TB DIAGNOSTICS: THE BIG PICTURE

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DIAGNOSIS: A WEAK LINK IN TB CONTROL

Deepti and Nandita are not alone!

MANY TB PATIENTS STRUGGLE TO GET QUALITY DX & RX

Missing patients and major access issues

Long, complex pathways to TB care & diagnostic delays

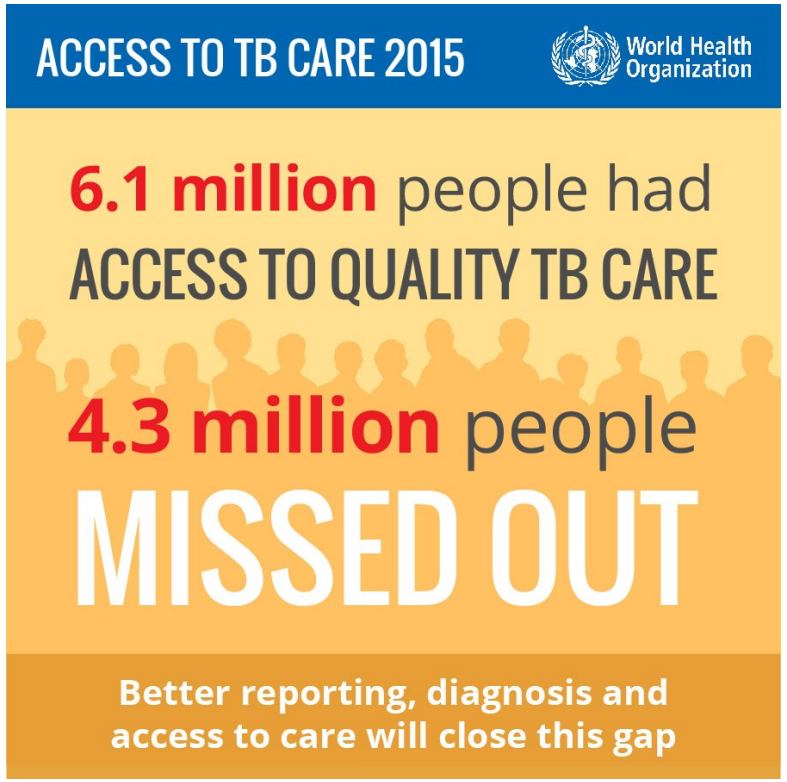
Broken care cascades

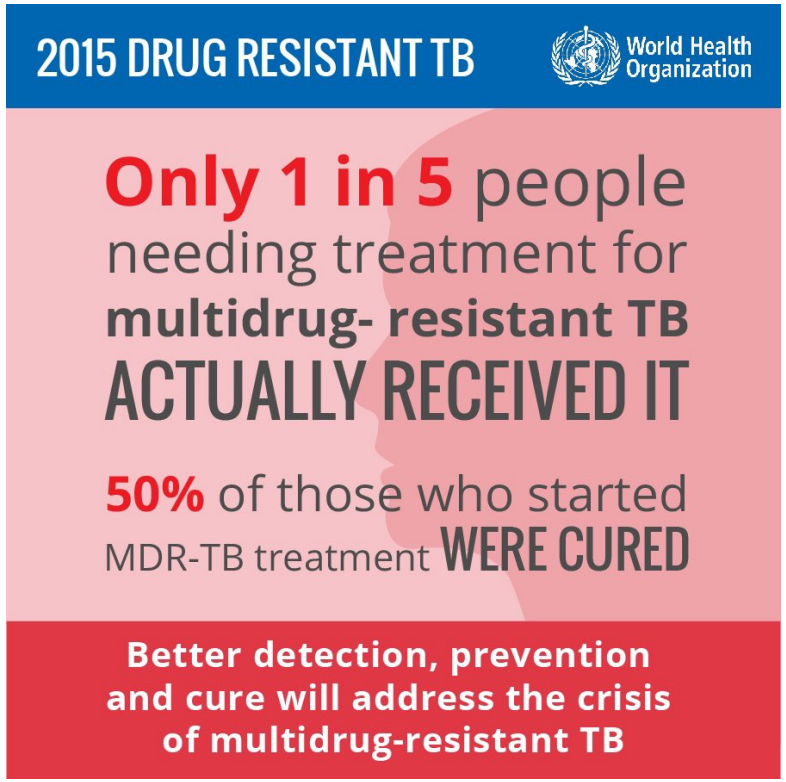
Challenges in getting decentralized care

