FIND

Because diagnosis matters

Detecting cases earlier and detecting earlier cases: potential synergies and risks

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TB MAC Modelling Research Group Meeting

Detecting cases earlier vs detecting earlier cases

Competing options for improved case detection?

Detecting cases earlier

- By getting them tested earlier in their disease process
- e.g. via active case finding

If done with low-sensitivity diagnostics:
expected to miss patients with early disease

Detecting earlier cases

- By detecting earlier disease among cases that receive testing
- e.g. via more sensitive diagnostics for active TB

Both may be needed…

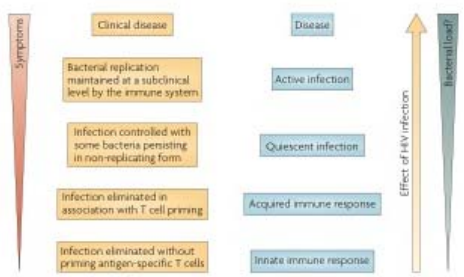
If used only in patients late in disease process:
expected to provide limited incremental yield over low-sensitivity diagnostics

Topics for this talk

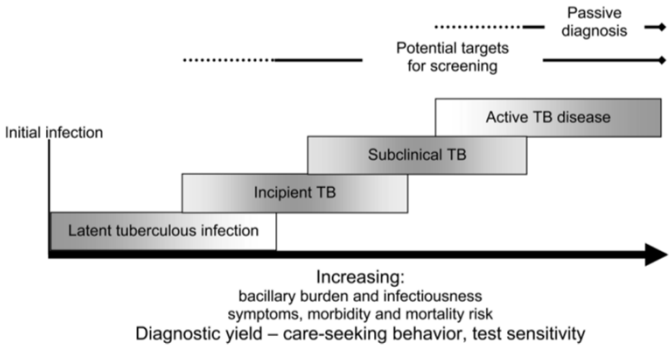
- Synergies
- Risks
- Spectrum of *active* TB

The spectrum of TB

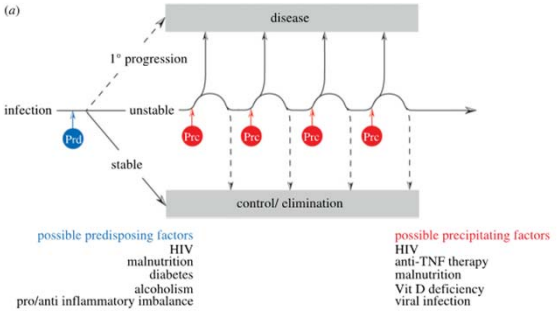
A lot of discussion of this in recent years

