The future of TB screening: What's on the horizon?

Pren Naidoo
BMGF (TB Delivery Team, SA)
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Empowering Health for 15 years ICAP
Columbia University Mailman School of Public Health

World Health Organization

HIV LEARNING NETWORK
The CQUIN Project for Differentiated Service Delivery

Systematic screening for TB

- **Objective of screening:**
  - Early detection and treatment of active TB (reduces risk of poor treatment outcomes, health sequelae and the adverse socio-economic impact; reduces TB transmission)
  - Rule out active disease to identify those eligible for TB preventive therapy
- **Move away from "passive case-finding" to provider-initiated case-finding**
  - Targets people who do not seek health care (failure to recognize symptoms; inability to discern severity of problem; barriers to accessing care etc.)
  - Target people seeking health care who are asymptomatic, but may have TB
- **Systematic screening**
  - Aims to efficiently differentiate people with a high probability of having active TB from those who are unlikely to have active TB.
  - Those screened positive, will need to undergo confirmatory diagnostic testing (using test with high accuracy)

Symptom screening has low accuracy; is subjective

Screening tool	Pooled sensitivity % (95% confidence interval)	Pooled specificity % (95% confidence interval
Chest radiography		
Any abnormality compatible with TB (active or inactive)	98 (95–100)	75 (72–79)
Abnormalities suggestive of active TB	87 (79–95)	89 (87–92)
After positive screening for symptoms[a]	90 (81–96)	56 (54–58)
Symptom screening		
Prolonged cough (lasting >2–3 weeks)	35 (24–46)	95 (93–97)
Any cough	57 (40–74)	80 (69–90)
Any TB symptom (settings with low prevalence of HIV)	70 (58–82)	61 (35–87)
Any TB symptom (settings with high prevalence of HIV)	84 (76–93)	74 (53–95)
Any TB symptom (settings with low prevalence or high prevalence of HIV)	77 (68–86)	68 (50–85)

Systematic screening for active tuberculosis: principles and recommendations. WHO. 2013

1% Prevalence		**Cough >2 weeks**		
		+	-	
Disease status	+	4	7	10
	-	50	941	990
		53	**947**	**1000**
		Any cough		
		+	-	
Disease status	+	6	4	10
	-	198	792	990
		204	796	1000
		Any symptom (all areas)		
		+	-	
Disease status	+	8	2	10
	-	317	673	990
		325	676	1000
		Any symptom (high HIV prev)		
		+	-	
Disease status	+	8	2	10
	-	257	733	990
		266	734	1000

High proportion missed cases; 92-97% confirmatory tests neg

TB TRIAGE TEST – WHO 2014 TPP SPECIFICATIONS

Characteristic	Optimal	Minimal
Diagnostic sensitivity	>95% pulmonary TB	>90%
Diagnostic specificity	>80%	>70%
Time to result	<5 minutes	<30 minutes
Price	<$1.00	<$2.00
Instrument/capital cost	none	<$50.00

Most important

- ***Goal: a rapid, inexpensive point-of-care test that can rule out TB (i.e. accurately identify true negatives).***

The impact of a test that meets the WHO TPP for screening test

91% unnecessary confirmatory tests

1% Prevalence		WHO TPP Optimal		
		+	-	
Disease status	+	9.5	0.5	10
	-	99	891	990
		108.5	891.5	1000
		WHO TPP Min		
		+	-	
Disease status	+	8	2	10
	-	297	693	990
		305	695	1000

97% unnecessary confirmatory tests

46% unnecessary confirmatory tests

10% Prevalence		WHO TPP Optimal		
		+	-	
Disease status	+	95	5	100
	-	90	810	900
		185	815	1000
		WHO TPP Min		
		+	-	
Disease status	+	80	20	100
	-	270	630	900
		350	650	1000

