Improving Tuberculosis Diagnostic Services in High Burden Countries

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Professor of Medicine and Public Health, University of California Irvine
Michael D. Iseman Lectureship
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Disclosures

- Medical Advisory Board + Stock Options: Medaica
  - Not relevant to current presentation

- Grant/Research Support: NIH, USAID, Bill and Melinda Gates Foundation, Global Health Labs

The End TB Strategy: Great vision and Ambitious Targets

Vision:

A world free of TB

Zero TB deaths, Zero TB disease, and Zero TB suffering

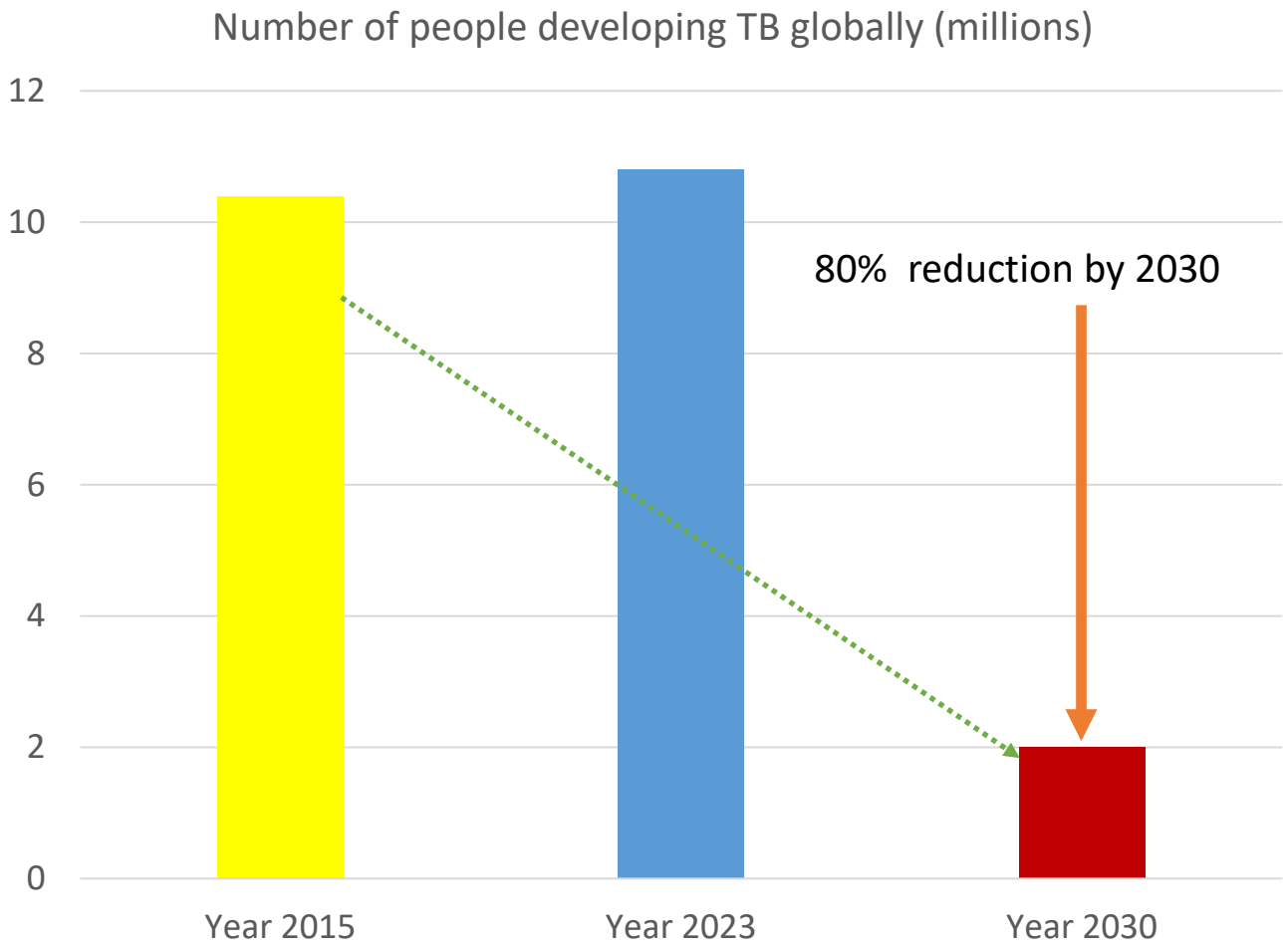
Goal:

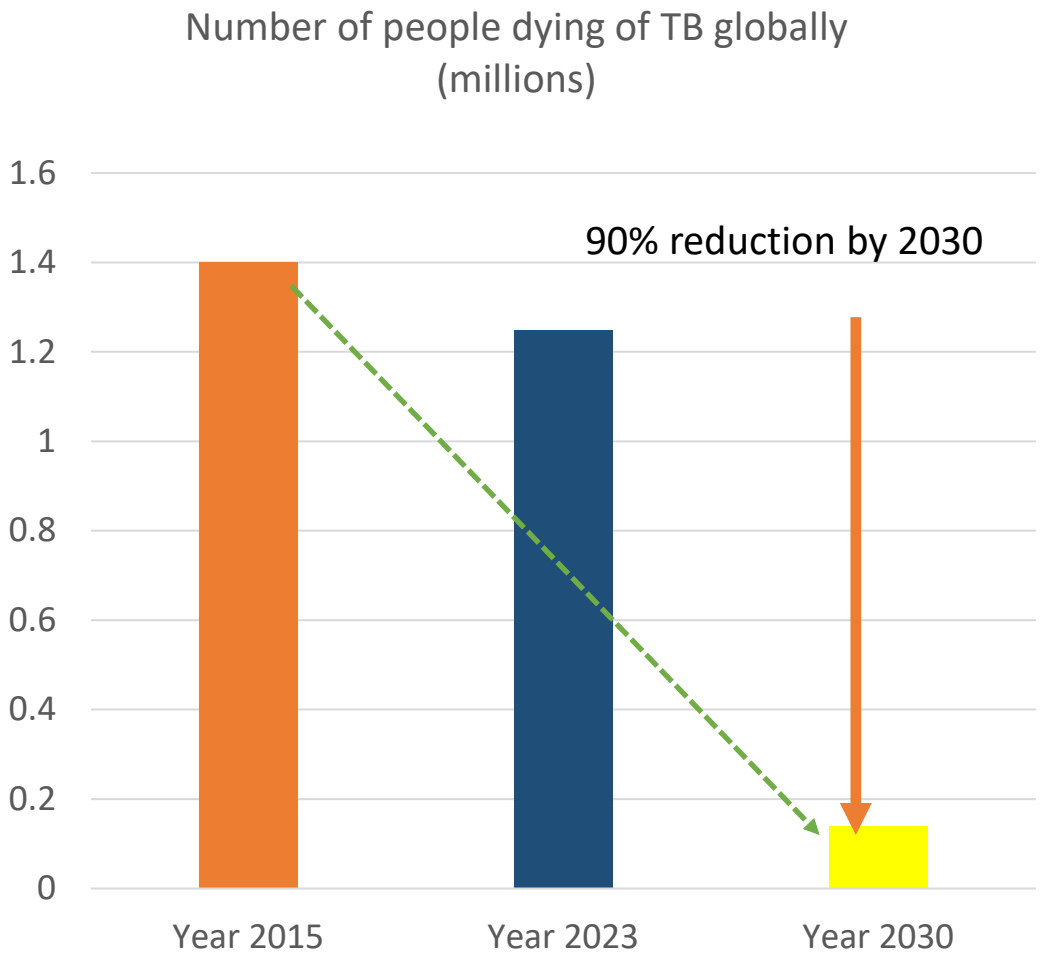
End the Global TB Epidemic

	MILESTONES		TARGETS	
	2020	2025	SDG* 2030	END TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20%	50%	80%	90%
TB-affected families facing catastrophic costs due to TB (%)	0%	0%	0%	0%

*SDG= UN Strategic Development goal

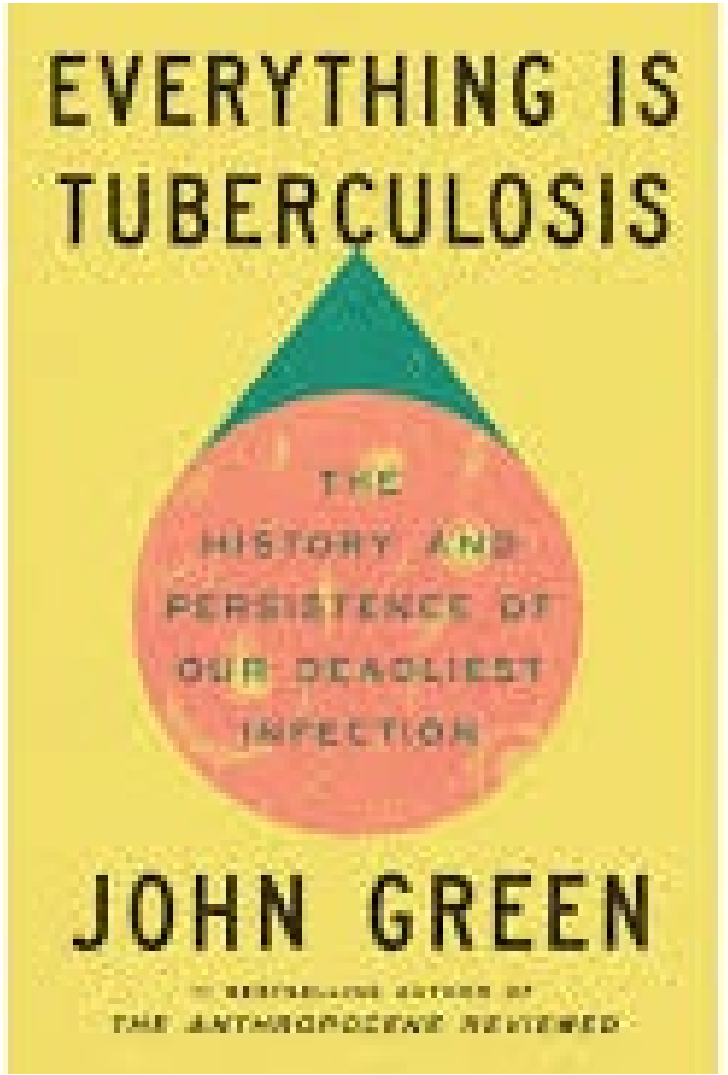
Problem: The world is not on track to achieve End TB Targets





Why are we not on track?

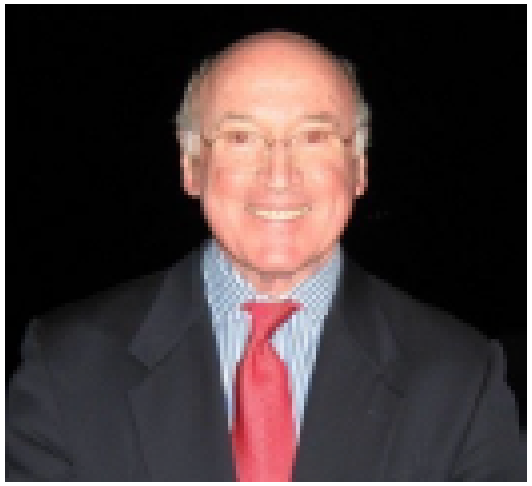
“The infection has long exploited human biases and blind spots. Of course, tuberculosis doesn’t know what it’s doing, but for centuries, the disease has used social forces and prejudice to thrive wherever power systems devalue human lives….”