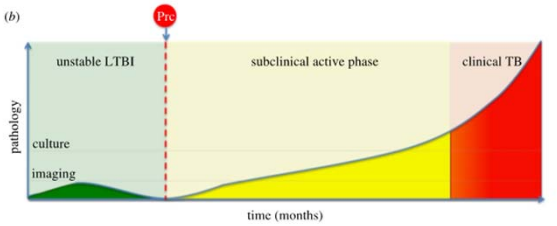


Barry, 2009

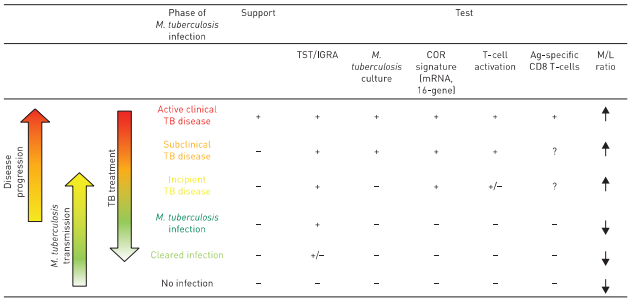


Golub, 2013

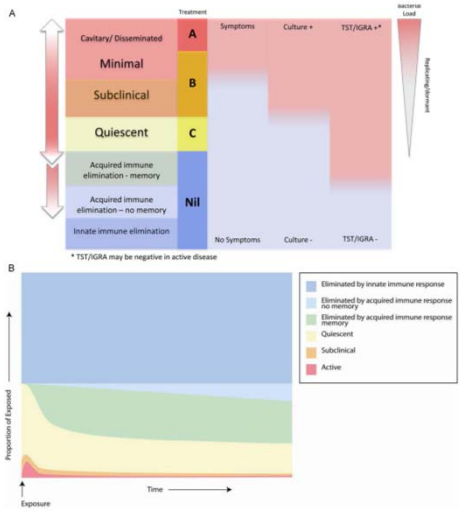




Esmail, 2014



Petruccioli, 2016



Scriba, 2017

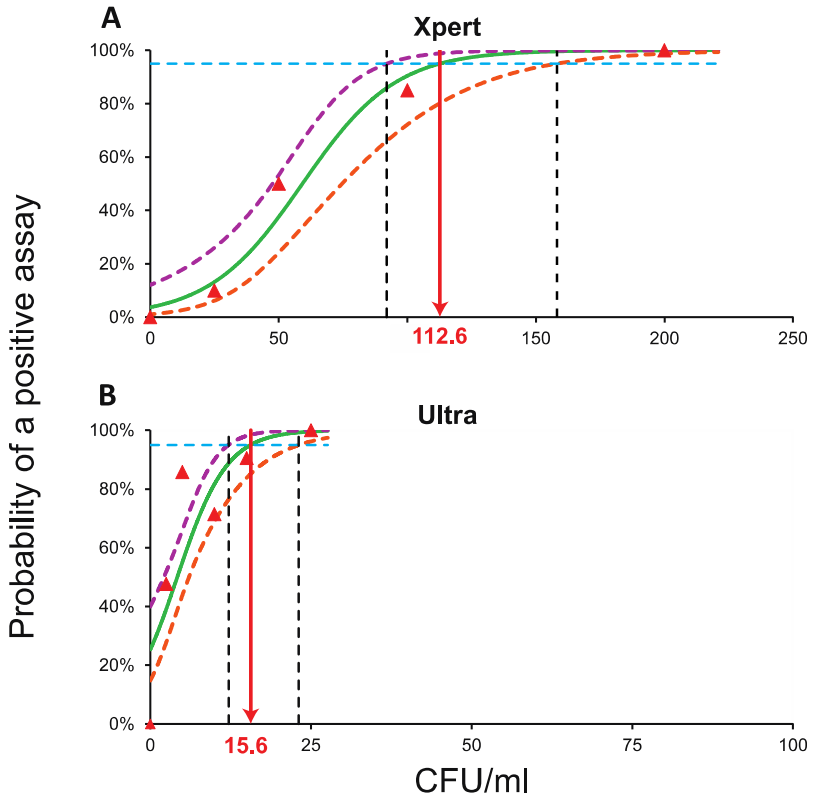
The spectrum of active TB

Not much reflection beyond distinguishing smear+ from smear- TB

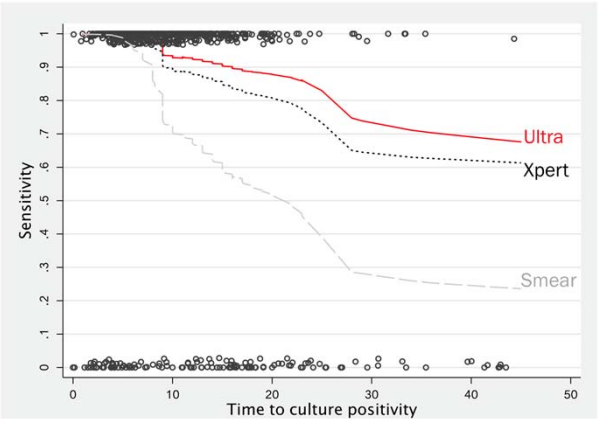
?

The spectrum of active TB

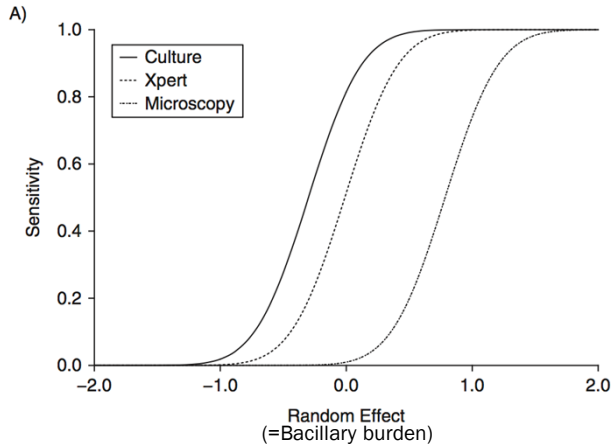
LOD studies & CFU-specific sensitivity



Chakravorty, 2017



FIND Ultra report, 2017



Schumacher, 2017

Dichotomizing the spectrum of active TB: a bad idea?

