to better tests



Products in pipeline

- QFT-Plus and QFT-Predict (Qiagen)
- QIA-TB Signature (Qiagen)
- T-cell Immune Profiling (BD)
- RTT TB (Lophius)
- Incipient TB Assay (Abbott)
- and others

Biomarkers:

- RNA signatures
- IFN- γ release after T-cell stimulation with new antigens
- Cell differentiation markers (eg. CD27)
- Cytokine levels in blood (eg. IP-10)

- 2-3% PPV of existing products to detect latent TB (IGRA and TST) is too low
- Doubling the PPV is required to meet the Minimum TPP target (6%)
- Several companies are working on products with higher PPV («driven» by high-income country market)
- Market Entry ≥ 2020



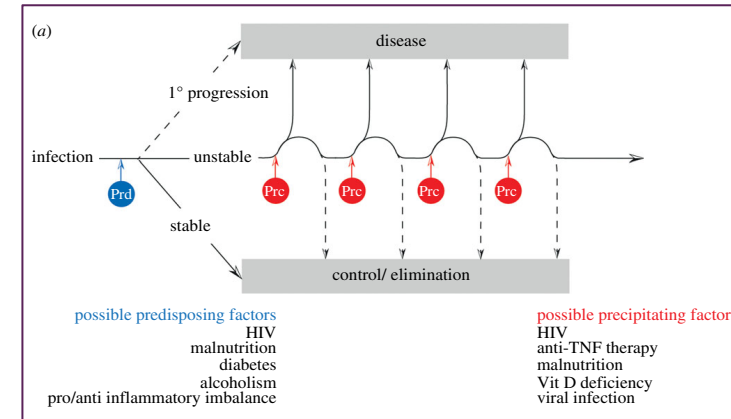
Challenges



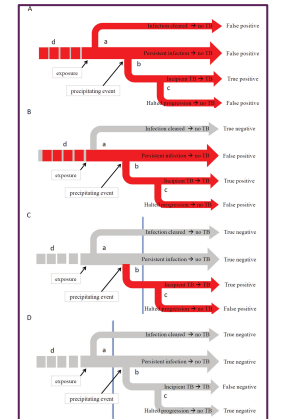
Predicting a rare event: a dual challenge

Prediction ≠ diagnosis

- Example of prediction within TB: 2-month culture conversion
 - Sensitivity <30%
 - Specificity <80%
- Example of prediction outside of TB: Framingham risk score
 - AUC 0.6-0.8



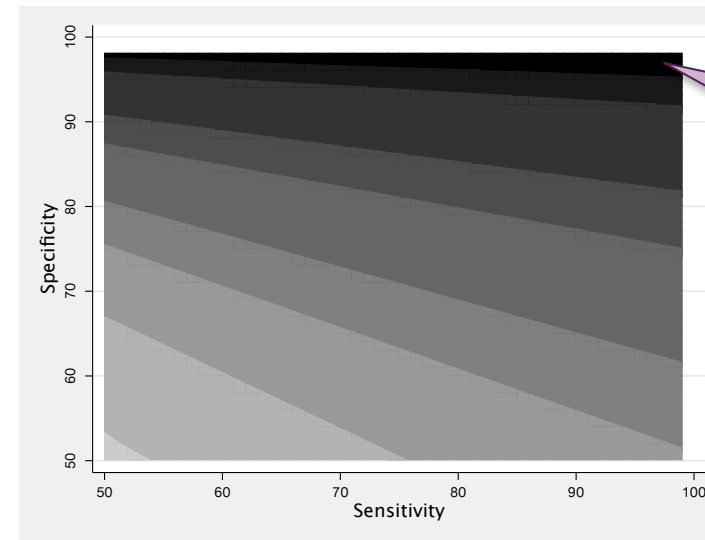
Esmail 2014



Cobelens, 2016

PPVs for rare events are bound to be low

- At 2% cumulative incidence
- Sensitivity & Specificity 99%
- Positive Predictive Value: 67%



Note that a test with Se/Sp 99/99 would yield PPV=67%



Operational/implementation challenges

Population

- **Broad** (high impact... BUT low relative yield / cost-effectiveness)
- **Narrow** (lower impact ...BUT higher relative yield / cost-effectiveness)

