How should diagnostics for incipient TB be utilized to reduce population-level transmission?

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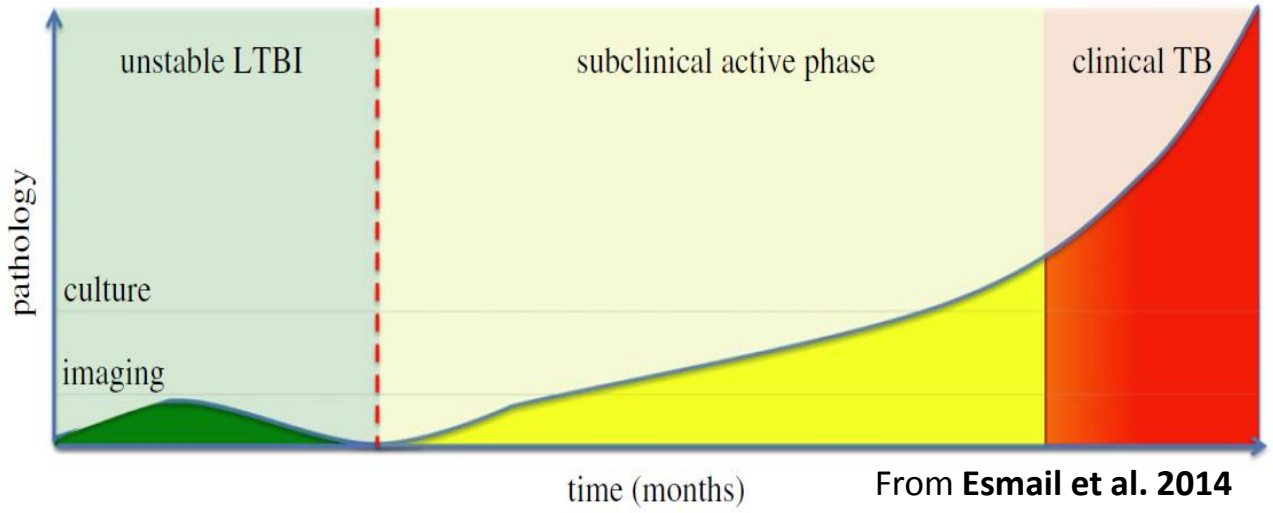
What do we need to know to quantify diagnostic impact on transmission ?

- At the individual level, how does pathology correspond to transmissibility?
- At the population level, what is clinical vs subclinical contribution to transmission?
- Depends on:
  - Existing diagnostics (for TB, LTBI)
  - Health systems/access
  - Treatment success rates
  - Natural disease progression rates