Statistics Notes

The cost of dichotomising continuous variables

Douglas G Altman, Patrick Royston

STATISTICS IN MEDICINE
Statist. Med. 2006; **25**:127–141
Published online 11 October 2005 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/sim.2331

Dichotomizing continuous predictors in multiple regression: a bad idea

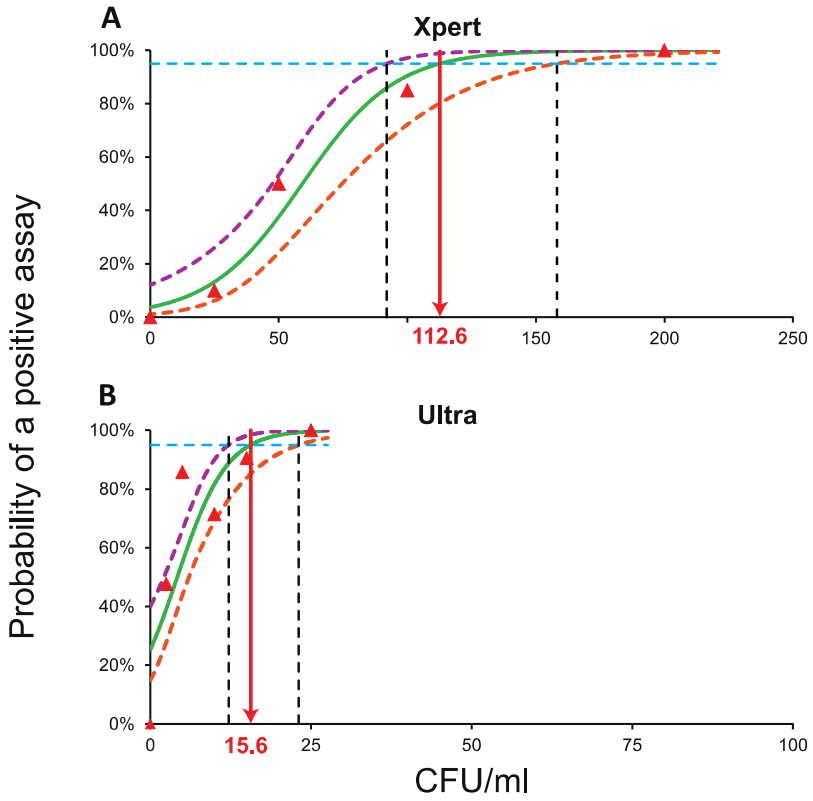
Patrick Royston[1,*,†], Douglas G. Altman[2] and Willi Sauerbrei[3]

- We use a simple division into smear+ vs smear- TB
  - When reporting accuracy estimates
  - When modeling impact of new diagnostics
- However, there is a continuous spectrum of active TB and the smear+/- division…
  - is ill-defined
  - is not very reliable
  - is extremely crude
- As a result we can get wildly varying accuracy estimates
  - Xpert-Sensitivity in smear-negative changed from 60% to 45% depending on how “smear-positive” was defined

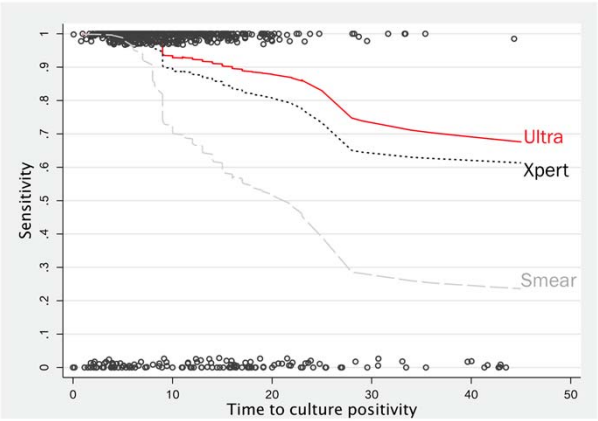
* FIND study on Xpert MTB/RIF Ultra

The spectrum of active TB

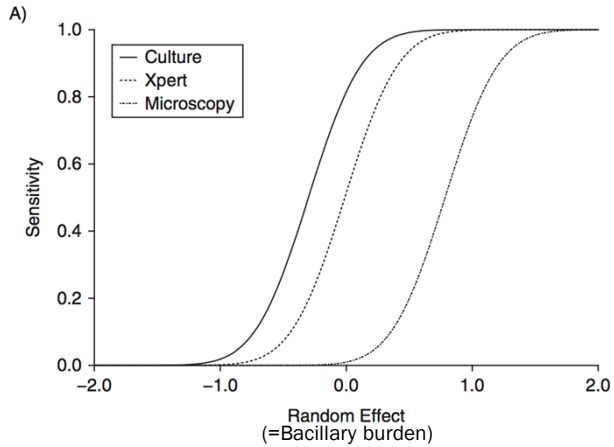
Viewed via LOD studies, CFU-specific sensitivity and LCA