77% unnecessary confirmatory tests

Some current / future screening options

POC test
Done on pts with low CD4

	Sensitivity ≥90%, specificity ≥70%*	Cost ≤US$2*	Available at lower-level clinics†	Other limitations
Recommended				
Symptom screening	No	Yes	Yes	Subjective
Standard chest x-ray	No	No	No	Subjective, high resource requirements
Under evaluation				
C-reactive protein	Yes	Yes	Yes	Utility might be limited to patients with highest risk
Digital chest x-ray with computer-aided detection	No	No	No	Cost, implementation‡
Proof-of-concept				
5-transcript signature[11]	Yes§	Unknown	Unknown	Cost, implementation‡
6-protein signature[12]	Yes¶	Unknown	Unknown	Cost, implementation‡
ESAT-6 + CFP-10[13]	Yes¶	Unknown	Unknown	Cost, implementation‡

*Based on the WHO target product profile for a tuberculosis screening test. †Facilities at the peripheral and district level (ie, lower level than national health-care facilities). ‡Will depend on the ability to translate these approaches to simple and affordable tuberculosis screening tests. §Evaluation restricted to case-control studies of antiretroviral therapy-naive people living with HIV undergoing tuberculosis screening. ¶Evaluation restricted to patients with presumptive tuberculosis.

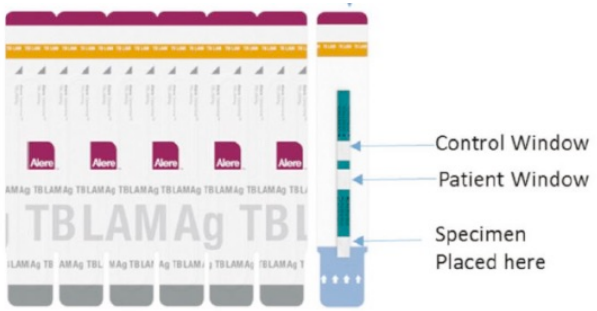
Table: **Characteristics of currently available and novel tests to screen for active tuberculosis**

Done on presumptive TB Complex

Screening for tuberculosis: time to move beyond symptoms. Lancet Respir Med. 2019 Mar;7(3):202-204. C Yoon, DW Dowdy, H Esmail, P MacPherson, SG Schumacher

Urine Lipoarabinomannan Assay
(Determine TB-LAM; Alere, MA, USA)

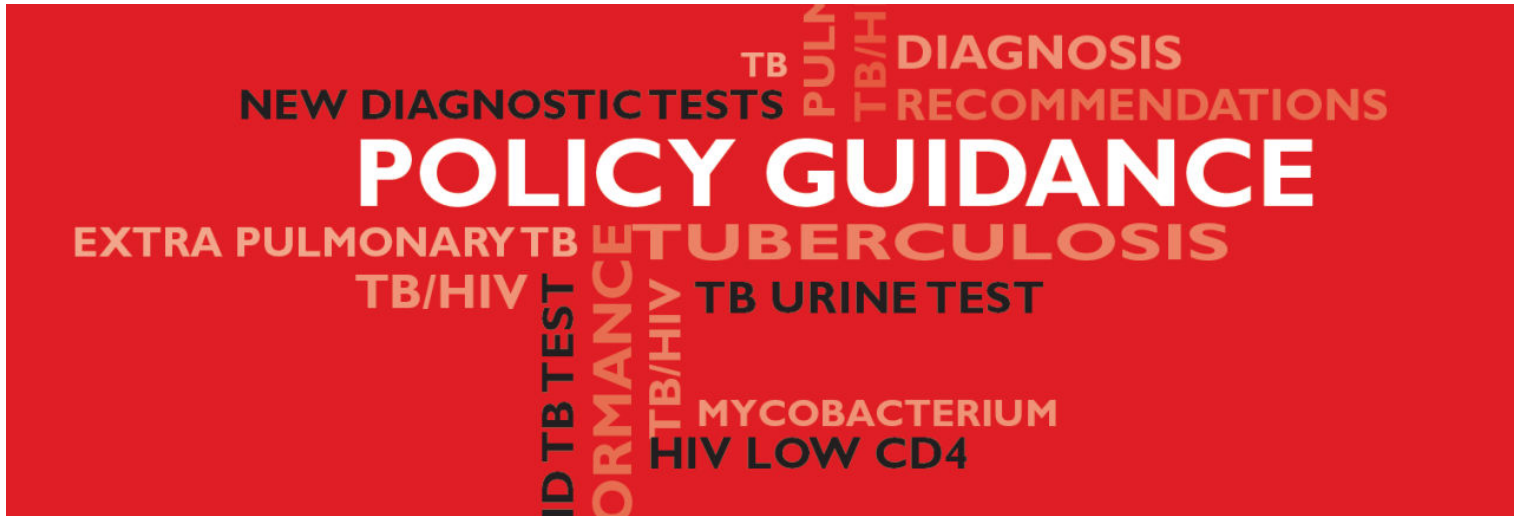
- LAM is a lipopolysaccharide found in Mycobacterium TB cell wall - released from metabolically active or degenerating bacterial cells
- Present predominately in people with active TB disease
- Enters urine if kidney involved in disseminated disease; other mechanisms unclear
- Simple lateral flow assay using drop of urine placed on strip; read in 30 min
- Low cost ($3.5)