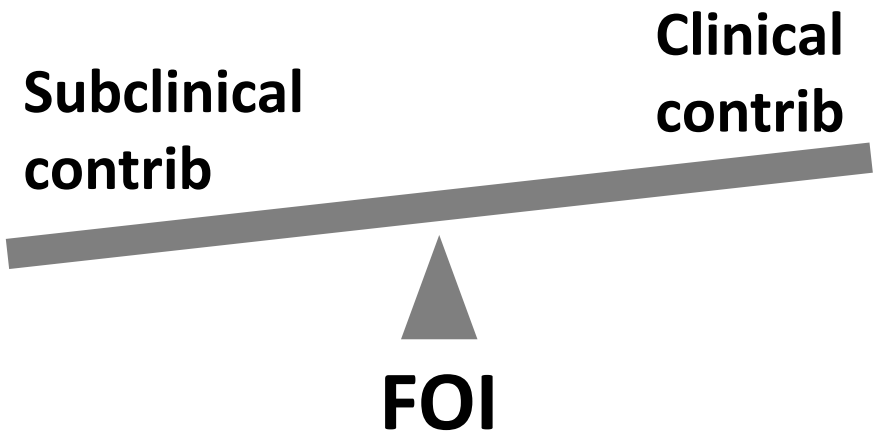


From **Esmail et al. 2014**

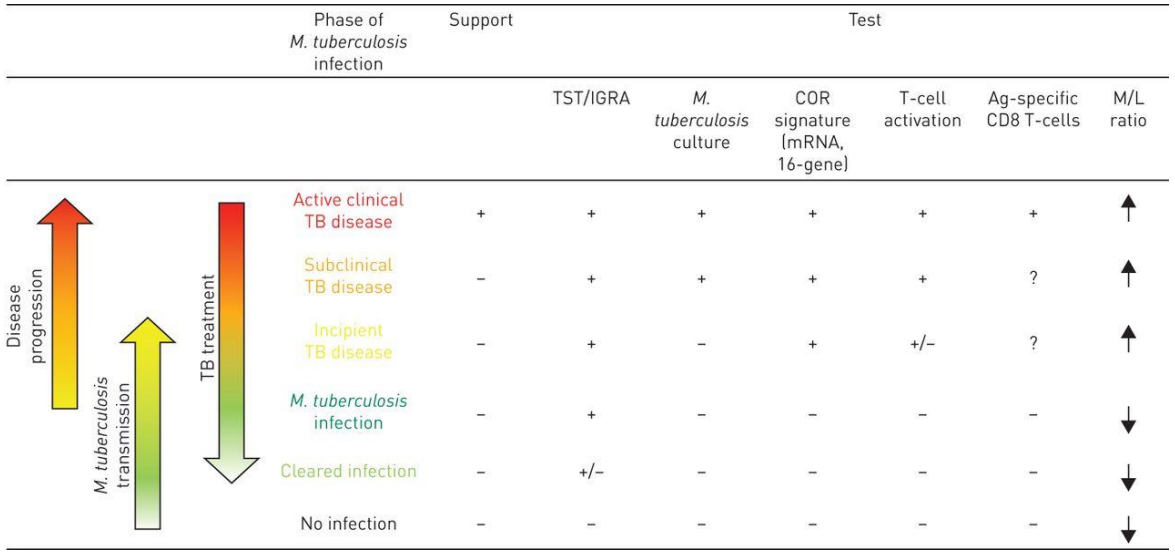
- How does diagnostic sensitivity and specificity vary across pathology?

Drivers of transmission and diagnostic impact

- Trade-offs in modeling transmission:
  - Scenarios with greater contribution of subclinical TB will show greater impact of incipient TB diagnostic
- Infectiousness, prevalence of subclinical TB not well understood
- Subclinical TB prevalence can be characterized by:
  - Adding subclinical Dx (e.g., COR) to prevalence surveys



Example: Modeling COR Test



Phase of *M. tuberculosis* infection	Support	Test					
		TST/IGRA	*M. tuberculosis* 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	–	+	–	+	+/–	?	↑
M. tuberculosis infection	–	+	–	–	–	–	↓
Cleared infection	–	+/–	–	–	–	–	↓
No infection	–	–	–	–	–	–	↓

From **Petruccioli et al. 2016**

- Correlates of Risk (COR)
  - Blood based transcriptomic biomarker test
  - 6+ gene signature
  - Prognostic for activation with 2 years
  - Diagnostic for active TB
  - Improved sensitivity nearer to activation