Chakravorty, 2017



FIND Ultra report, 2017

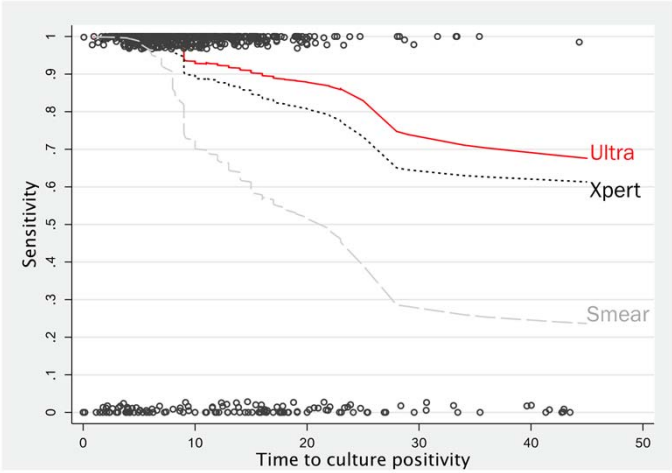


Schumacher, 2017

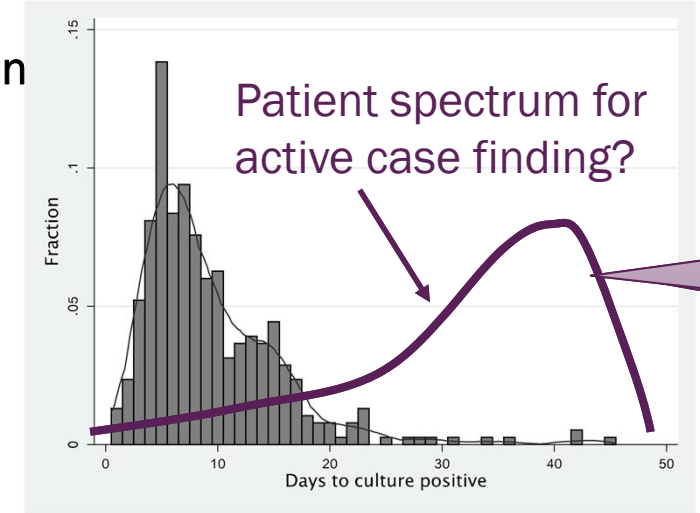
Synergies

More sensitive diagnostics most needed in patients tested early in disease

CFU-specific sensitivity
(as proxy of analytical sensitivity)



CFU-distribution
(as proxy of patient spectrum)



Sensitivity		Sensitivity (?)	
Ultra	~90%	Ultra	8(
Xpert	~85%	Xpert	70%
Smear	~60%	Smear	20%

Kranzer, 2013:
"All studies found that those who were identified through screening were more likely to be at an earlier stage of disease"

Risks of improving case finding

1. **Lower prevalence** in active case finding context means lower PPV

2. **Increased sensitivity may come at the cost of reduced specificity because of challenges with picking a cut-off when aiming for high sensitivity**
   - Almost certainly for host-biomarker-based tests (e.g. host-RNA)
   - Likely also for new pathogen-biomarker based tests (e.g. Xpert Ultra)

3. **Increased sensitivity may come at the cost of reduced specificity because of natural history**
   - More sensitive tests detect patients with fewer bacilli, which may mean detecting patients earlier in the disease process, who have higher spontaneous cure rates
   - The earlier we detect patients in their disease process, the more of those that we would be calling “TB” would “self cure”
   - This is already the case with culture (as can be seen e.g. in prevalence surveys)

Conclusions

- **Spectrum of active TB:** while we appreciate the spectrum of TB as a whole, we don't talk much about the fact that even within "active TB", there is a spectrum as well (usually crudely approximated with smear- vs smear+ TB)
  - this oversimplification may lead us to false conclusions.

- **Synergies:** Detecting cases earlier (e.g. via active case finding) and detecting earlier cases (e.g. via more sensitive diagnostics) are typically looked at as competing options for improved case finding
  - however, there may be important synergies between these, which have been explored or exploited much to date.

- **Risks:** At the same time, in particular combining active case finding with more sensitive diagnostics risks more "false-positives" (for at least 3 different reasons)
  - this means we need to think harder than ever about appropriate balance of risks and benefits.