OBITUARY

Michael Dee Iseman

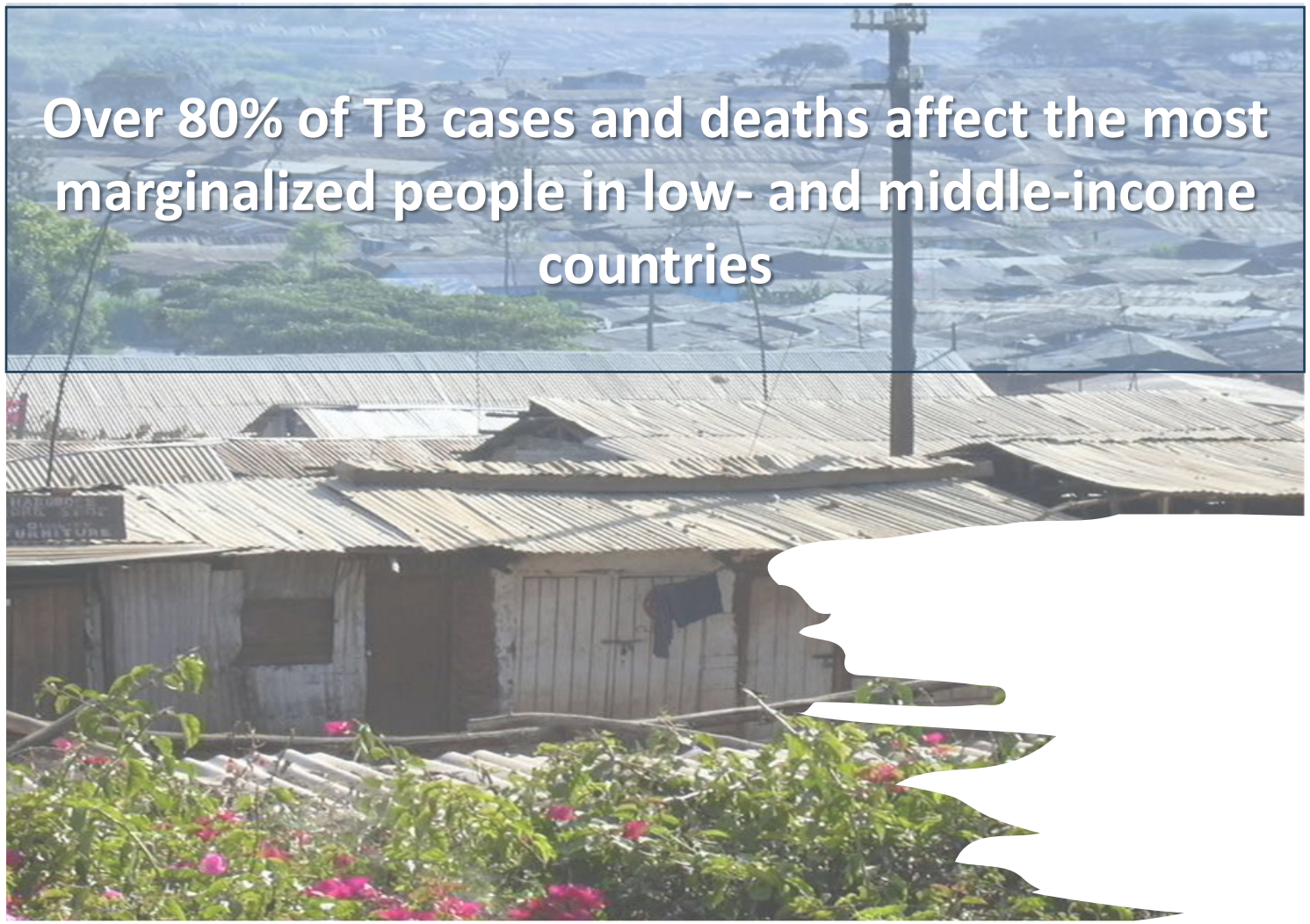
MARCH 3, 1939 – NOVEMBER 20, 2022



“He prided himself on making patients feel more human and treating them with dignity and empathy.”

Why are we not on track?

1. Poverty, social deprivation and growth of urban slum populations



- 8.5% of the global population (700 million) lives on less than US $2.15 a day
- Little or NO progress with global poverty reduction in recent years

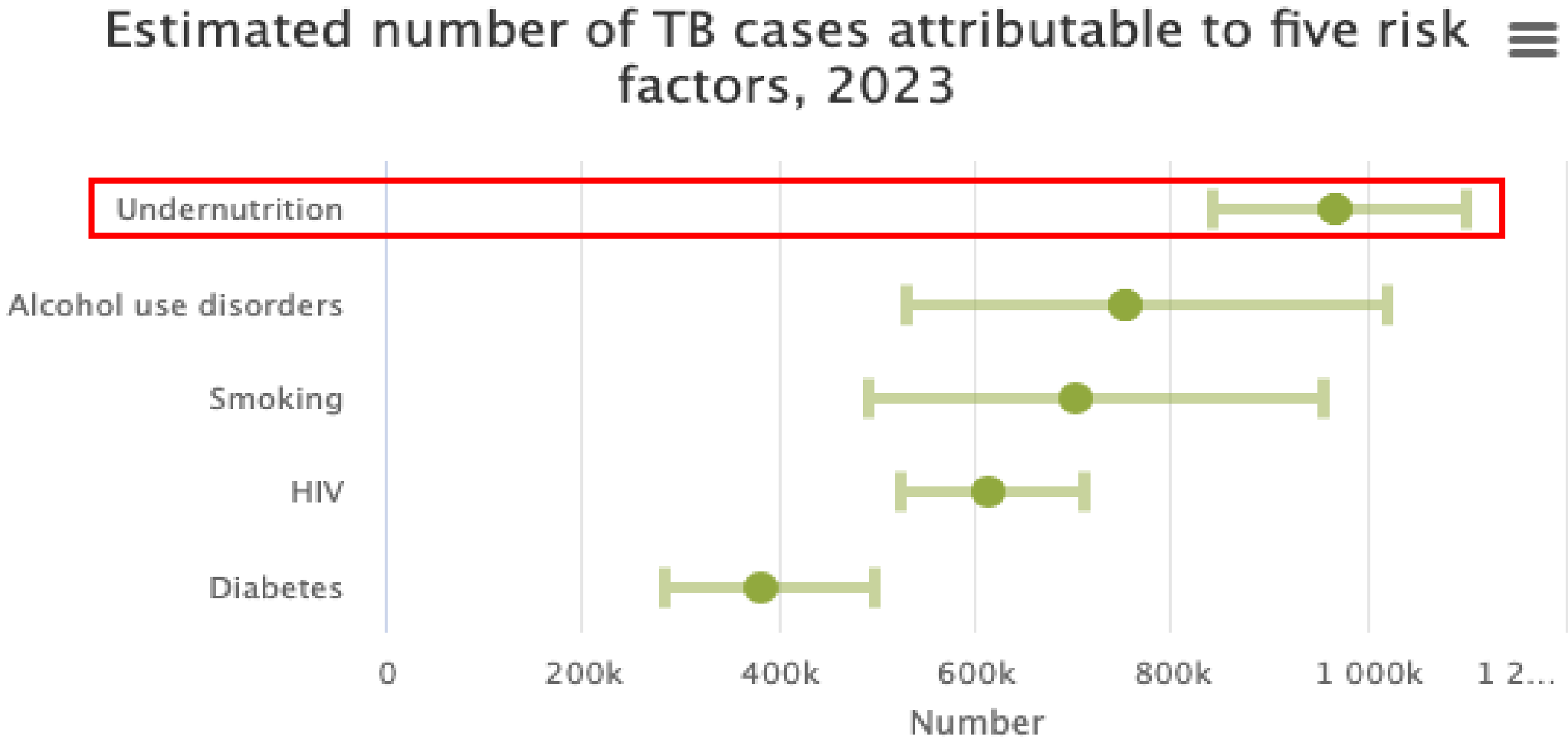
Real causes of TB: “poverty, bad housing, bad sanitation, bad working conditions, long hours, high rent, and poor food” – Dr. A. Wilberforce Williams

S16/Nature/Vol 605. 19 May 2022

World Bank Blogs (blogs.worldbank.org)

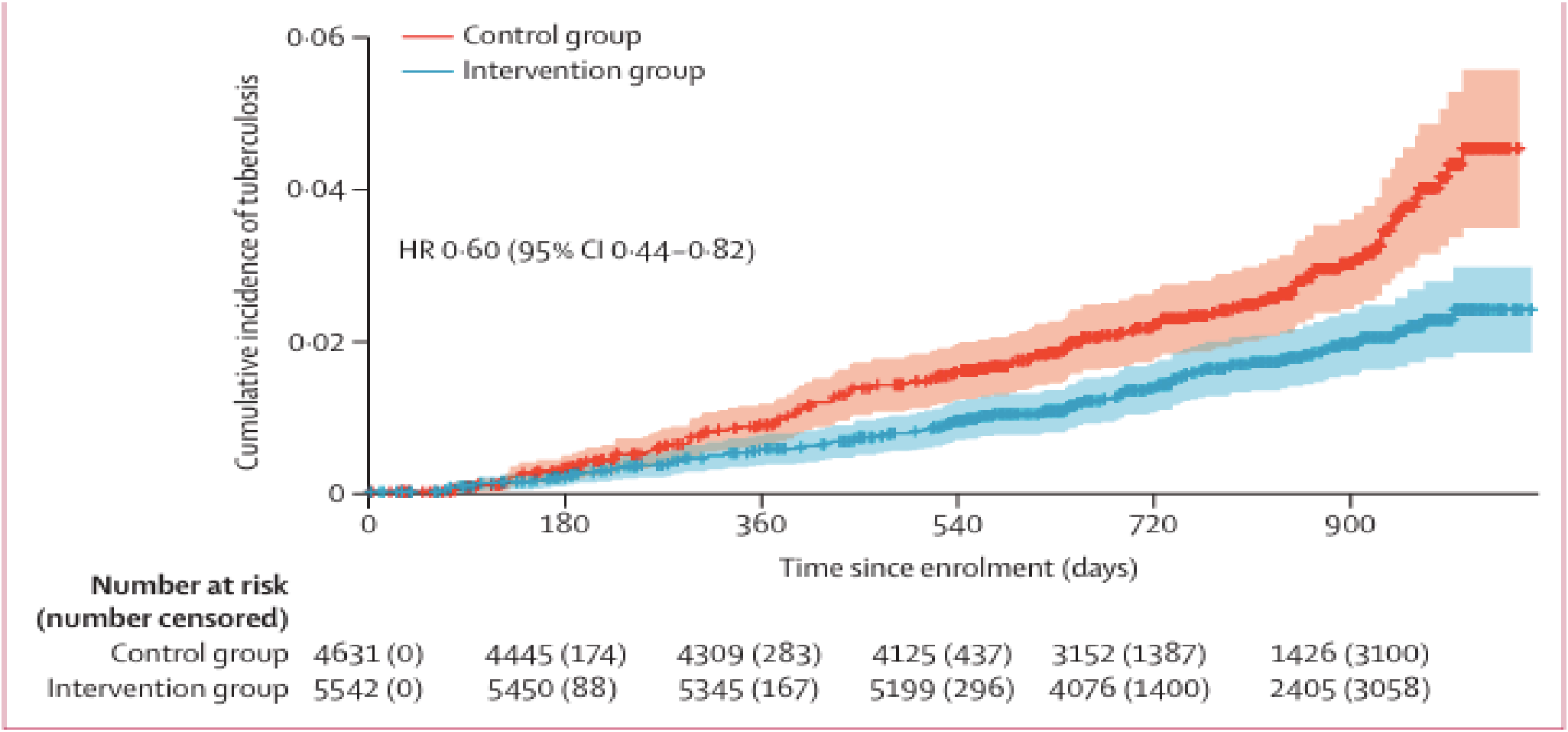
Why are we not on track?