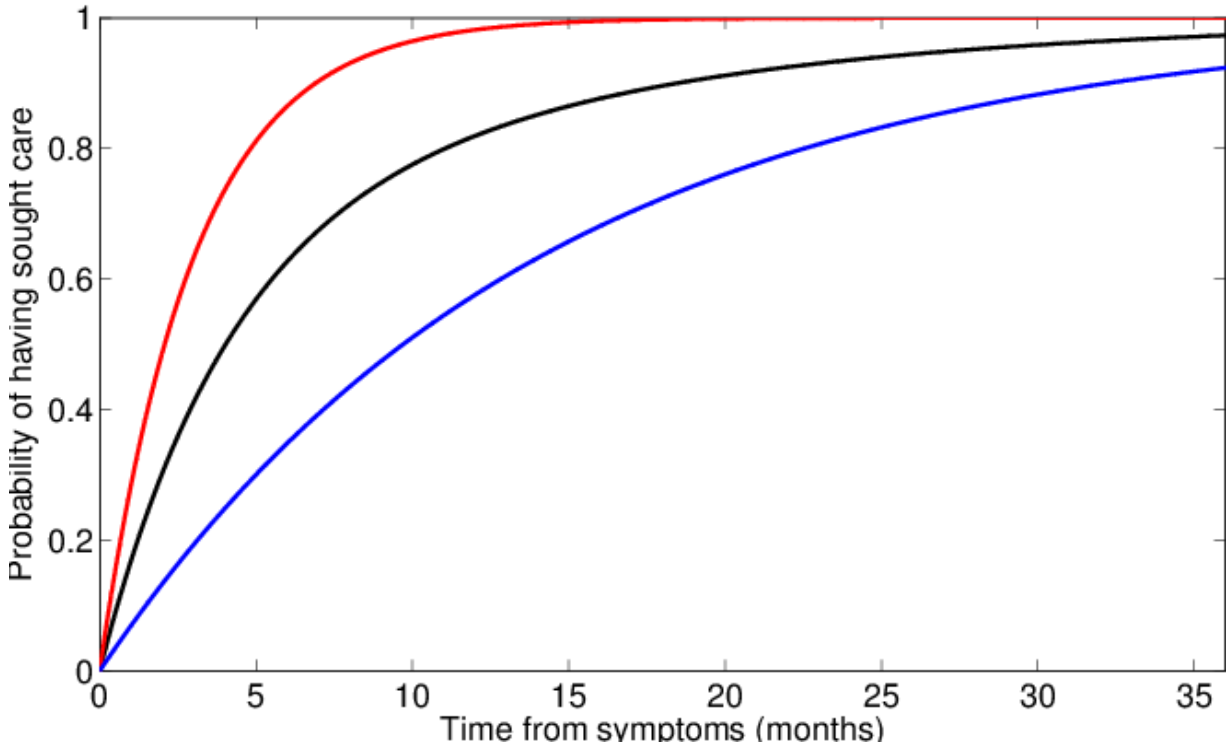
Example: Modeling COR tests applied to all South Africa

Simulated parameter value sets across key ***programmatic***, ***testing***, *and* ***treatment*** *uncertainties*

	Model assumptions	Real-life premise
Coverage / accessibility	Varied, whole pop (HIV+/-), all ages: **10%, 30%, 50%**	Vaccination in 1-2 y.o.'s: 55%[1]
Test frequency (COR)	Annual, random screening	CD4 monitoring in HIV+'s: 2x/yr
Test sensitivity (COR)	Matches Zak et al: **median, lower, upper bounds**	Example: 66% (63-69%) <1 yr prior to active[2]
Linkage / adherence (3HP)	18% loss pre-treatment	18% (13-22%) in meta-analysis of Sub-Saharan Africa[3]
Cure rate (3HP)	Varied: **30%, 50%, 70%**	30% based on modeling isoniazid study data[4]
Relative cure rate in HIV+ (3HP)	Varied: **50%, 80%**	40% relative risk reduction in IPT-treated HIV+ TST- vs TST+[5]
HIV prevalence / ART scale-up	Matches UNAIDS estimate	Example: 19% adult prev 2014
Other health systems interventions for TB	Status quo for (Dx) symptom screen, TST, Xpert; (Rx) first-line drugs	

1. South Africa DHS 2003
2. Zak *Lancet* 2016
3. MacPherson *Bull. WHO* 2013
4. Sumner *AIDS* 2016
5. Ayele *PLOS One* 2015

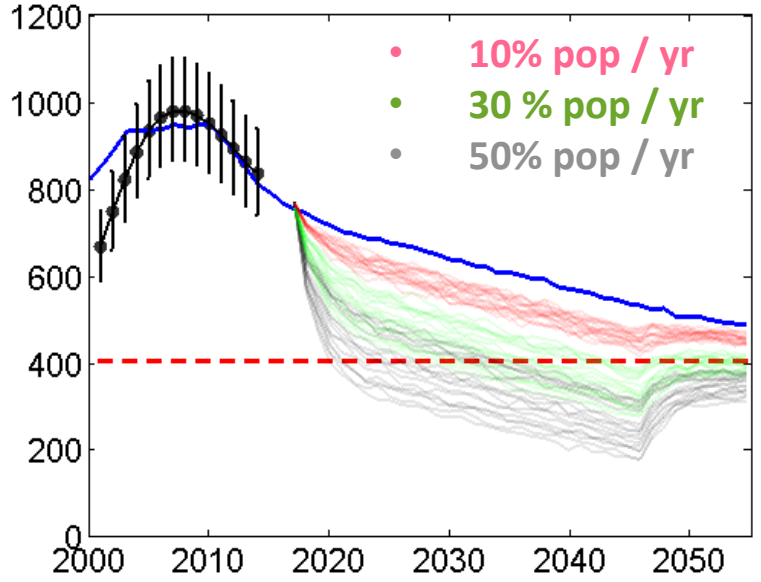
Model parameters: Initial care-seeking in South Africa