Limited access to new tools

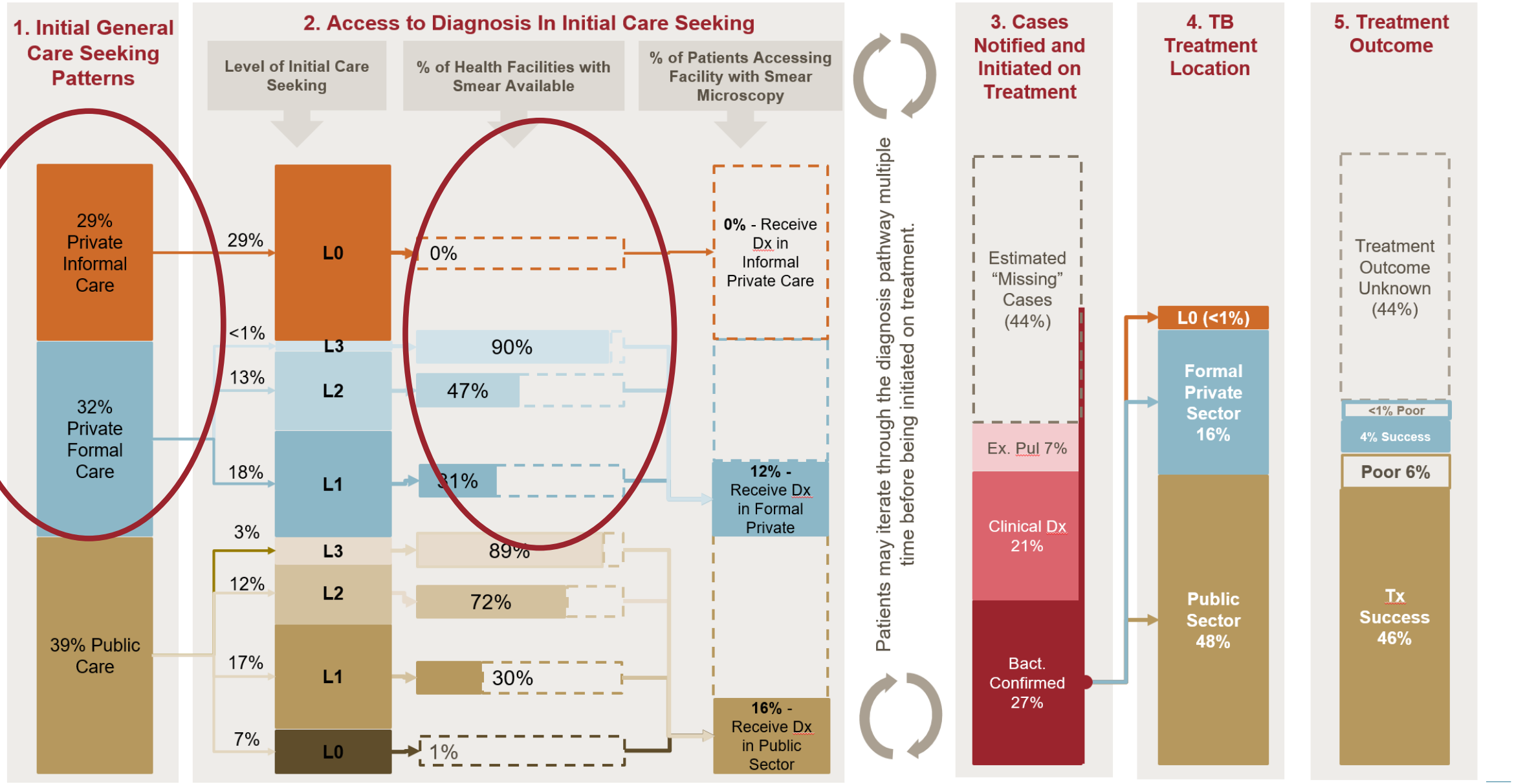
Cost and out-of-pocket expenses

MISSING PATIENTS AND POOR ACCESS TO CARE





Patient pathway analysis: 11-Country Summary



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INT J TUBERC LUNG DIS 18(3):255–266
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http://dx.doi.org/10.5588/ijtld.13.0585
E-published ahead of print 9 January 2014

LONG PATHWAYS TO CARE

Delays in diagnosis and treatment of pulmonary tuberculosis in India: a systematic review

C. T. Sreeramareddy,* Z. Z. Qin,† S. Satyanarayana,† R. Subbaraman,‡ M. Pai†

*Department of Population Medicine, Faculty of Medicine and Health Science, University Tunku Abdul Rahman, Selangor, Malaysia; †Department of Epidemiology and Biostatistics, McGill International TB Centre, McGill University, Montreal, Quebec, Canada; ‡Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts, USA