Placement

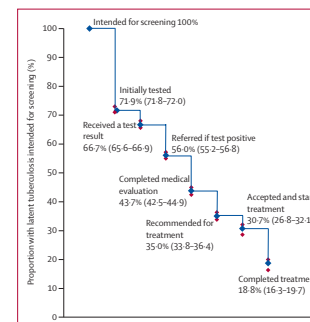
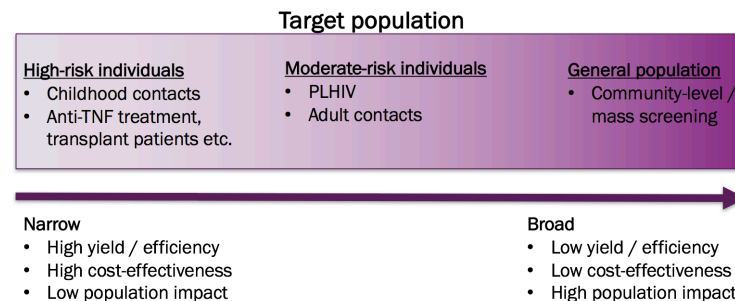
- **POC** (clinical need, sample type, sample processing)
- **Centralized** (sample stability, transport, cascade of care)

Ruling out active TB

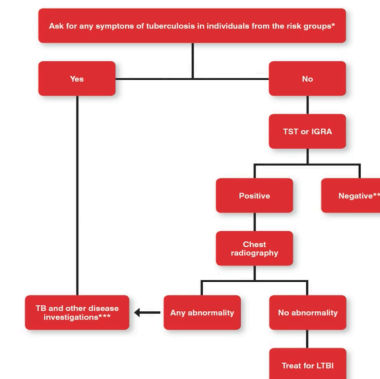
- Which tests (incipient TB test, symptom-screen, CXR, bacteriol. testing)
- Where in algorithm

Repeat testing

- Who and why
- When and how often



Alsdurf 2016



WHO LTBI guidelines



Cost

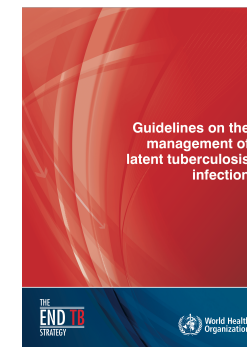
■ Affordability in settings with high burden of active TB?



■ Cost of introducing incipient TB test...compared to what?

- No LTBI program?
- Test and treat based on TST/IGRAs?
- No testing, i.e. empiric treatment of high-risk groups?

■ Linkage to care heavily affects **cost-effectiveness**



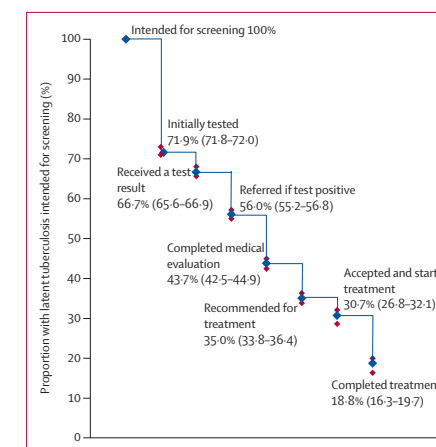
INT J TUBERC LUNG DIS 20(12):1566-1571
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<http://dx.doi.org/10.5588/ijtld.16.0241>

Policies and practices on the programmatic management of latent tuberculosis infection: global survey

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25% of low-TB burden countries do not have an LTBI program



Alsdurf 2016



Outlook: ongoing work

■ **Modeling:** to estimate impact and cost-effectiveness of incipient TB tests

- Erasmus (Suzanne Verver)
- LSHTM (Tom Summer)
- IDM (Brad Wagner)
- Imperial College (Nim Pathy)

■ **Specimen collections:** to facilitate test development and performance validation

- Existing specimen sources
- Integration with ongoing trials
- Dedicated specimen collection

■ **CORTIS trial (NCT02735590)**

- Validation of performance of COR signature (HIV-/HIV+)
- Efficacy of preventive regimen for COR+ individuals
- Value of repeat testing



Conclusions

- We need better tests for incipient TB to reach the EndTB targets

- There are good reasons to be optimistic...
 - Growing recognition as an important need
 - Renewed interest in the area: ongoing conceptual and biomarker discovery work
 - Attractive high income market: helps drive assay development work
 - WHO report helps provide foundation for progress

- ...but important challenges and questions remain
 - Discovery: signatures with adequate performance for prediction (and finding sensitivity-specificity balance)
 - Validation: long follow-up, few events, ethical challenges
 - Development: need assays that are affordable and meet other TPP targets (fit lower income settings)
 - Implementation: operational and implementation challenges



Thank you!