- High access (65% of pop)
  - Median delay: 3 months
- Low access (35% of pop)
  - Median delay: 10 months

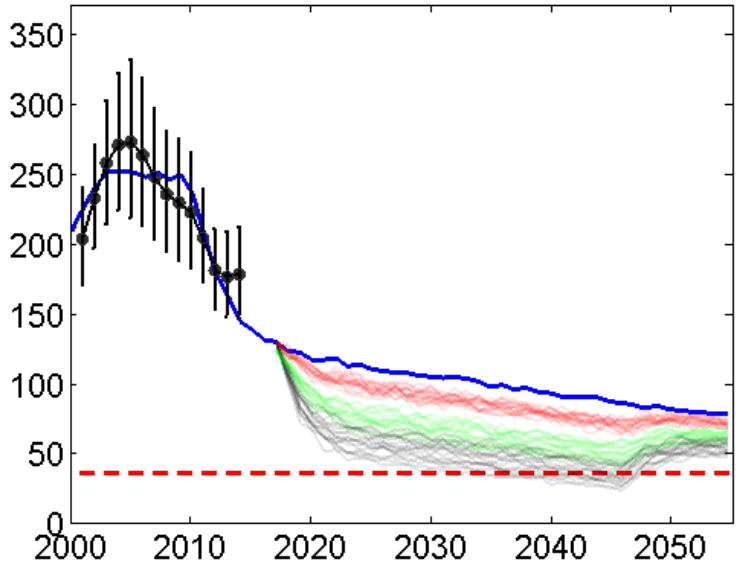
COR (w/3HP) population-wide rollout in South Africa

TB disease incidence (per 100k)

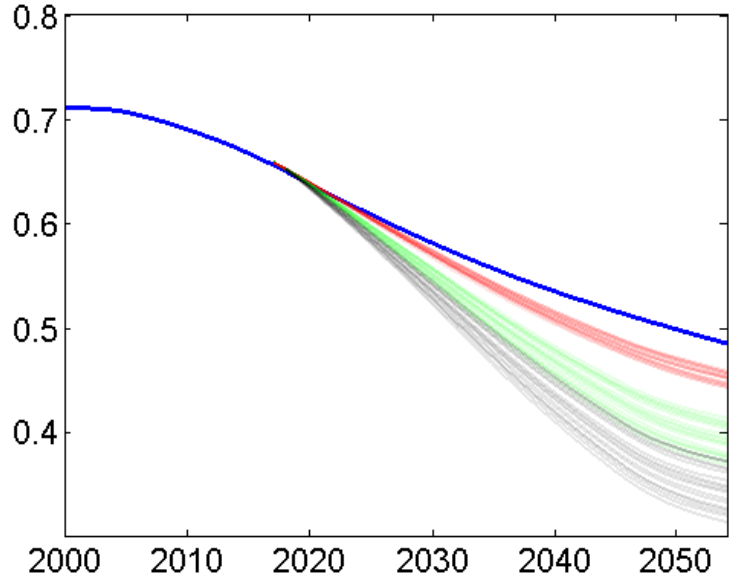


30-year intervention

TB mortality (per 100k)



Adult latent prevalence (proportion)