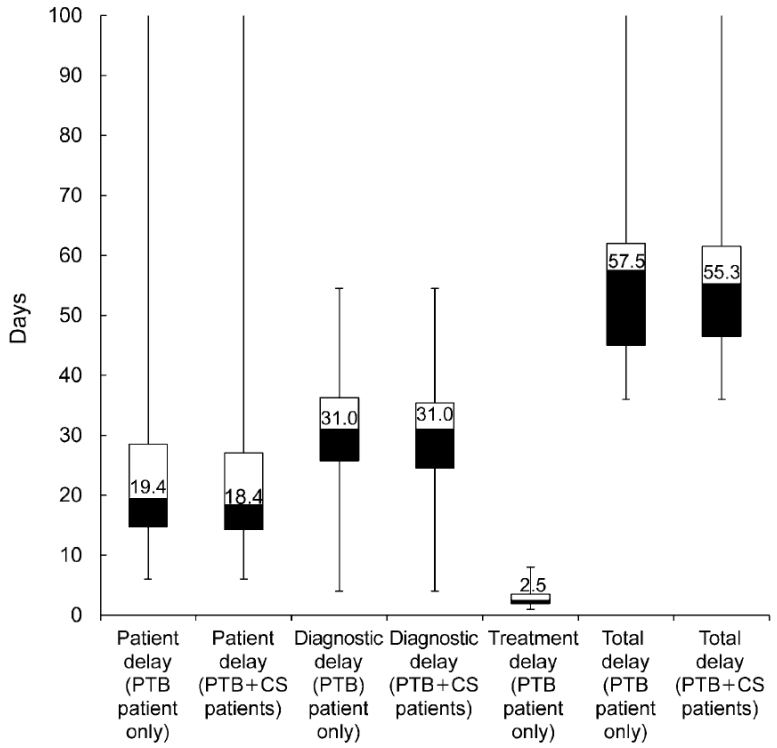
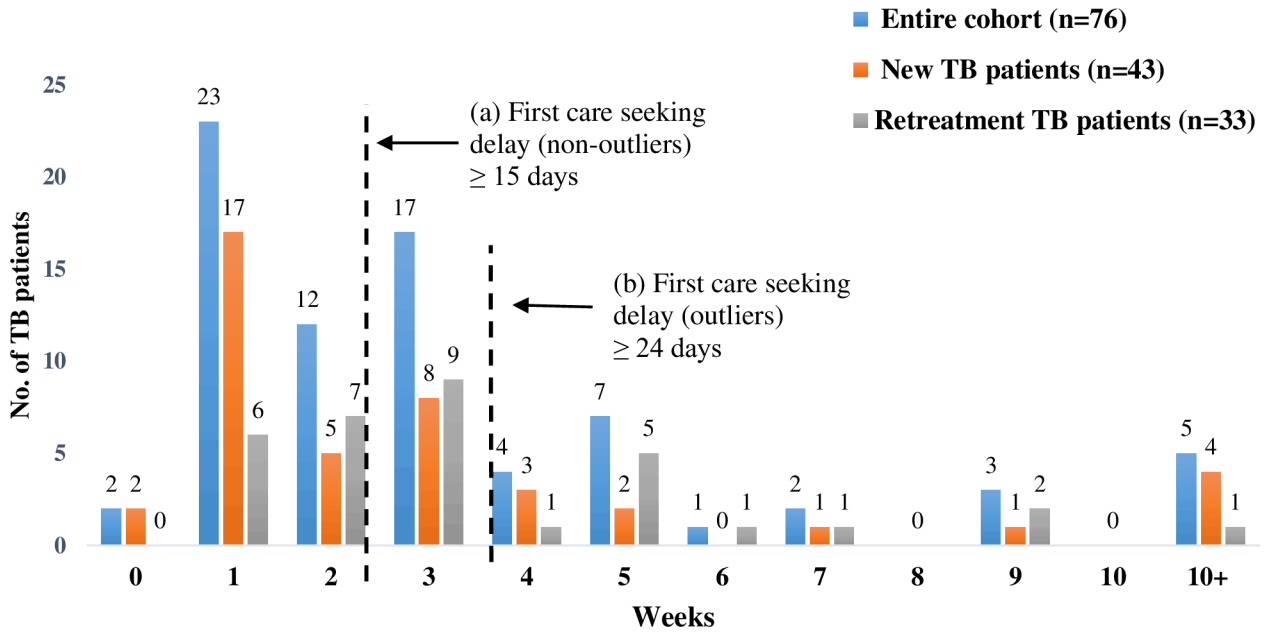