- STAMP Trial
  - 2600 HIV+ patients randomized to standard of-care screening (sputum Xpert MTB/RIF) and intervention screening group (sputum and urine Xpert plus urine LAM)
  - Primary endpoint of all-cause 56-day mortality: not significantly different (absolute adjusted risk reduction –2·8%, 95% CI –5·8 to 0·3; p=0·074)
  - A significant mortality reduction was observed in 3 of 12 prespecified patient groups in the intervention arm:
    - –7·1% (95% CI –13·7 to –0·4) in patients with CD4 counts less than 100 cells per µL,
    - –9·0% (95% CI –16·6 to –1·3) in patients with Hb < 8 g/dL
    - –5·7% (95% CI –10·9 to –0·5) in patients with TB suspected at admission

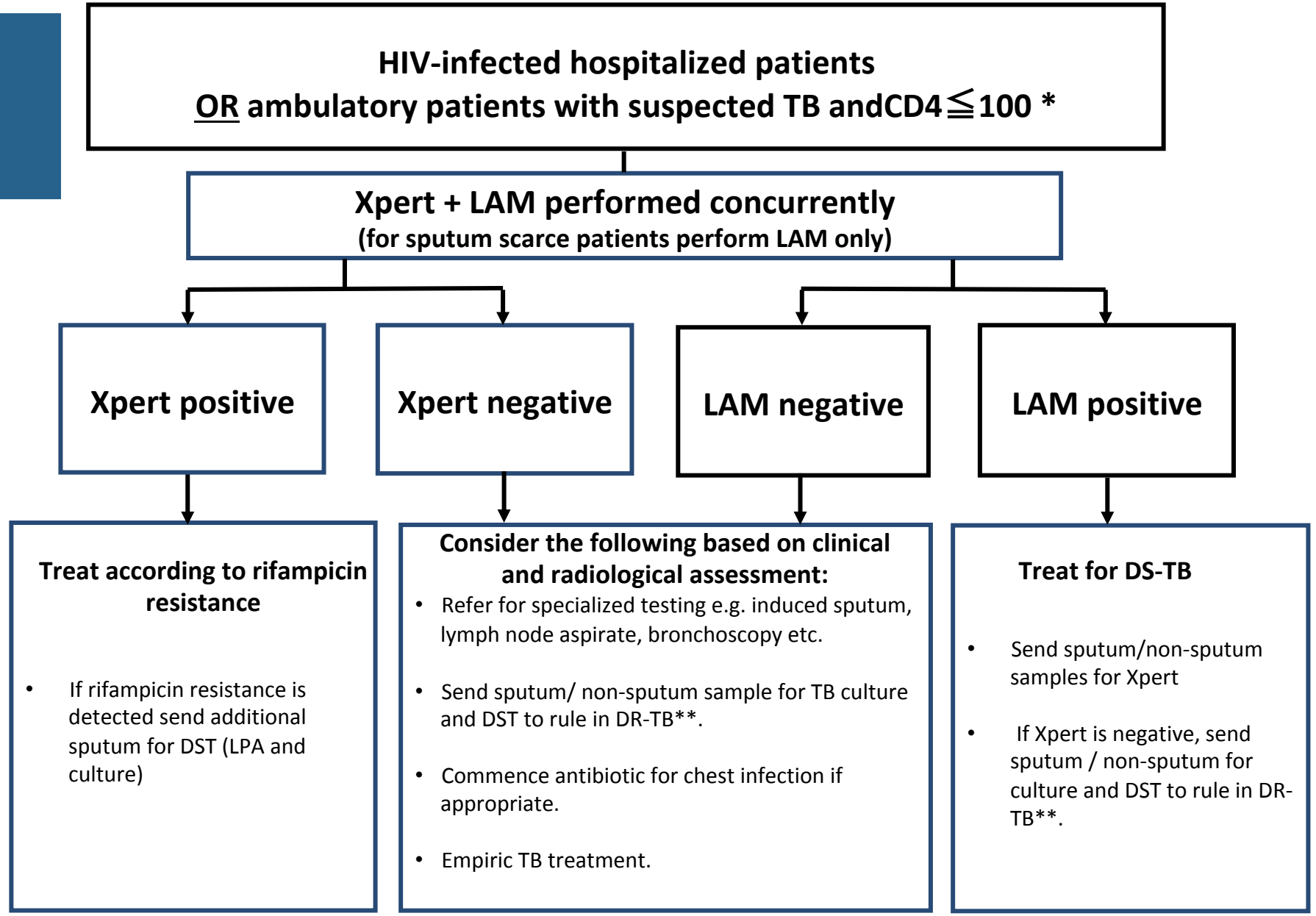
LAM Policy Guidelines

- Pooled analysis: 44% sensitivity; 92% specificity
- LAM conditionally endorsed by WHO in 2015
  - For use in HIV+ adults admitted to hospital with signs and symptoms of TB (CD4 count <100 cells/L) or who are seriously ill.



- Poor policy uptake

LAM Policy, South Africa 2018



Annotations:

* LAM is indicated in hospitalized patients admitted to the medical wards (or seen in the emergency unit) with HIV stage 3 or 4 disease (suspicion of TB is not necessary and obtaining a CD4 count is not mandatory though the best yield is in with a CD4 ≤100). Patients with danger signs (respiratory rate >30 per minute, temperature >39°C, heart rate >120 beats per minute and unable to walk unaided) are most likely to be LAM positive, however, these signs are not necessary to initiate LAM testing.