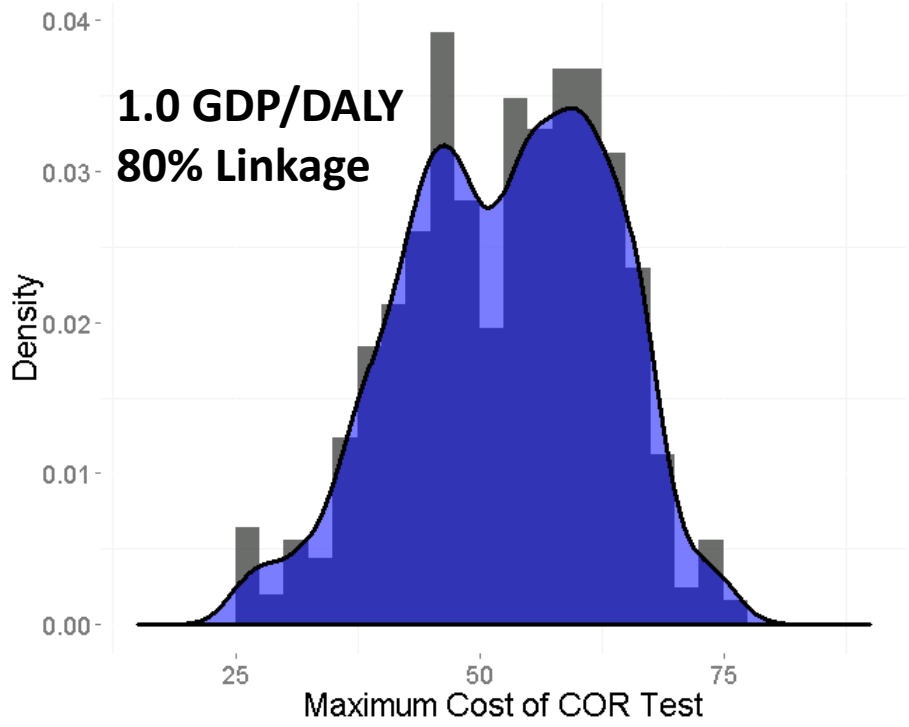


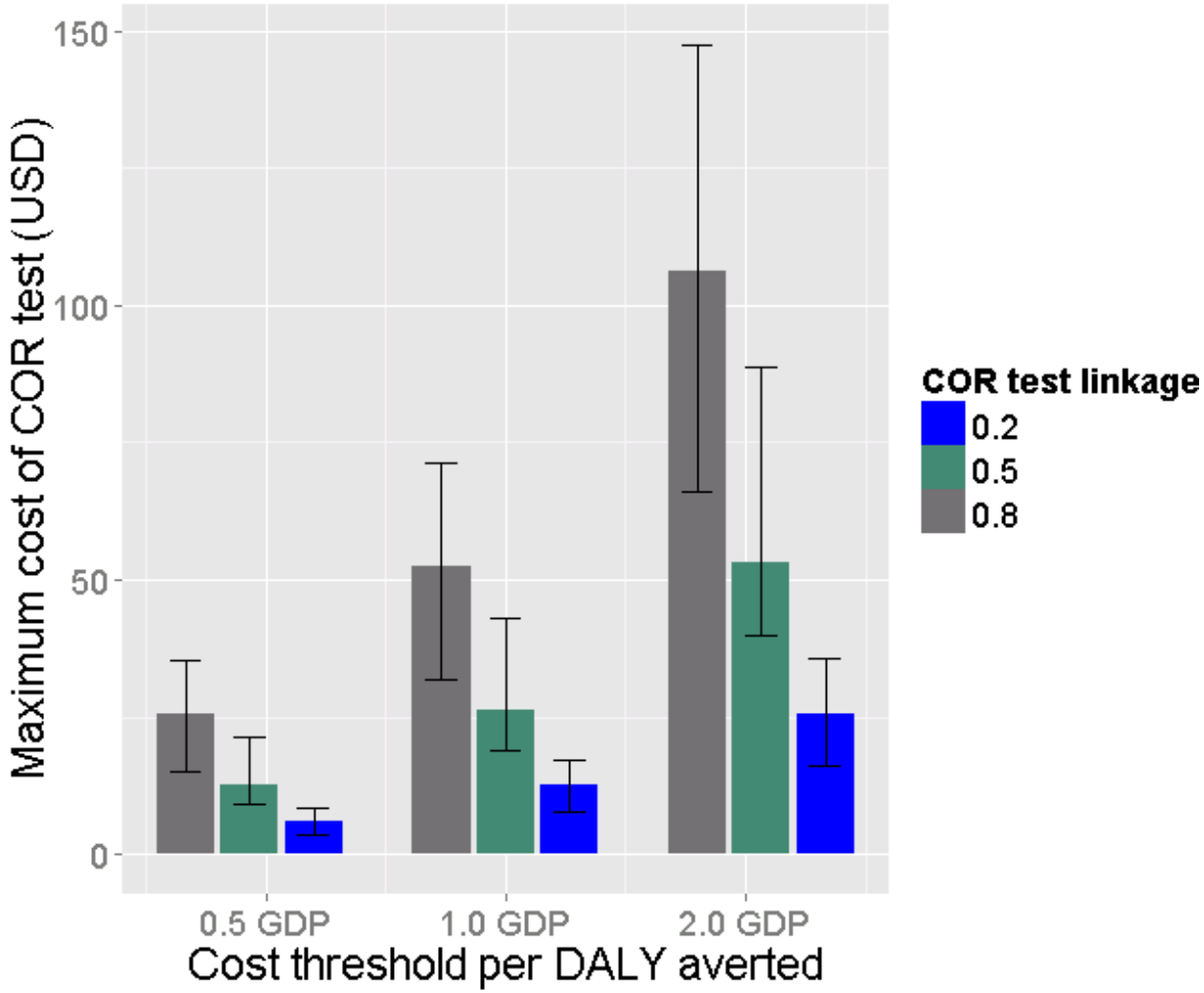
- Epidemiological features: Rapid initial decline, slow steady decline, rebound after ending program
- Improvements in other indicators (such as prevalence of latent infection)
- *Depending on coverage, burden declines nearly to 2025 Global Targets (---)*
- *However, no reasonable scenario completely eliminates rebound after program ends*