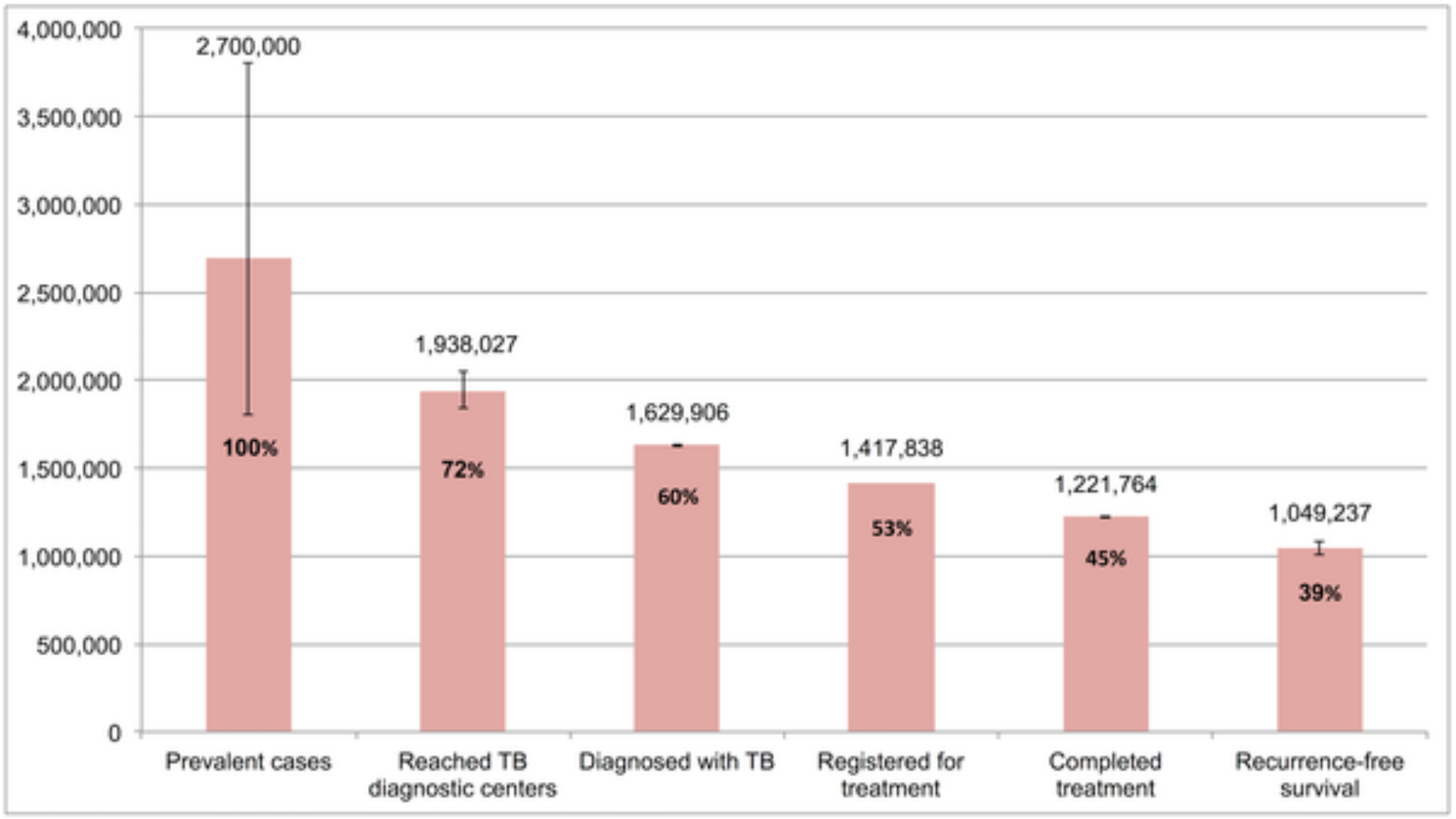