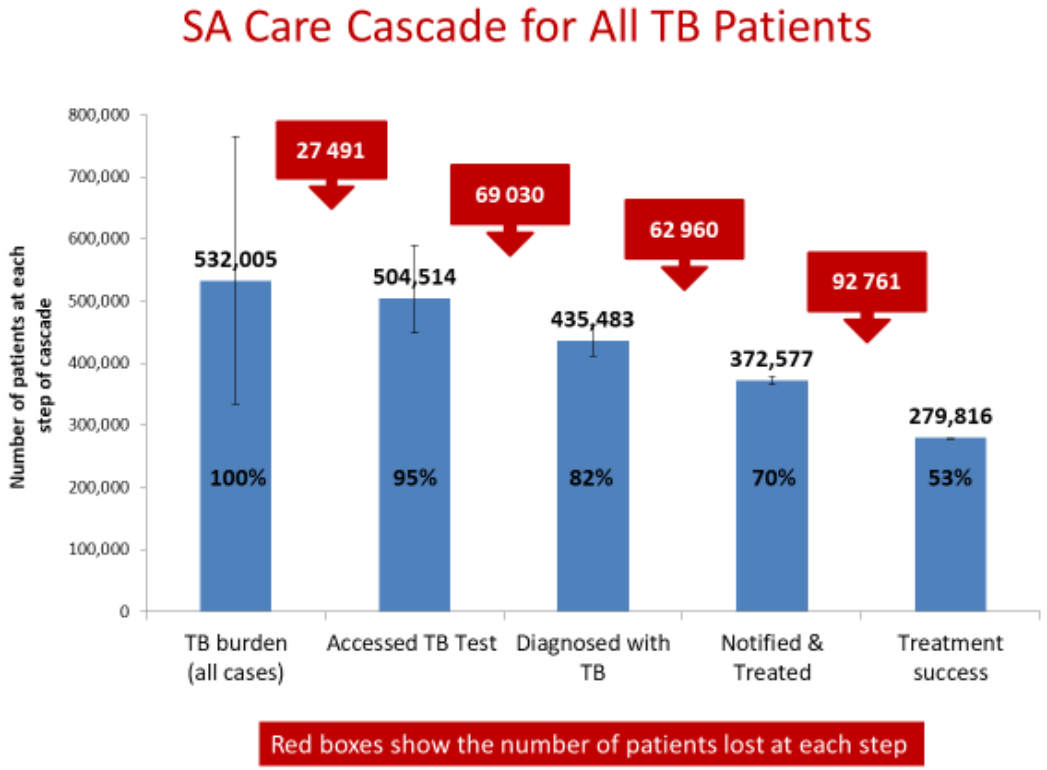
Improving LAM Accuracy

- Several groups and companies currently working on increasing sensitivity of LAM-based tests through improving:
  - Pre-analytical processing
  - LAM capture
  - LAM detection
- Example: Nanocage and copper dye technique (Luisa Paris et al)
  - Urine samples underwent centrifugation and supernatants analysed
  - Used copper-based reactive dye that binds LAM with very high affinity to improve LAM detection
  - Sensitivity: 96% and specificity 81% (at assay cutoff of 14 g/mL)
  - Complex processing; not suitable for POC

(Paris L, Magni R, Zaidi F, Araujo R, Saini N, Harpole M, et al. Urine lipoarabinomannan glycan in HIV-negative patients with pulmonary tuberculosis correlates with disease severity. Sci Transl Med 2017;9)