COR/3HP: Test cost thresholds

- 20-year time horizon
- 3% annual discount rate
- 50% coverage

Assumes 95% test sensitivity





Putting novel diagnostics in context of the health system

- Could novel diagnostics be bottlenecked by L0/L1 availability?

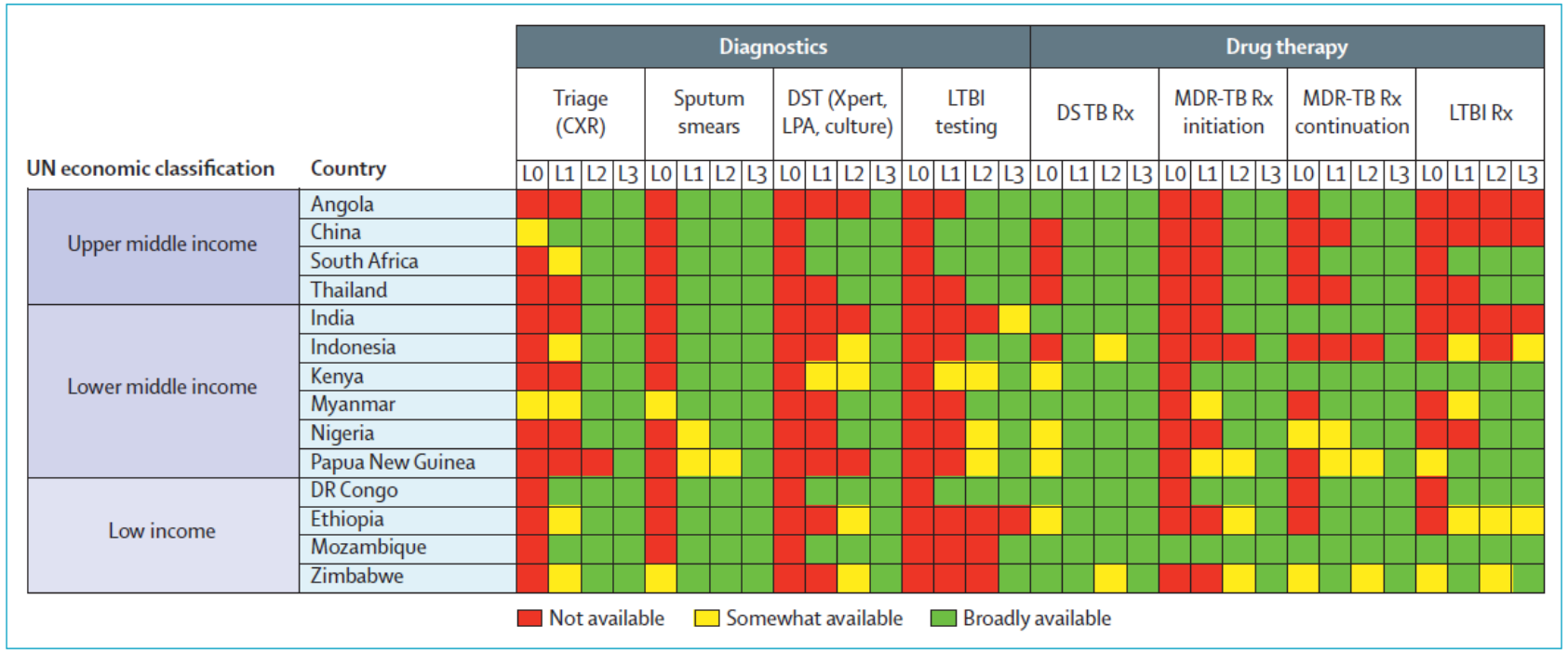


Figure 1: Availability of tuberculosis diagnostic and treatment services across various health-care levels in 14 highest burden countries