Figure 3 Distribution of patient delay, diagnostic delay, treatment delay and total delay among PTB patients and CS in India. Box plots depict the median (central line), interquartile range (box) and range (whiskers). PTB = pulmonary TB; CS = chest symptomatic.



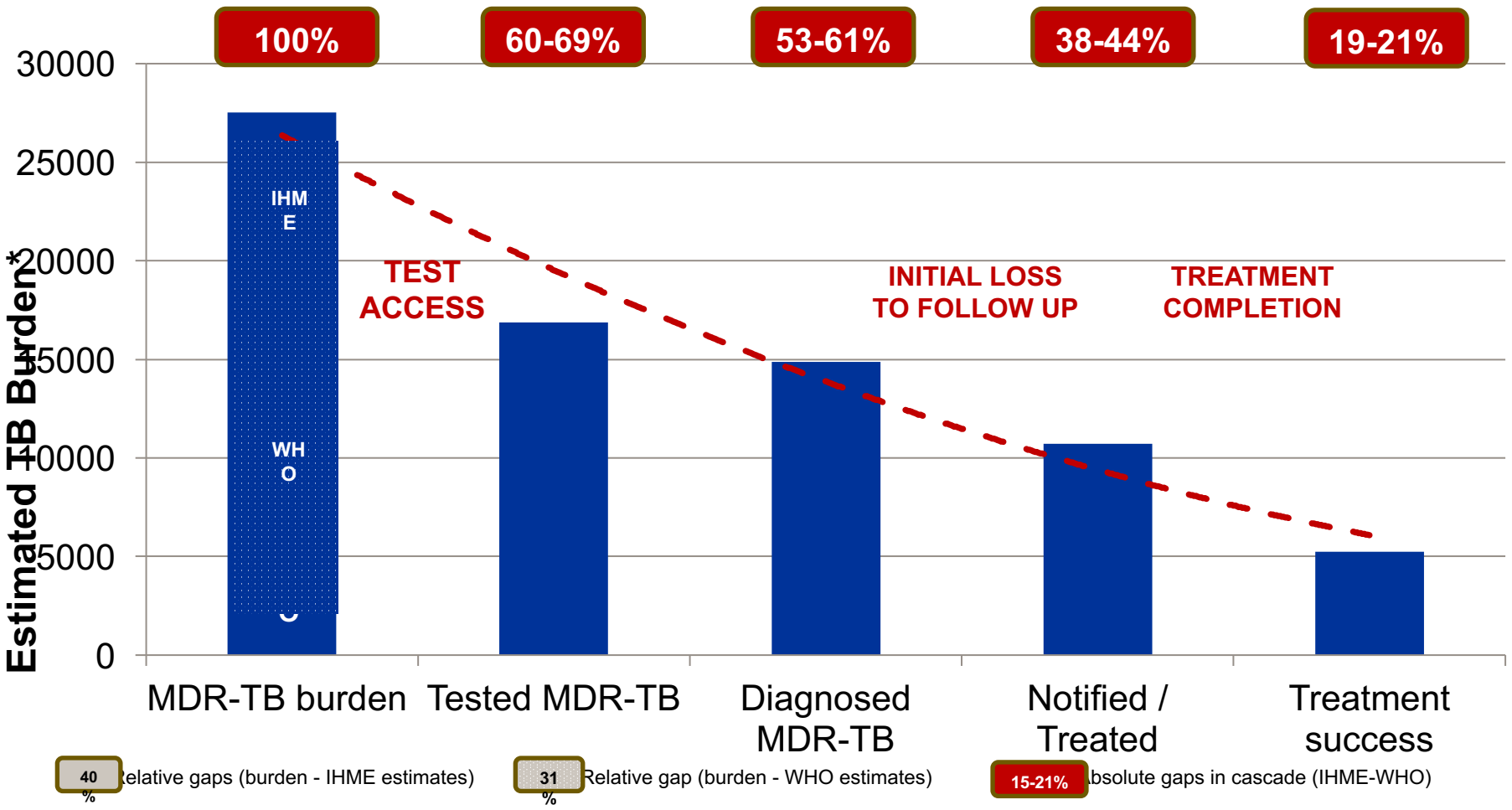
An average TB patient in India is diagnosed with TB after a delay of 58 days, and is seen by 3 healthcare providers before diagnosis