Concluding comments

- Non-sputum based, low cost screening test at POC would be helpful
- No “silver bullet”
- Understand the health system failures contributing to diagnostic gaps

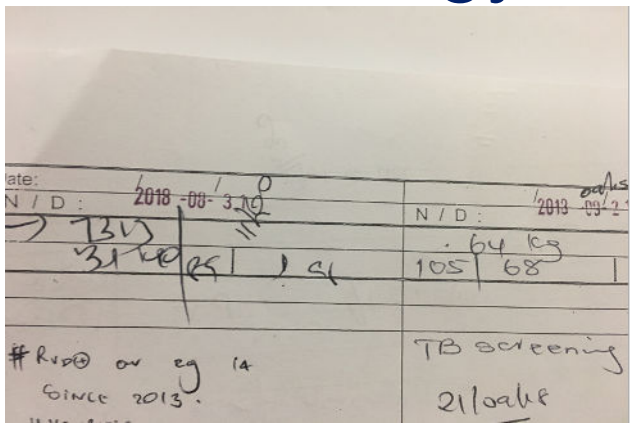


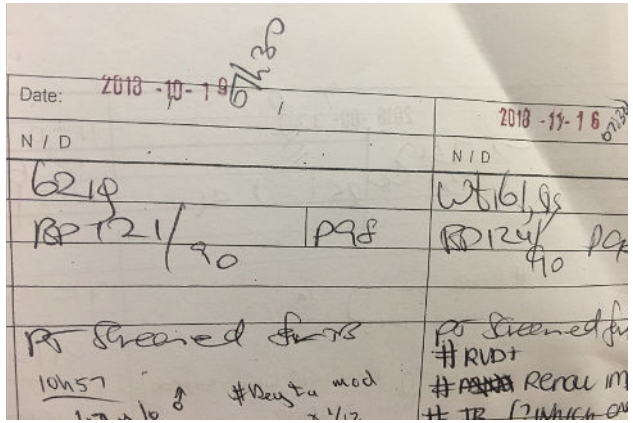
Diagnostic gaps:

- Only 60% individuals with presumptive TB diagnosed by Xpert, despite national roll-out two years prior
- Failure to screen individuals presenting with symptoms
- Failure to test symptomatic individuals

Concluding comments

- Use quality improvement methodology to optimize use of current tools
  - Routine review of weight





  - Quality (not just quantity) screening