2. Risk factors for TB remain highly prevalent (but beyond the scope of TB programs to influence)



WHO Global TB Report 2024

Provision of food to household contacts of people with TB reduces TB incidence



Number at risk (number censored)						
Control group	4631 (0)	4445 (174)	4309 (283)	4125 (437)	3152 (1387)	1426 (3100)
Intervention group	5542 (0)	5450 (88)	5345 (167)	5199 (296)	4076 (1400)	2405 (3058)

Figure 2: **Kaplan-Meier plot for cumulative incidence of tuberculosis disease in household contacts stratified by trial group over the follow-up period**

Lancet 2023; 402:627-40

Why are we not on track?
(and might be going further off track)

3. The threat of climate change.

Climate change: sending shivers down the spine of (most) people.

- Risk of natural disasters such as heat waves, droughts and flooding
- Displacement of people
- Increased food insecurity
- Increased TB transmission (the seed) and or vulnerability (the soil) of populations

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Review article

The impact of climate change on the risk factors for tuberculosis: A systematic review

Sahil Kharwadkar [a,b,*], Vinal Attanayake [a], John Duncan [a], Novindu Navaratne [a], Jill Benson [c]

[a] School of Medicine, The University of Adelaide, Australia
[b] School of Public Health, The University of Adelaide, Australia
[c] Discipline of General Practice, School of Medicine, The University of Adelaide, Australia

Public Health Action

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

VOL 11 NO 2 PUBLISHED 21 JUNE 2021

CORRESPONDENCE

Climate change and TB: the soil and seed conceptual framework

P. Sinha,[1,2] M. E. Carwile,[1] C. Cintron,[1] E. Coughlan de Perez,[3,4] N. S. Hochberg[1,2,5]

Then, there’s the elephant in the room

Financing of the Global TB response

Estimated need between 2023-2030: US$ 209.8 billion

Target for 2023: TB prevention, care and treatment: US$ 22 billion

Funds mobilized for TB prevention, care and treatment in 2023: US$ 5.7 billion

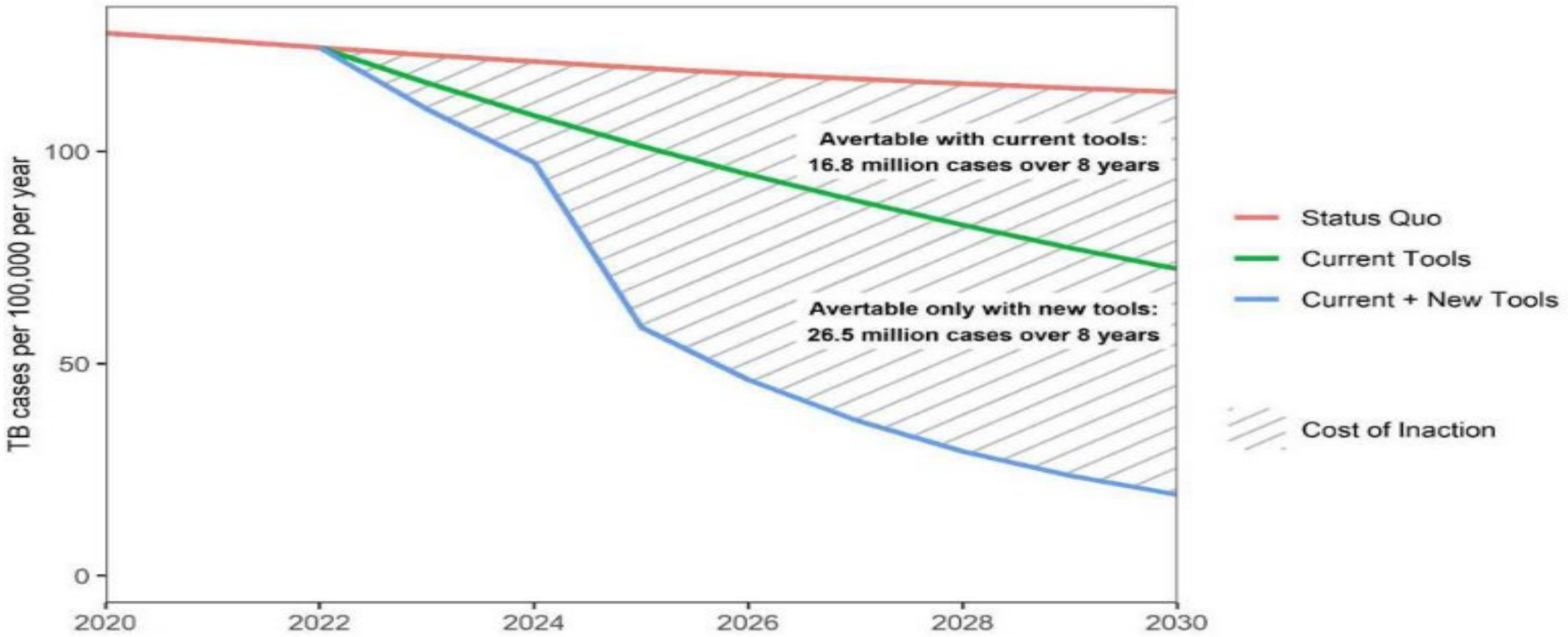
5.7/22=26%

GLOBAL HEALTH

Tuberculosis Resurgent as Trump Funding Cut Disrupts Treatment Globally

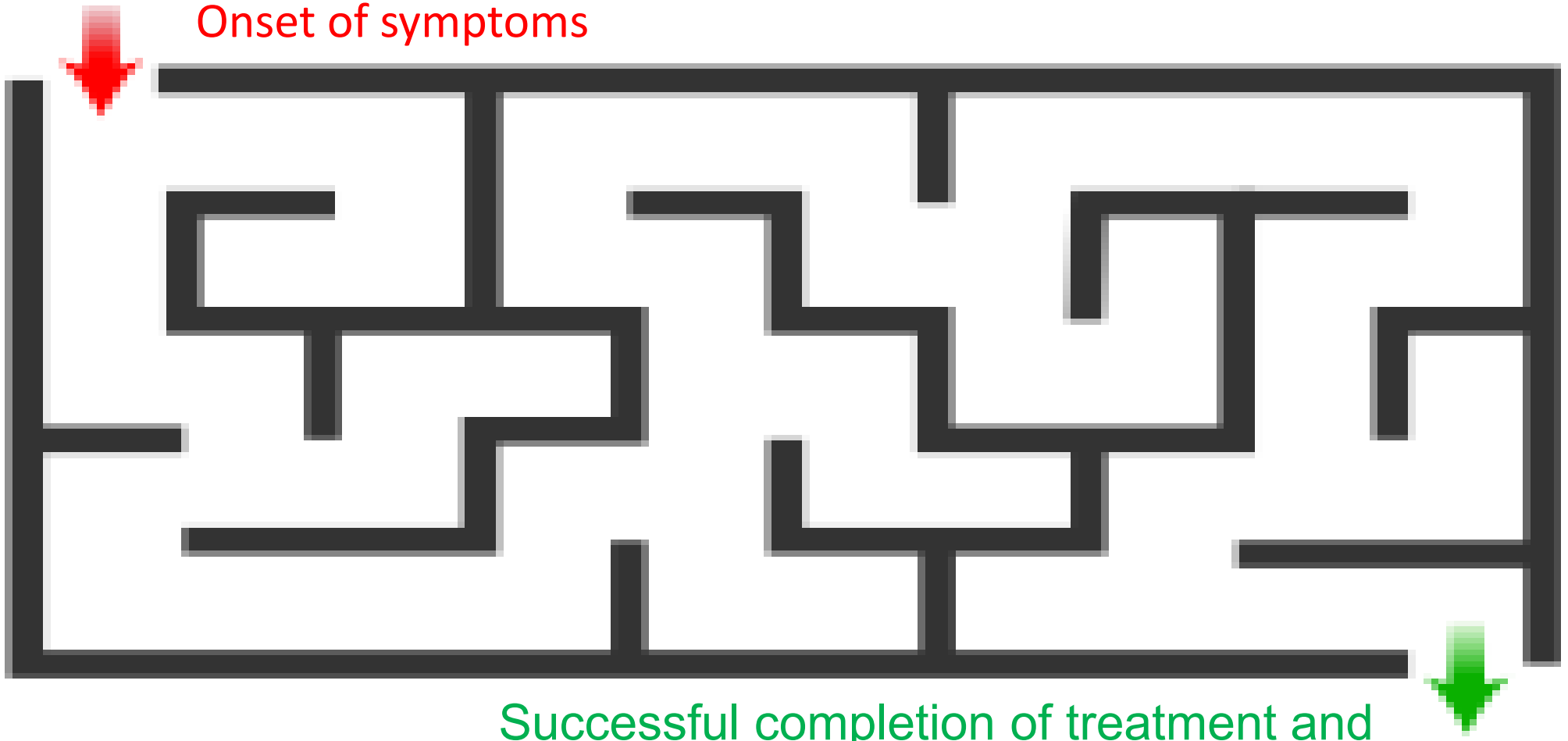
The United States was the major funder of tuberculosis programs. Now hundreds of thousands of sick patients can't find tests or drugs, and risk spreading the disease.