Cascade of care for all forms of TB in India's TB Control Program, 2013

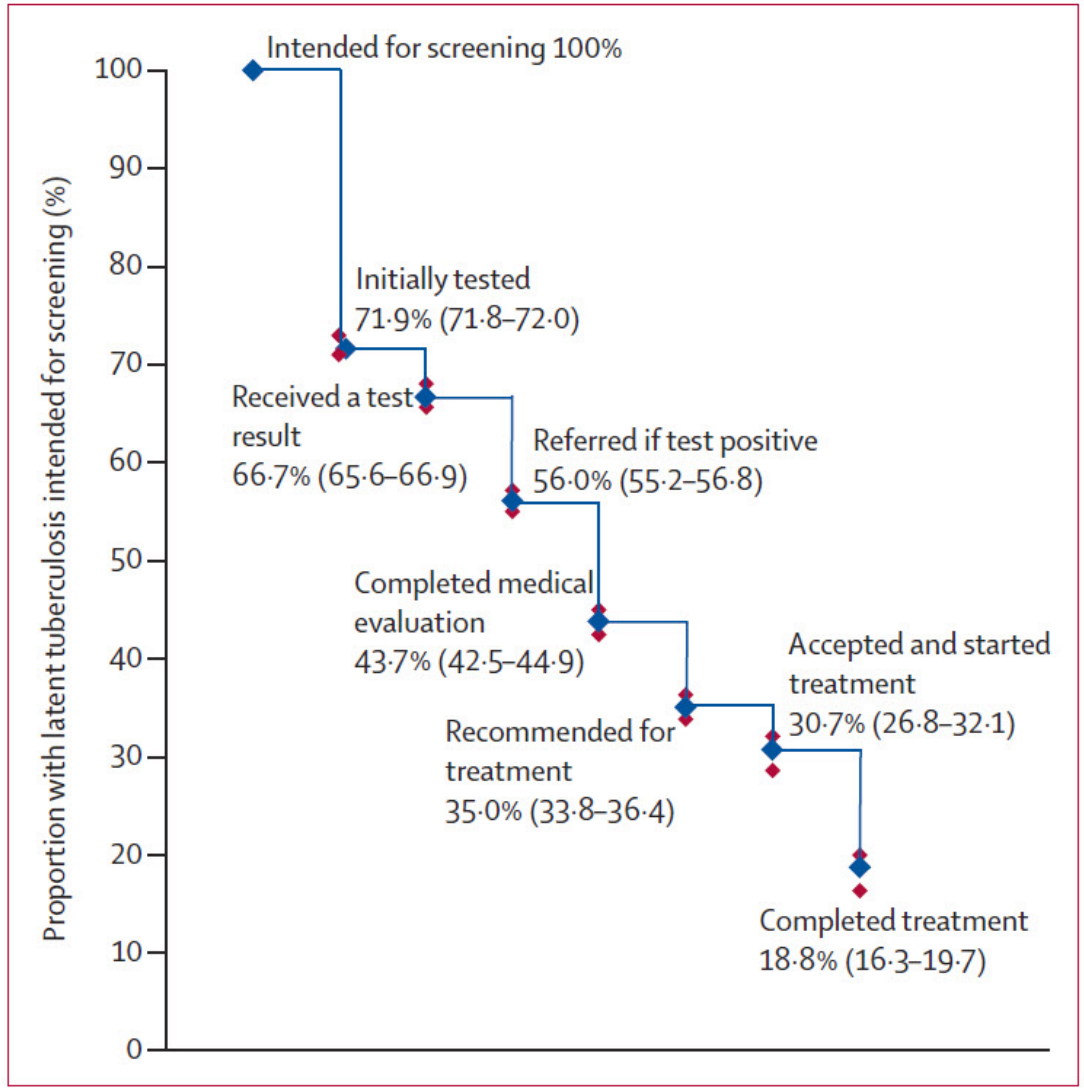


Subbaraman R, Nathavitharana RR, Satyanarayana S, Pai M, Thomas BE, et al. (2016) The Tuberculosis Cascade of Care in India's Public Sector: A Systematic Review and Meta-analysis. PLOS Medicine 13(10): e1002149. doi:10.1371/journal.pmed.1002149
http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002149