From **Huddart et al. 2016**

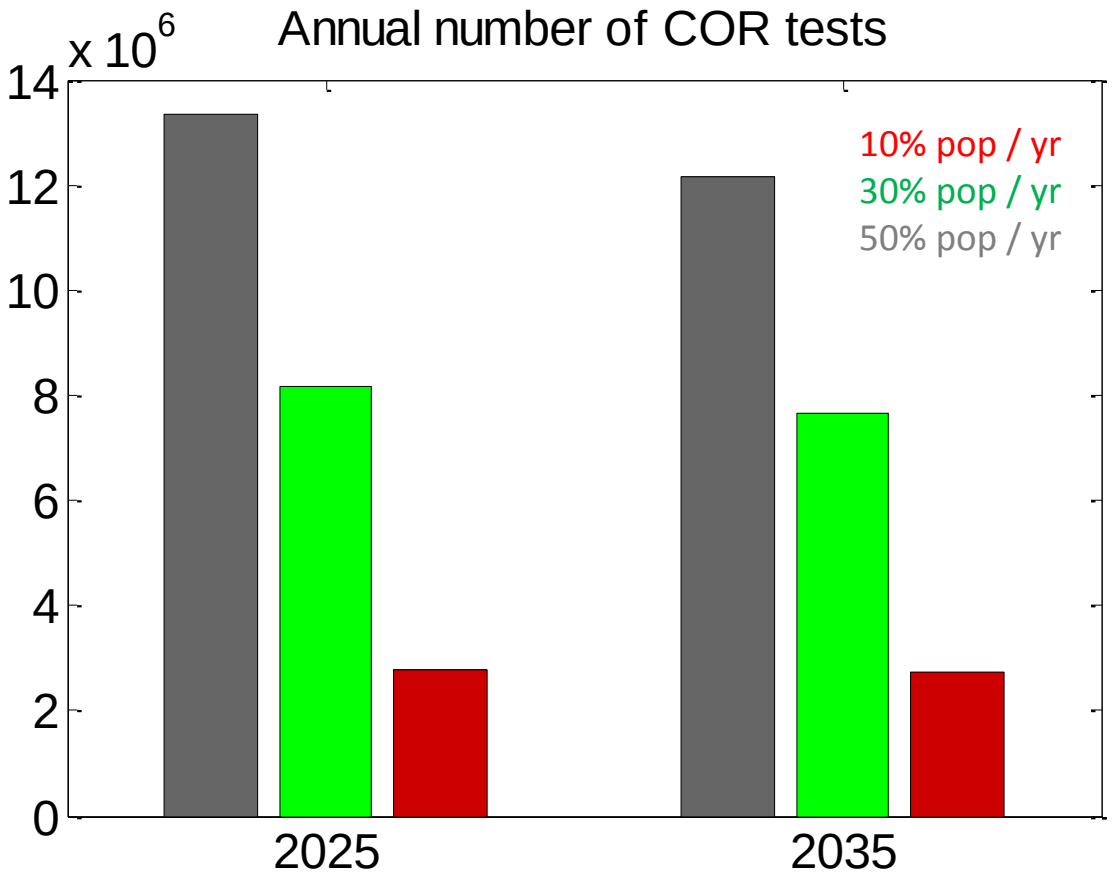
L0 Community health workers

L1 Primary health centers

L2 District hospitals

L3 Reference hospitals

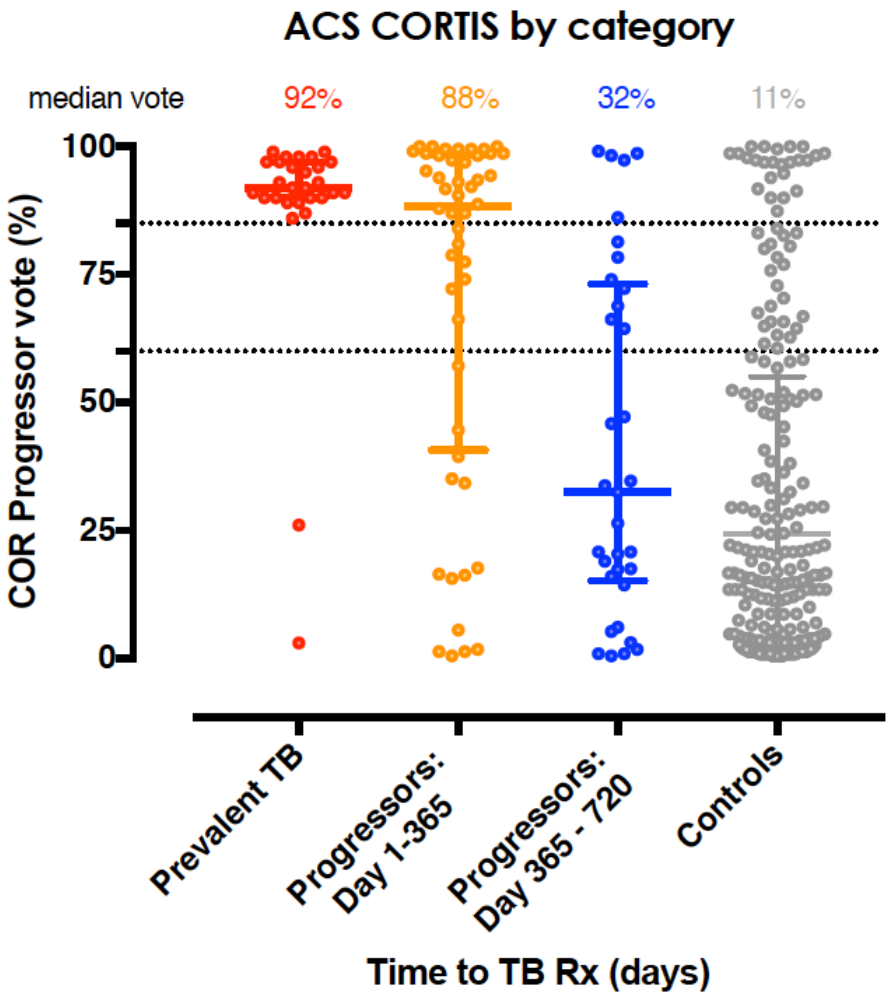
Feasibility: Annual numbers tested



- Gated on high sensitivity specificity test for infection (comparable to IGRA)
- At 90% specificity
  - ~ 130,000 3HP treatments at 50% coverage

For context, in South Africa 2012, 9.2 x 10^6 TB tests performed across all platforms

Balancing specificity and impact



From ***Hatherill, Scriba, Penn-Nicholson, Suliman, Darboe, Kimbung et al. SATVI***

Ways to improve specificity?

- Multiple thresholds
  - (Investigation of) active disease
  - Preventative therapy
  - Follow up
- Targeting high-risk populations
  - e.g. HIV positive

Predicting diagnostic impact

Epidemiological impact in target populations will depend on:

- Current access to health care system
- Mechanism of deployment
  - Periodic (yearly) testing (POC)
  - Targeted campaigns
  - HIV clinics
  - Geographic targeting
- Linkage and adherence to treatment
  - How available is LTBI therapy at L0/L1 levels
  - Effectiveness of LTBI therapy (3HP vs 6H, 9H)

Predicting diagnostic impact

- Model of diagnostic rollout needs to reflect access mechanisms
  - Realistic bounds on coverage/epi impact
  - Opportunity costs
- Uncertainty in diagnostic impact depends on uncertainty in epidemic drivers
  - Heterogeneity in health-care access
  - Patient and health system delays
- Need to balance sensitivity and specificity in designing rollout