Incipient TB assays to support TB Elimination: opportunities and challenges
Samuel G. Schumacher, PhD
Scientific Officer, FIND

11th October 2017
Union Conference, Guadalajara
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

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

Petruccioli, 2016

Cobelens, 2016

Scriba, 2017
TPP and framework for evaluation
For tests predicting progression from tuberculosis infection to active disease

- 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

• 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

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)
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

**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
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**
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!