MDR-TB CARE CASCADE IN SOUTH AFRICA



CARE CASCADE FOR LATENT TB INFECTION



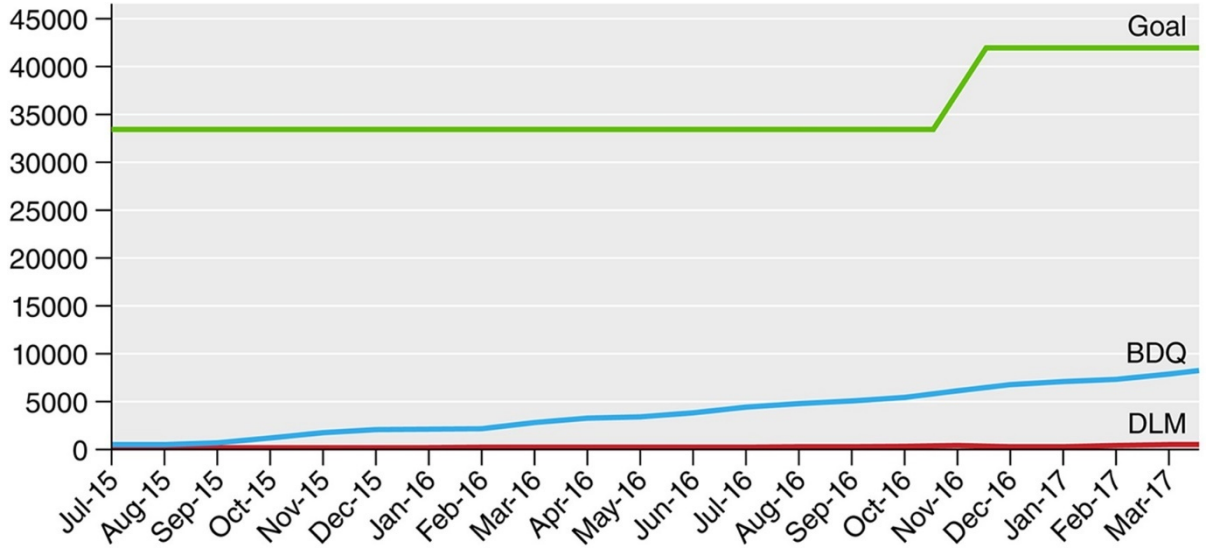
Alsdurf H et al. Lancet Infect Dis 2016

RIGHT NOW, TB DX AND RX IS MAINLY AT L2 AND L3 LEVELS

UN Economic Classification	Country	Diagnostics												Drug therapy											
		Triage (CXR)				Sputum smears				DST (Xpert, LPA, culture)				LTBI testing				DS TB Rx				MDR-TB Rx initiation				MDR-TB Rx continuation				LTBI Rx			
		L0	L1	L2	L3	L0	L1	L2	L3	L0	L1	L2	L3	L0	L1	L2	L3	L0	L1	L2	L3	L0	L1	L2	L3	L0	L1	L2	L3	L0	L1	L2	L3
Upper Middle Income	Angola																																
	China																																
	South Africa																																
	Thailand																																
Lower Middle Income	India																																
	Indonesia																																
	Kenya																																
	Myanmar																																
	Nigeria																																
	Papua New Guinea																																
Low Income	DR Congo																																
	Ethiopia																																
	Mozambique																																
	Zimbabwe																																

Not available Somewhat available Broadly available

ACCESS TO NEW TOOLS: NEW DRUGS



Progress in bedaquiline and delamanid global uptake by month compared with estimated need

eLIFE elifesciences.org FEATURE ARTICLE

POINT OF VIEW

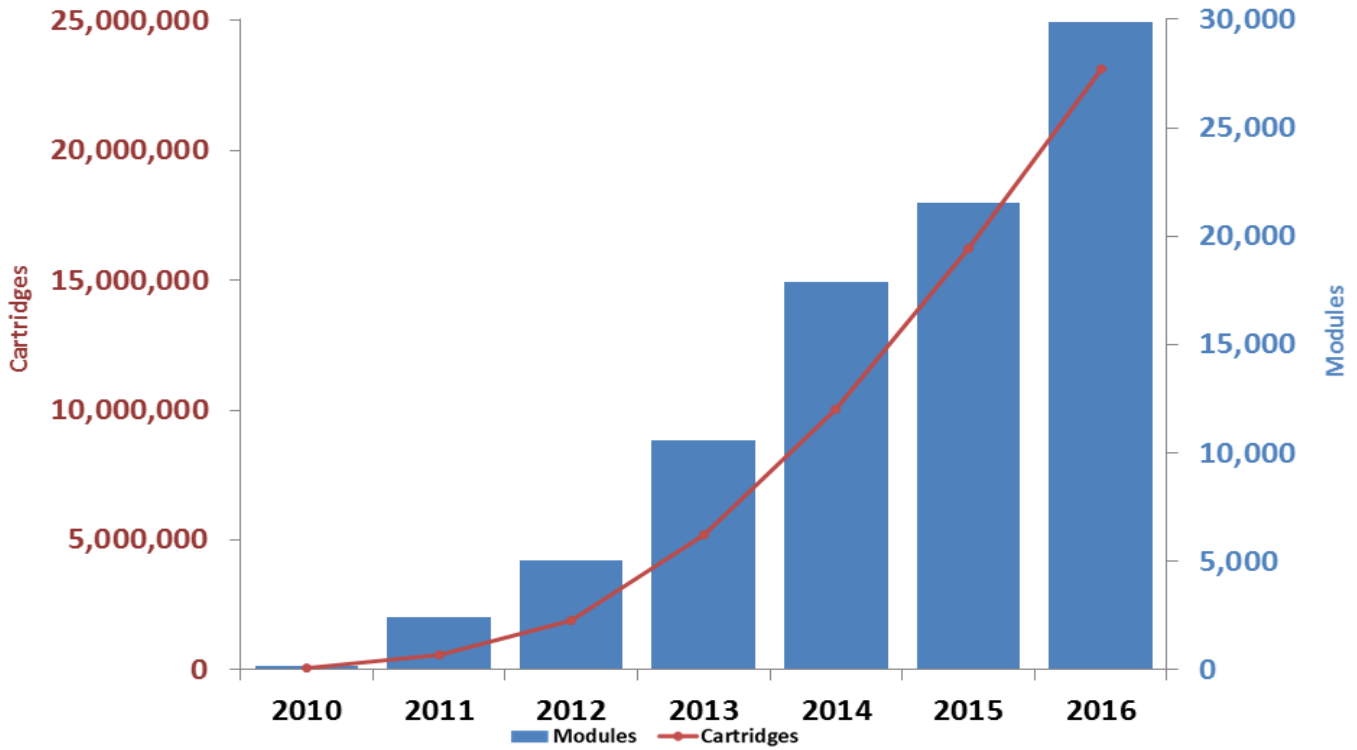
Tuberculosis innovations mean little if they cannot save lives