Global Plan to End TB: Costs of Inaction

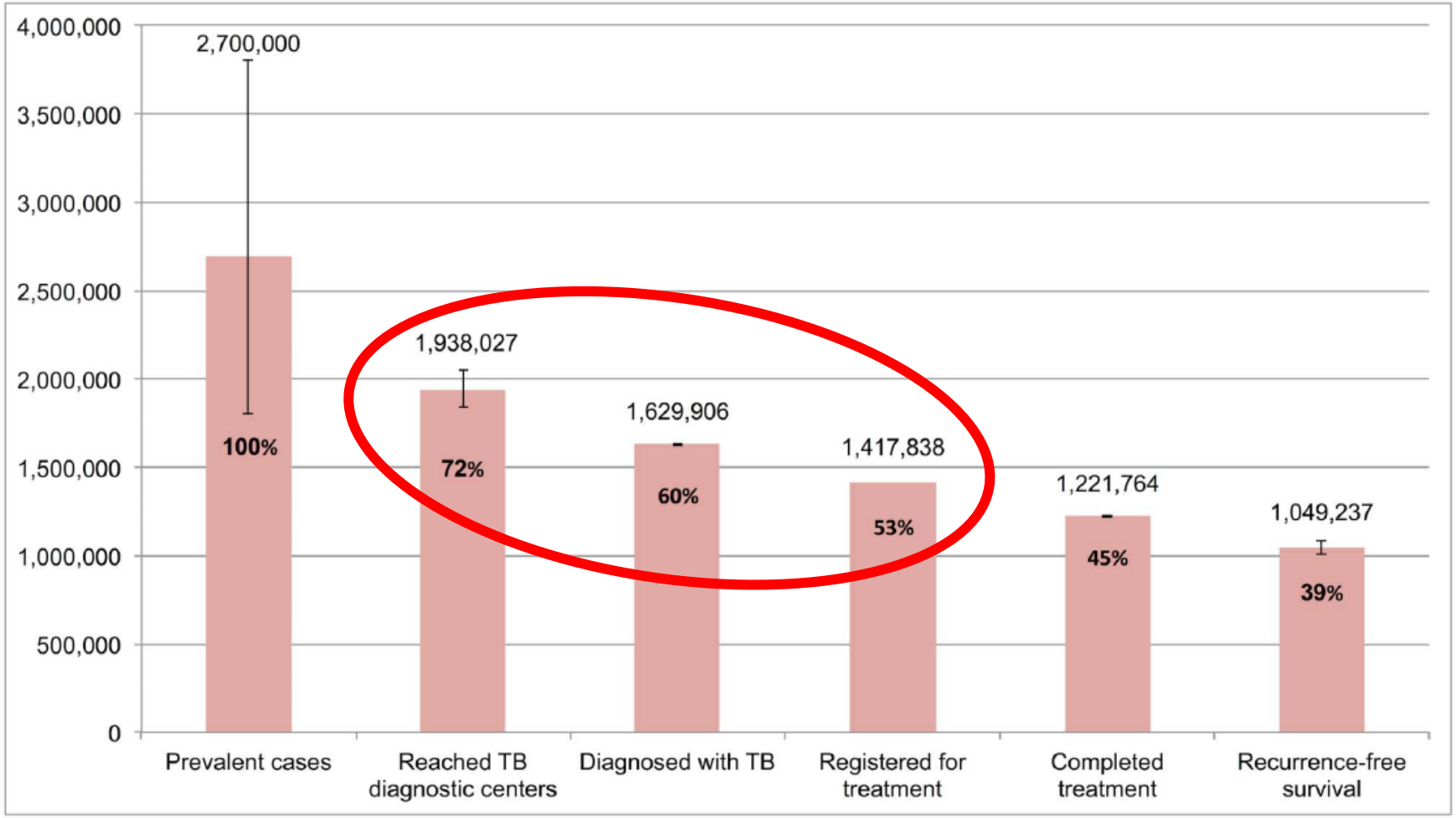


The Global Plan to End TB 2023-2030

The TB Prevention, Care and Treatment Maze: Systems barriers and gaps

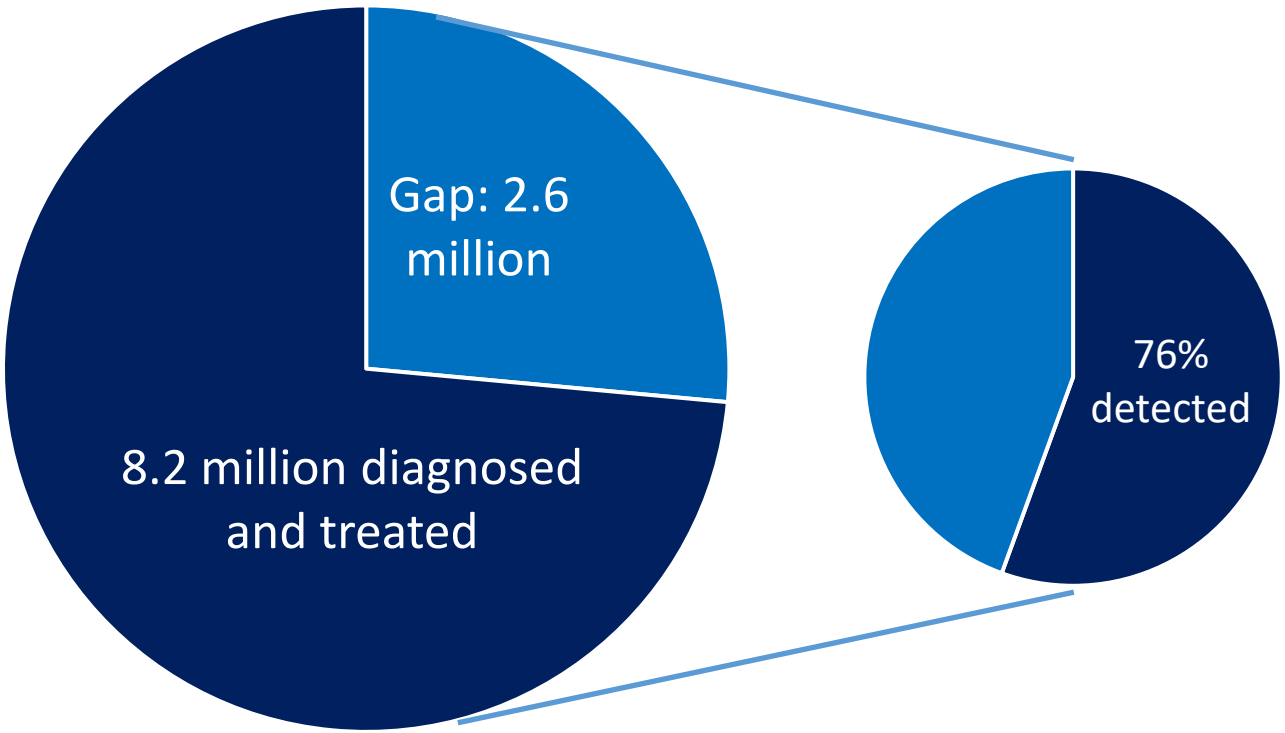


Diagnosis is the largest gap in the TB care cascade



Subaramman R et al, PLoS Med 2016

Millions of people still do not have access to a TB diagnosis



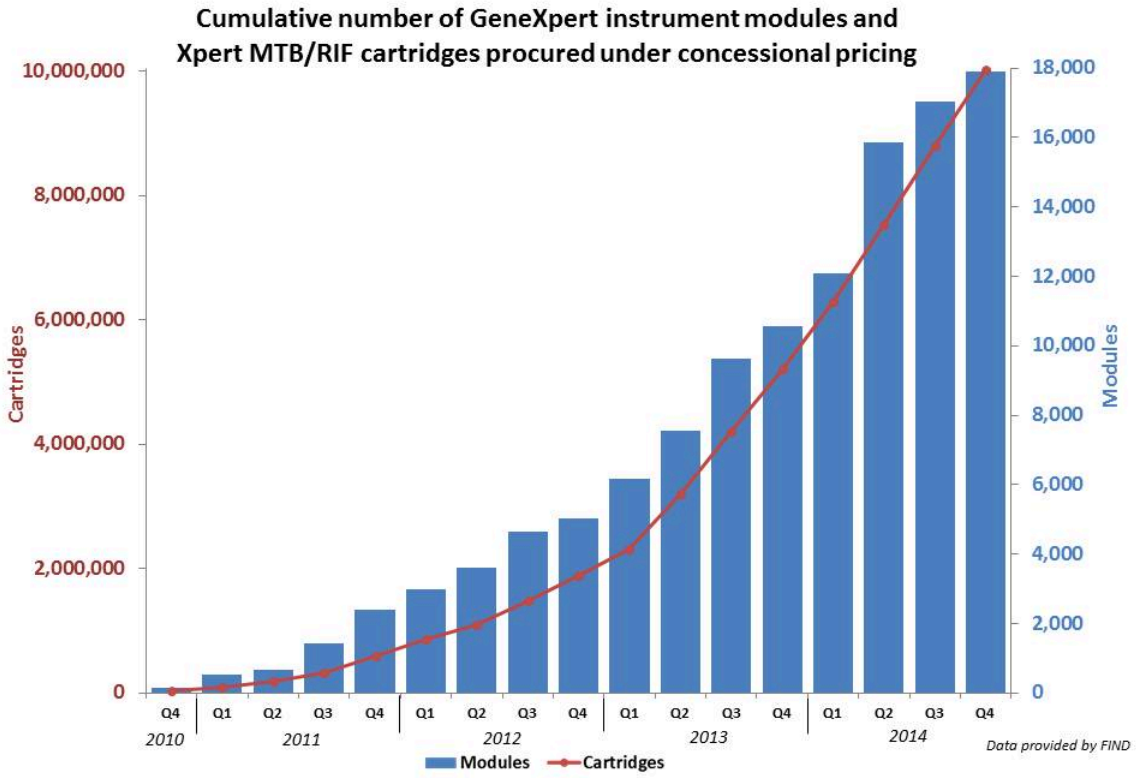
- <50% of diagnostic sites had access to WHO-recommended rapid diagnostics (WRDs) in 23 of 30 high burden countries
- WRD used as the initial test in only 48%
- Only 62% of pulmonary TB cases were bacteriologically-confirmed
- Only 79% of people with confirmed TB were tested for rifampin resistance

WHO Global TB Report 2024

Xpert MTB/RIF - a game changer?

- First molecular TB test to be endorsed by WHO (2010)
  - Semi-automated
  - Detects TB and RIF resistance in 2 hours
  - Sensitivity 85%, Specificity 98%

- Significant donor and country investment → rapid scale-up in high burden countries



As of 31 December 2014, a total of 3,763 GeneXpert instruments (comprising 17,883 modules) and 10,013,600 Xpert MTB/RIF cartridges had been procured in the public sector in 116 of the 145 countries eligible for concessional pricing.

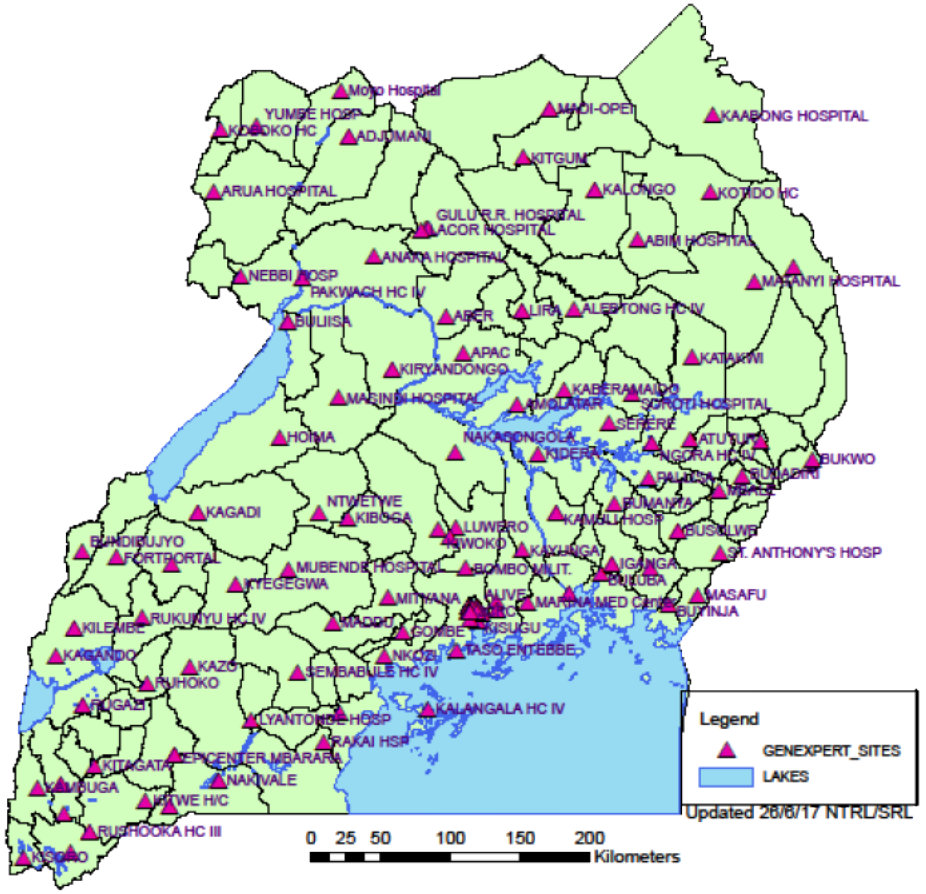
Uganda Context – Key successes

- Among global leaders in Xpert scale-up
  - >200 GeneXpert devices (**hub-and-spoke model**)
  - >400,000 Xpert MTB/RIF cartridges

- Nearly 4-fold increase in confirmed MDR TB patients (2009 → 2015)

- ? increase in total TB cases notified annually
  - 40-42000 → 44-45000 cases (pre-2010 → 2015)

- ? increase in proportion of bacteriologically-confirmed TB cases
  - 60-65% → >70% (pre-2010 → 2015)



Unresolved questions

- How well are Xpert referral networks functioning?
- What is the quality of TB diagnostic care within Xpert referral networks?
- What policy changes and co-interventions can further enhance Xpert (and future rapid molecular test) implementation?

Xpert Performance Evaluation to facilitate Linkage to TB care (XPEL TB)

AIMS

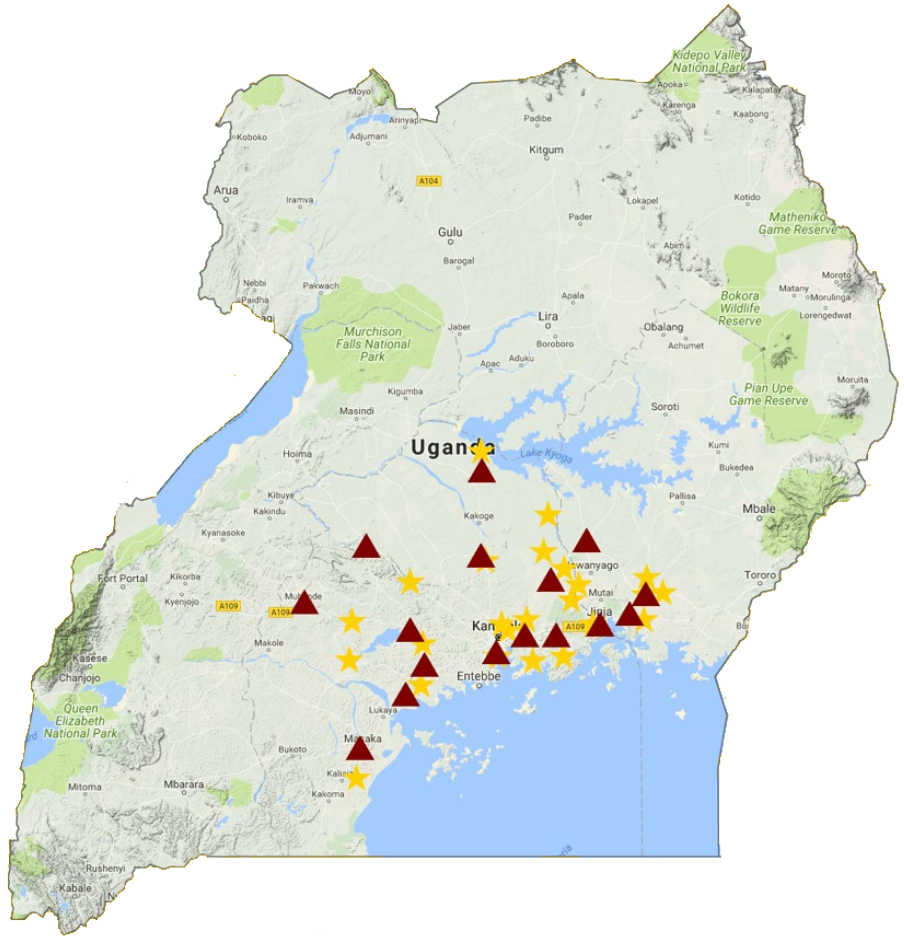
- To quantify gaps in TB diagnosis at health centers linked to Xpert testing sites

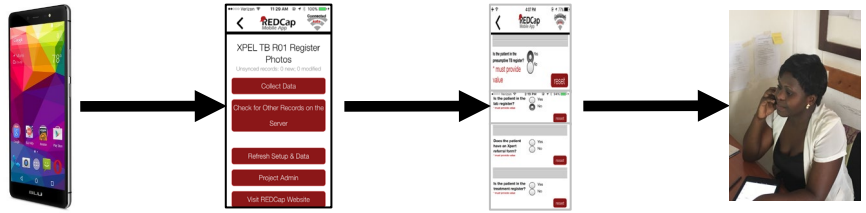
- To identify modifiable barriers to high-quality TB diagnostic services
  - Provider-level
  - Patient-level
  - Health system-level

- To develop and test a theory-driven intervention to improve the quality of TB diagnostic services

Aim 1: "Define quality gap"

- **Study setting**
  - 24 health centers (spokes) linked to 16 Xpert testing sites (hubs)
  - Selected based on 2015 NTLP case notification data
- **Study design:** Prospective cohort study
- **Participants:** All adults undergoing TB evaluation
- **Data collection**: TB test and treatment information extracted from TB registers





Quality of TB diagnostic evaluation

2594 adults undergoing pulmonary TB evaluation	%	Range
Indicator 1: Proportion referred for sputum-based TB testing	81%	55 – 96%
Indicator 2: Proportion completing recommended TB testing (if referred)	55%	13 – 80%
Indicator 3: Proportion treated within 14 days (if smear- or Xpert-positive)	73%	60 – 100%
Indicator 4: Cumulative probability of being diagnosed and treated	**33%**	4 – 77%

Davis JL, Katamba A et al. AJRCCM. 2011
Farr K, Nalugwa T et al. JC TUBE 2019

Utilization of Xpert testing

- 17% (365/2091) of patients referred for Xpert testing
  - 34% (267/779) of HIV-positive adults
  - 7% (98/1312) of HIV-negative adults

- <5% (14/365) of patients referred for Xpert as first-line test

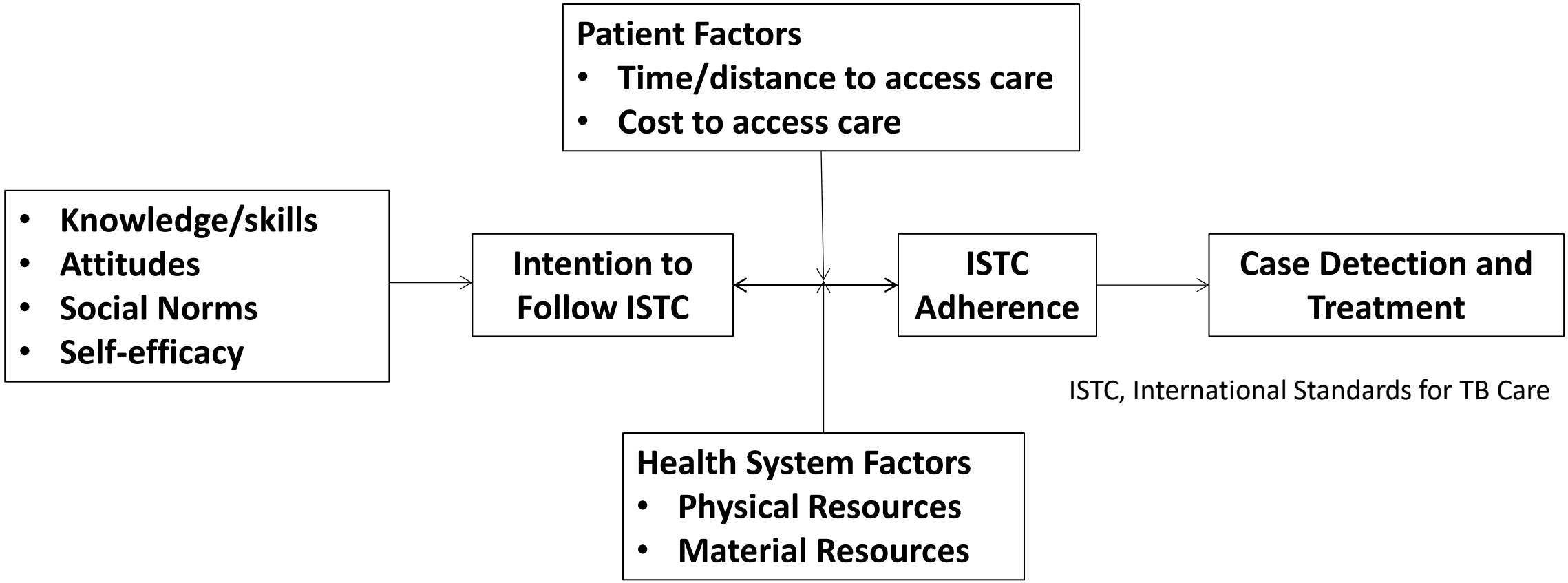
- <50% (20/48) of Xpert-positive patients initiated treatment within 14 days
  - Median time-to-treatment: 7 days (IQR 1 – 17)

High coverage of Xpert testing services ≠ High quality care

Farr K, Nalugwa T et al. JC TUBE 2019

Aim 2: “Understand quality gap”

- Conceptual Model: Theory of Planned Behavior



ISTC, International Standards for TB Care

Aim 2 Summary: Barriers to high-quality TB evaluation

PRECEDE framework	Recurring themes
Predisposing factors (Knowledge, attitudes, beliefs, intention)	• Time and resource constraints (*i.e.,* high workload) → low self-efficacy • Belief that TB evaluation is not urgent
Enabling Factors (Factors that if addressed make it easier to initiate the desired behavior)	• Failure of patients to return after initial visit (due to time and costs) • Inconsistent/delayed specimen transport to Xpert testing sites • Inability to track and follow-up patients *"When they have a cough for more than 2 weeks they are sent to the lab. But the problem is they get the first sample and sometimes, actually most times they don't bring the second sample."*
Reinforcing Factors (Factors that if addressed make it easier to continue the desired behavior)	• Lack of communication and coordination among staff • Insufficient oversight from NTP *"…Actually at times we have met but we don't meet [regularly], only when we realize there is a problem that's when we communicate and say why is this happening, then we try to rectify."*

1. Shete P, Haguma P et al. IJTLD 2015; 2. Nalugwa T, Shete PB et al. BMC Health Serv Res 2020; 3. Cattamanchi A et al. BMC Health Serv Res. 2015

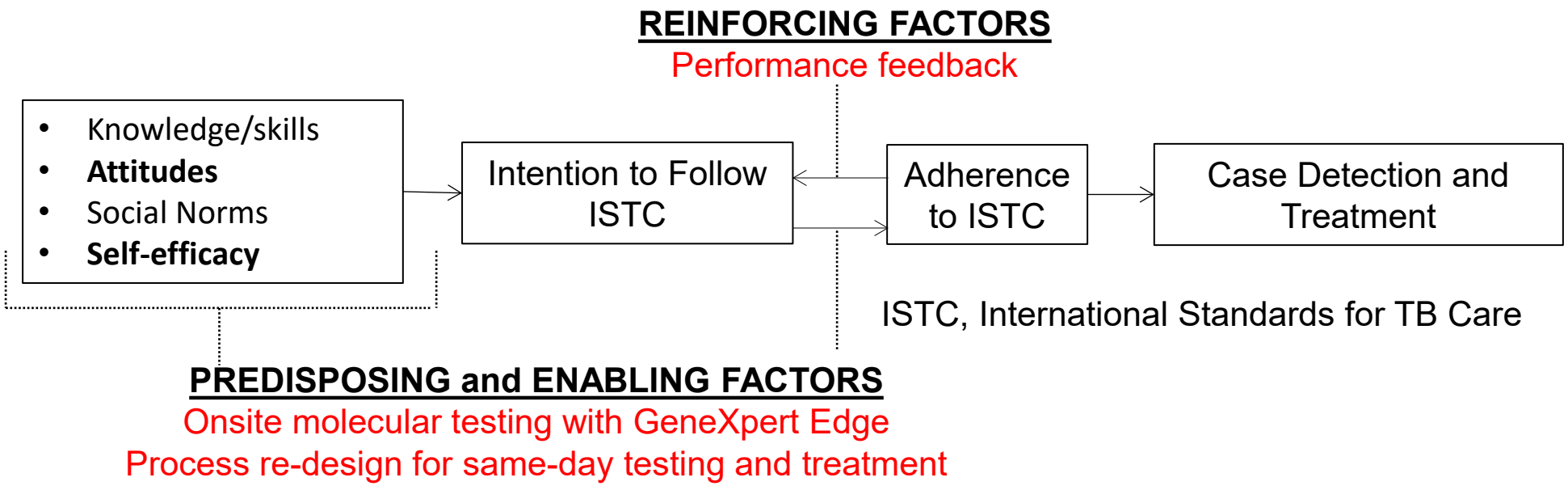
Aim 3: “Improve quality gap”

Intervention design process:

- Evidence review
- Stakeholder consultation
- Feasibility

1. Prioritize barriers
2. Select interventions
3. Specify how interventions delivered

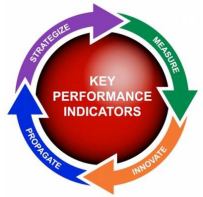
Theory-informed intervention components: XPEL TB strategy



1. **Onsite Xpert testing using GeneXpert Edge at health clinic**
   - Reduce workload, increase speed and accuracy of testing

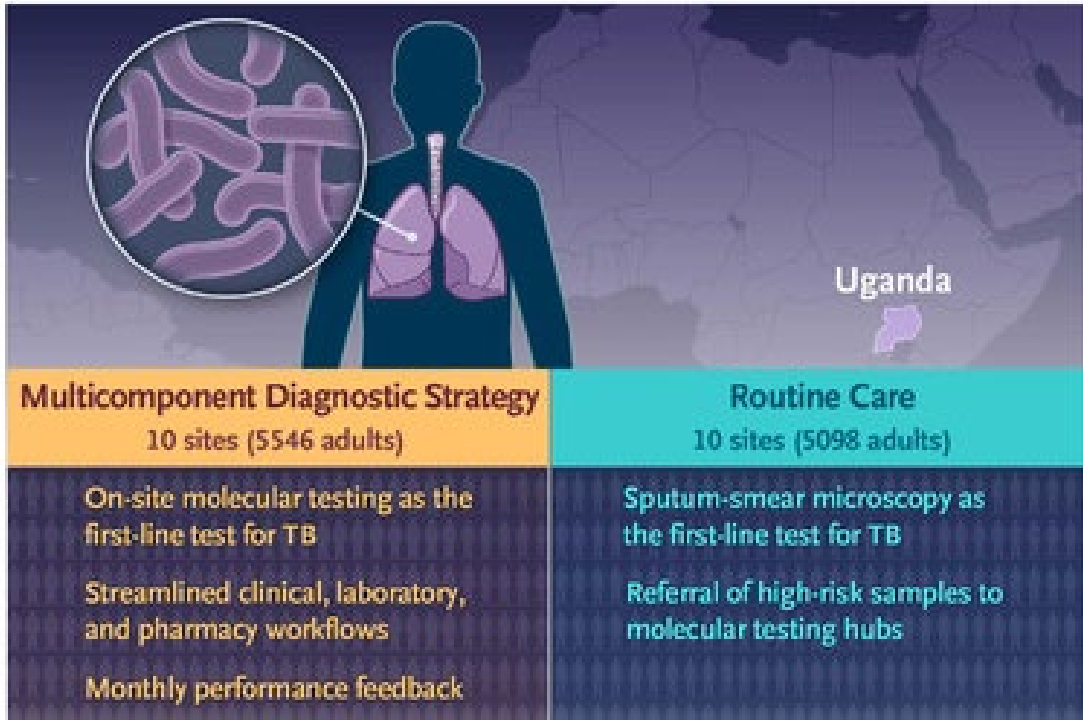
2. **Clinic process redesign to facilitate same day testing and treatment of TB**
   - Address lack of urgency and failure of patients to return

3. **Monthly feedback of quality metrics to health facility staff**
   - Improve communication, coordination and oversight



XPEL TB trial design and population

- **Objective**: To evaluate the effectiveness, implementation and costs/cost-effectiveness of the XPEL TB strategy at community health centers.
- **Design**: Cluster-randomized, hybrid effectiveness implementation (Type 2) trial at 20 community health centers in Uganda



- **Population**: All adults evaluated for pulmonary TB from Oct 2018 to Mar 2020
  - Patients with RIF resistance excluded from analysis

Reza T, Nalugwa T et al. Implement Sci 2020
Cattamanchi A et al. NEJM 2021

XPEL TB trial procedures

- Public randomization ceremony
  - restricted + stratified randomization using 2017 TB data

- “Ultra-pragmatic features”
  - Waiver of informed consent
  - No trial-specific changes to usual care (e.g., no CXR, culture, additional patient contact)
  - Outcomes assessed using routine data sources (*i.e.,* TB registers)
  - Minimal contact with health centers
    - initial training visit + quarterly site visits to resolve data queries and conduct nested sub-studies

Reza T, Nalugwa T et al. Implement Sci 2020

XPEL TB trial outcomes

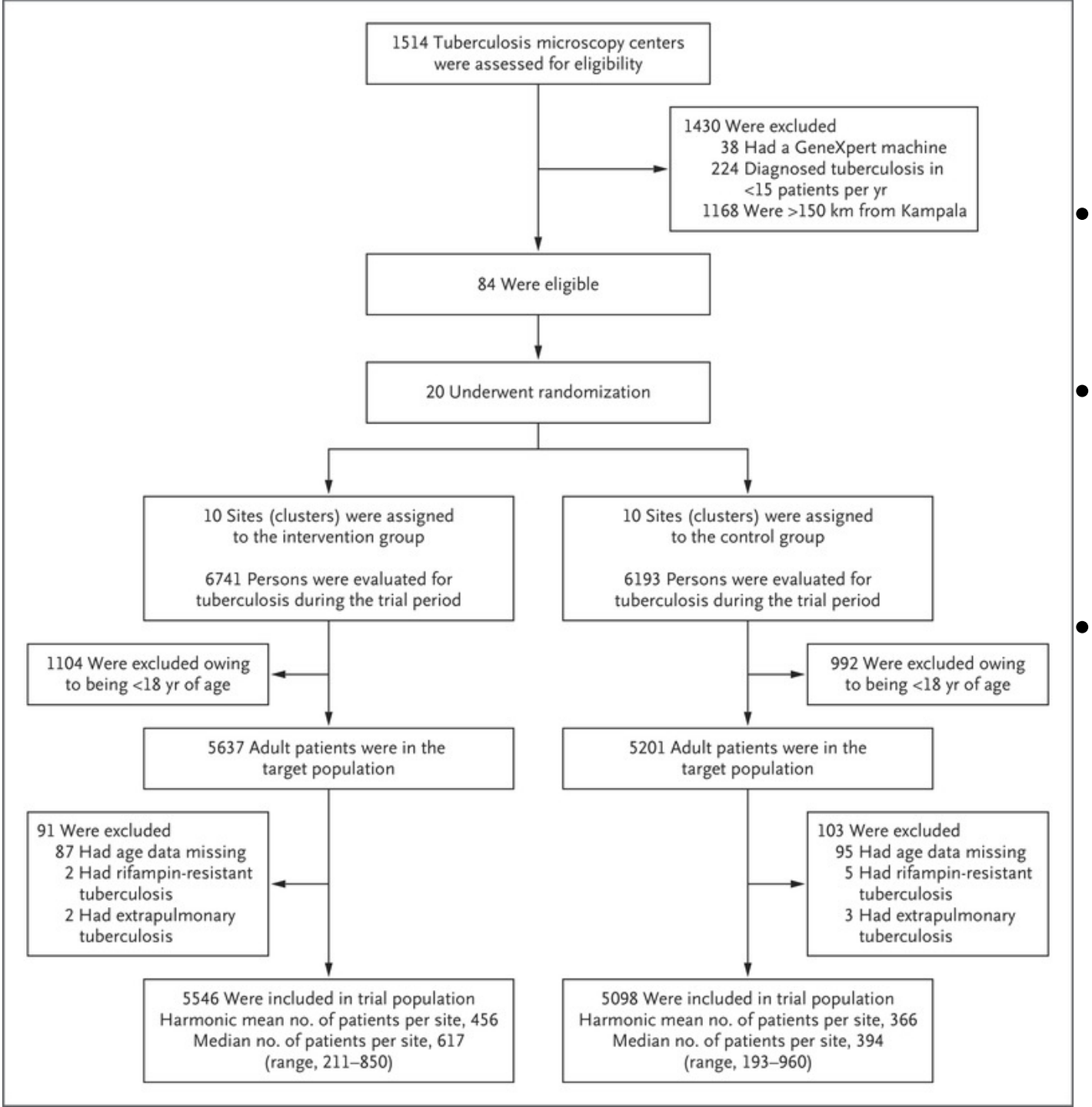
Primary outcome:

Number of patients treated for microbiologically-confirmed TB within 14 days

Secondary outcomes:

Care Cascade	Outcome
Testing	Number completing TB testing per national guidelines
Diagnosis	Number diagnosed with confirmed TB*
Treatment	Number treated for confirmed TB*
Treatment	Number treated for TB*

*Assessed within 1-day (same-day) and 14 days



Trial flow chart

- 20 of 84 eligible health centers selected and randomized
- >10,000 in target population (adults evaluated for pulmonary TB)
  - <2% excluded
- Harmonic mean number of patients higher in intervention arm (456 vs. 366)

Cattamanchi A et al. NEJM 2021

Patient-level characteristics

Characteristic	Intervention (n=5,546)	Control (n=5,093)
Female – no. (%)	3289 (59.3)	3112 (61.0)
Age in years – median (IQR)	40 (30-52)	38 (27-50)-
HIV status* – no. (%)		
Positive	2,285/5273 (43.3)	1,905/4290 (44.4)
Negative	2,988/5273 (56.7)	2,385/4290 (55.6)

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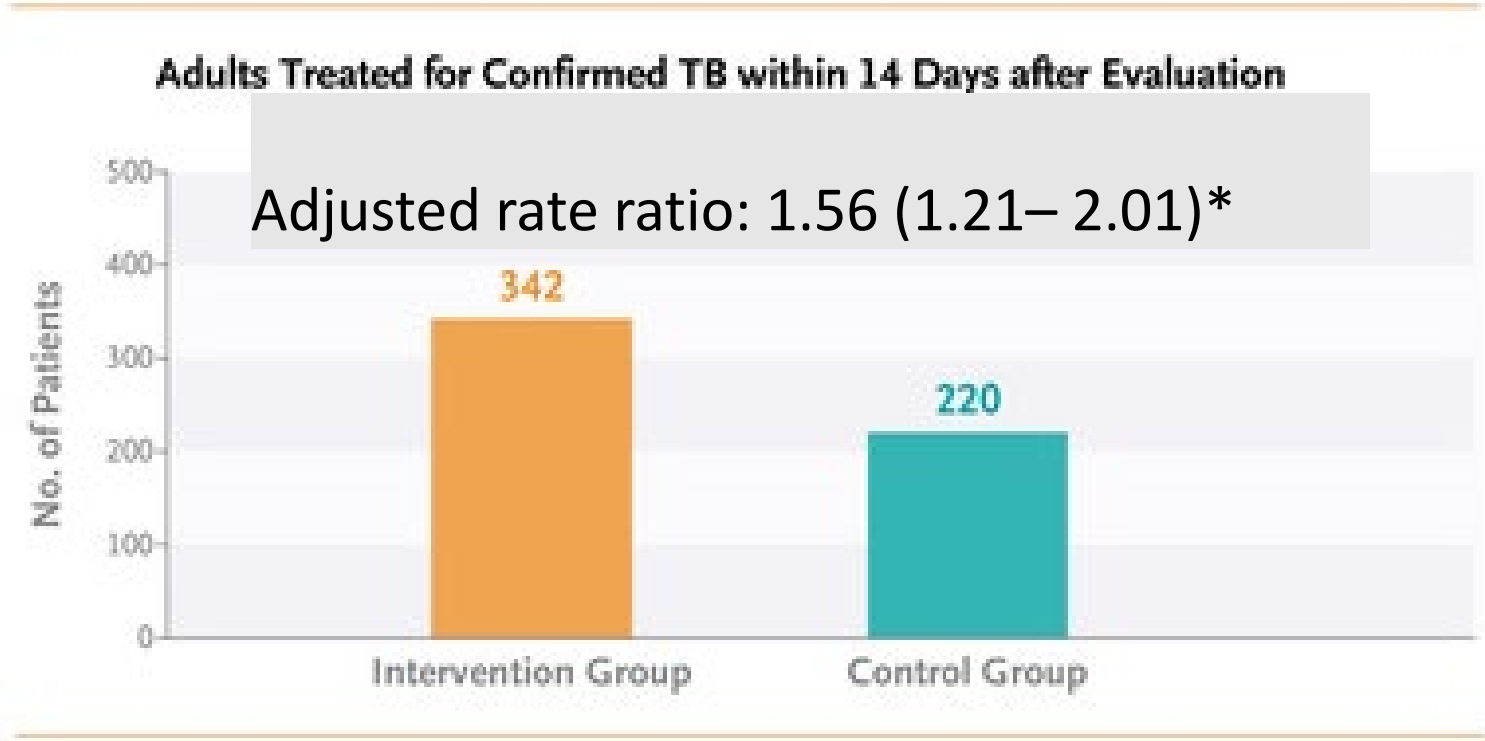
Primary outcome

- Cluster-level analysis using negative binomial regression models



* Adjusted for: Randomization strata, number of patients treated for confirmed TB within 14 days in 12-month pre-trial period

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Subgroup analyses of primary outcome

Table 2. Subgroup Analysis of Treatment for Confirmed Tuberculosis within 14 Days after Presentation (Primary Outcome).*

Subgroup	Intervention	Control	Unadjusted Rate Ratio (95% CI)†	Adjusted Rate Ratio (95% CI)‡
	number of patients			
All patients	342	220	1.55 (1.16–2.08)	1.56 (1.21–2.01)
Sex				
Male	234	147	1.59 (1.17–2.17)	1.59 (1.21–2.09)
Female	108	73	1.48 (1.02–2.15)	1.46 (1.03–2.07)
HIV infection status§				
Positive	134	75	1.79 (1.13–2.83)	1.78 (1.15–2.77)
Negative	206	144	1.43 (0.94–2.18)	1.46 (0.98–2.18)

* Adjusted for: Randomization strata, number of patients treated for confirmed TB within 14 days in 12-month pre-trial period

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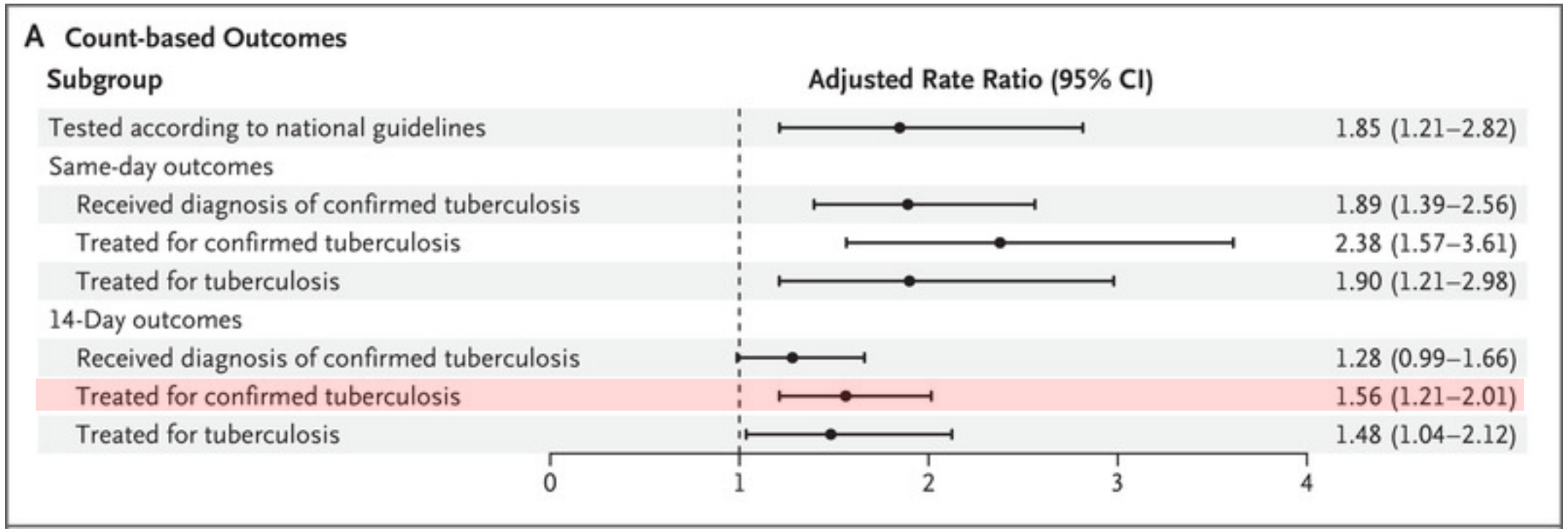
Secondary outcomes



High implementation fidelity and improved quality across the cascade of care

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Costs and incremental cost-effectiveness ratio (ICER)

	Total cost (95% UI)*	Number of patients tested (95% UI)*	Number of patients diagnosed with tuberculosis within 6 months (95% UI)*	Number of patients initiating treatment in 14 days (95% UI)*	Cost per patient (95% UI)*	Incremental cost-effectiveness ratio	
						Cost per additional tuberculosis diagnosis (95% UI)*	Cost per additional treatment initiation in 14 days (95% UI)*
Centralised	$37 123 (27 493–53 343)	3871 (2397–5044)	250 (145–347)	179 (102–247)	$9·59 (9·43–12·55)	..	..
Decentralised	$83 816 (69 585–111 758)	4135 (2540–5426)	285 (165–395)	247 (143–344)	$20·27 (18·90–29·29)	..	..
Difference	$46 693 (40 364–61 646)	264 (126–417)	35 (8–69)	68 (37–108)	$10·67 (8·78–17·04)	$1332 (763–5558)	$687 (501–1207)

UI=uncertainty interval. XPEL-TB=Xpert Performance Evaluation for Linkage to Tuberculosis Care. *The point estimates are based on empiric observations from the XPEL-TB trial for a 1-year period from Dec 1, 2018, to Nov 30, 2019. 95% uncertainty ranges were calculated using a Monte Carlo simulation (1000 iterations), with parameter inputs based on the variability in cost-effectiveness observed in the XPEL-TB trial. All costs presented in 2019 US$.

Table 3: **Total cost, total effectiveness, and incremental cost-effectiveness for 1 year of testing (Dec 1, 2018, to Nov 30, 2019)**

- Cost per test: 10% increase ($20.46 vs. $18.20)
- Cost per patient: more than double ($20.27 vs. $9.59)
- ICERs comparable to other case finding interventions

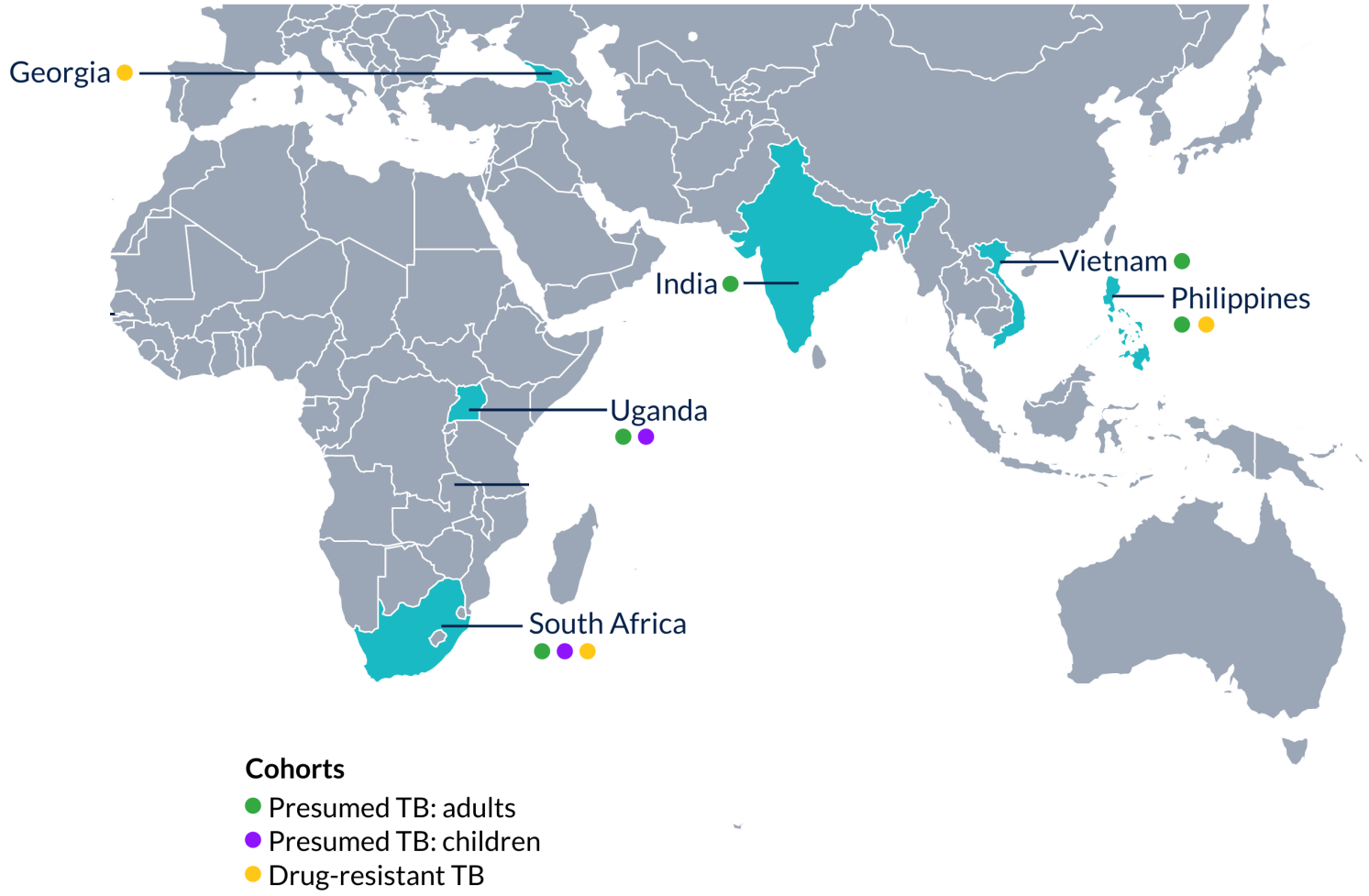
Thompson RR et al. Lancet GH 2023

Key limitations

- Potential imbalance in the underlying prevalence of TB and other factors by trial arm given relatively small number of clusters
- Multi-faceted intervention – effect of decentralized molecular testing alone unknown
- Generalizability – uptake and impact of intervention strategy in other high burden countries uncertain
- Cost – critical barrier to scale-up

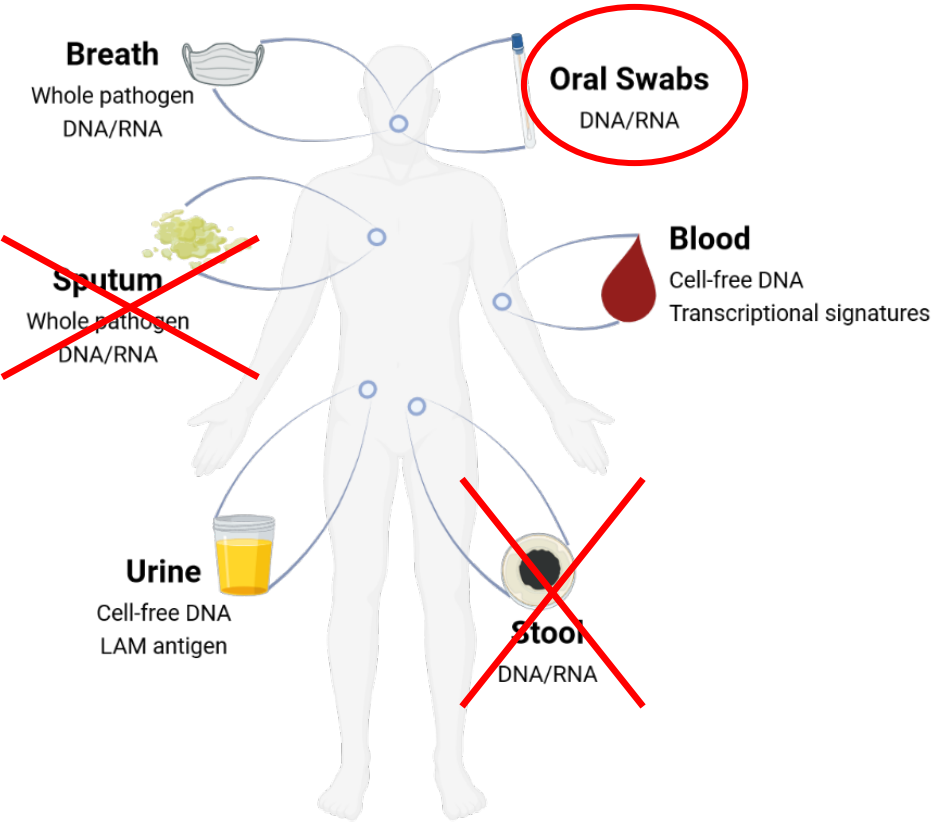
R2D2 TB Network

- U.S. NIH/NIAID U01-funded project to advance TB diagnostics
- Solicit and prioritize novel TB diagnostics for evaluation
- Conduct iterative studies of early-stage TB diagnostics to provide feedback to developers
- Conduct multi-center assessments of design-locked TB diagnostics to facilitate WHO policy review
- Assess the potential costs of novel TB diagnostics/algorithms



Website: https://www.r2d2tbnetwork.org
Twitter: @R2D2_Tbnetwork
Email: r2d2@ucsf.edu

Swab-based molecular testing



- Sputum is difficult to collect, transport and process
- Proof-of-principle studies demonstrate MTB detection from oral swabs
- Oral swabs are easily collected from people of all ages
- COVID-19 investments led to dramatic advances in swab-based molecular testing

Key lessons learned for swab-based TB molecular tests

- Swab type matters and should be validated before use (Luabeya et al, J Clin Micro 2019)
- Oral swabs are stable dry or in buffer, even at elevated temperatures
- Tongue swabs have higher yield than other nasal/oral swabs for TB detection (Luabeya et al, J Clin Micro 2019)
- Heat (to render sample biosafe and inactivate nucleases) AND mechanical lysis (to break open MTB cell wall) are likely required to achieve high clinical sensitivity
- Nucleic acid extraction and/or purification (which adds cost and complexity) is NOT required (Ahls CL et al, Clinical Micro 2023)
- Swabs dipped in sputum can be processed and tested in same manner as oral swabs (Mukwatamundu J et al, Union World Lung Health Conference 2024)

Novel Swab-based Molecular Diagnostics

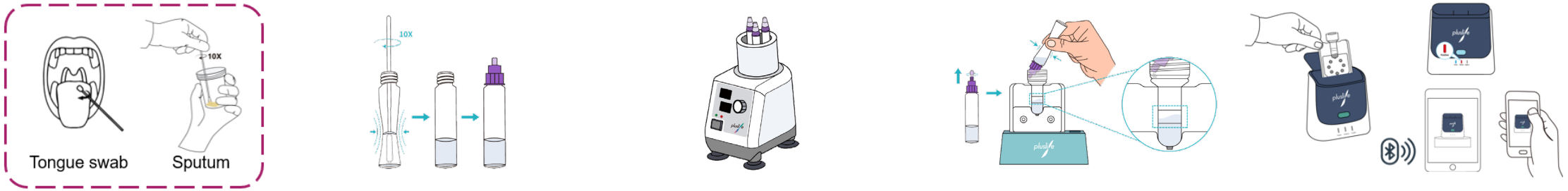
Platform: Integrated Nucleic Acid Testing Device (MiniDock)

Assay: Mycobacterium tuberculosis Nucleic Acid Test Card (MiniDock MTB Test)

Technology holder: Guangzhou Pluslife Biotech Co., Ltd., China

Workflow

Collect Sample → **Mix Sample** → **Lyse Sample** → **Fill Test Card (40ul)** → **Run Test and Output Result**



Operational characteristics

Time-To-Result	Hands-On-Time	Battery Operation	Daily Throughput	Maintenance
<35 min	2 min	Yes	>9 tests/day	None

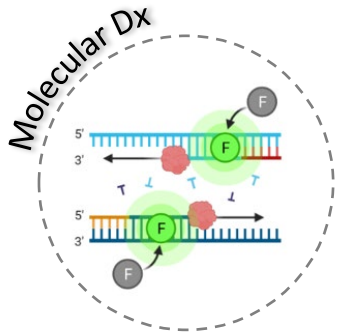
MiniDock MTB: Diagnostic accuracy against MRS (N=964)*

Study Population: Consecutive people ≥12 years with presumed TB presenting to outpatient clinics Nigeria, South Africa, Uganda, Zambia, India, Philippines and Vietnam from October 2024 – January 22, 2025

Test	Sample	Error Rate n/N (%)	Sensitivity^ n/N (%, 95% CI)	Specificity^ n/N (%, 95% CI)
MiniDock MTB	**Sputum swab**	9/964 (0.9%)	138/170 (81.2%, 74.5-86.8)	764/780 (97.9%, 96.7-98.8)
Xpert Ultra	**Sputum**	4/964 (0.4%)	146/170 (85.9%, 79.7-90.7)	767/780 (98.3%, 97.2-99.1)
MiniDock MTB	**Tongue swab**	6/964 (0.6%)	124/170 (72.9%, 65.6-79.5)	775/780 (99.4%, 98.5-99.8)
Microscopy	**Sputum**	N/A	91/170 (53.5%, 45.7-61.2)	779/780 (99.9%, 99.3-100.0)

* Excludes 148 participants with indeterminate or missing MRS results

^ Excludes 14 participants with missing/invalid first tongue swab, sputum swab or sputum Xpert results



Early development

Late development

Clinical validation

Commercialization

Low-complexity	X	X	X	X	X	X	X	X	X	X	X	X
Near Point-of-Care	X	X	X	X	X	X	X	X	X	X		
Point-of-Care	X	X										

CONCLUSIONS

- TB is thriving as a global public health threat, driven by social injustice, TB service access barriers and inadequate financing
- To have impact, new tools must be implemented in a manner that reduces access barriers and improves quality of TB services
- Decentralized molecular testing (along with appropriate implementation supports) dramatically increases case detection and linkage to treatment
- Lower cost molecular platforms are needed to scale up decentralized molecular testing for TB including in community settings, and are on the horizon

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