Abstract The past decade has seen the emergence of new diagnostics and drugs for tuberculosis, a disease that kills over 1.8 million people each year. However, these new tools are yet to reach scale, and access remains a major challenge for patients in low and middle income countries. Urgent action is needed if we are committed to ending the TB epidemic. This means raising the level of ambition, embracing innovation, increasing financial investments, addressing implementation gaps, and ensuring that new technologies reach those who need them to survive. Otherwise, the promise of innovative technologies will never be realized.

DOI: 10.7554/eLife.25956.001

MADHUKAR PAI* AND JENNIFER FURIN

ACCESS TO NEW TOOLS: NEW DIAGNOSTICS (GX)

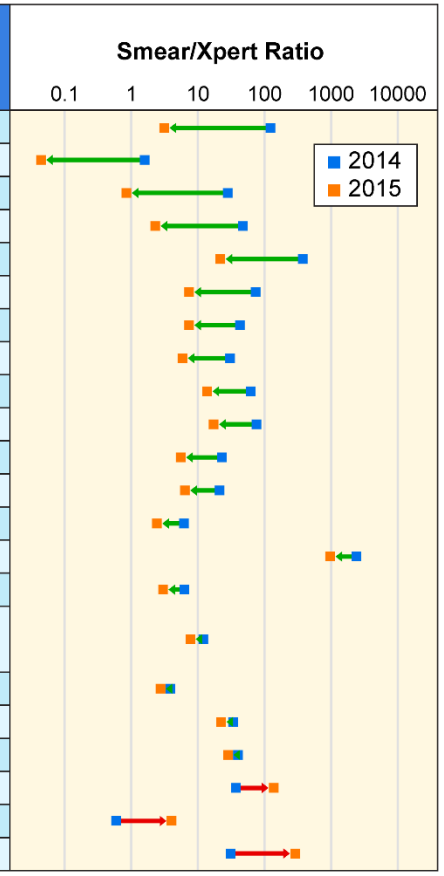


As of 31 December 2016, a total of 6,659 GeneXpert instruments (comprising 29,865 modules) and 23,140,350 Xpert MTB/RIF cartridges had been procured in the public sector in 130 of the 145 countries eligible for concessional pricing.

Data: Cepheid

ACCESS TO NEW TOOLS: NEW DIAGNOSTICS (GX)

Country (WHO classification)	Cartridges Procured β (n)	Modules Procured β (n)	Initial Smears € (n)	Smear/ Xpert Cartridge Ratio*f*	% change in smear/Xpert ratio 2014-2015	Algorithm#
Thailand	45,190	120	192,585	4.26	-96.56	HIV+, DR, Children, EPTB
South Africa	2,777,190	9	164,735	0.06	-96.29	All, HIV+, DR, Children, EPTB
Nigeria	152,450	377	165,968	1.09	-96.08	HIV+, DR, Children, EPTB
Kenya	199,150	252	570,000	2.86	-93.99	HIV+, DR, Children, EPTB
Ethiopia	165,300	36	4,600,000	27.83	-92.65	HIV+, DR, Children, EPTB
India	766,860	140	7,026,841	9.16	-87.18	HIV+, DR, Children, EPTB
Philippines	169,200	516	1,628,642	9.63	-77.03	HIV+, DR, Children, EPTB
Pakistan	181,800	106	1,384,621	7.62	-75.43	HIV+, DR, Children, EPTB
Vietnam	88,400	84	1,651,749	18.68	-70.15	HIV+, DR, Children, EPTB
China	220,000##	3600##	5,079,636	23.09	-68.92	DR
Myanmar	110,800	132	850,000	7.67	-66.93	HIV+, DR, EPTBμ
Cambodia	38,300	135	344,345	8.99	-57.39	HIV+, DR, EPTB
Mozambique	66,550	128	207,441	3.12	-49.72	HIV+, DR, Children, EPTB
Russia	4,550	N/A	6,096,500	1,339.89	-43.85	All, Children, HIV+, DR, EPTB
Brazil	207,350	280	820,000	3.95	-36.22	All, HIV+, DR, Children, EPTB
United Rep. of Tanzania	33,990	64	362,054π	10.65	-11.24	All, HIV+, DR, Children, EPTB
Uganda	84,280	24	309,068	3.67	-10.56	HIV+, DR, Children
Bangladesh	116,800	2	3,615,109	30.95¶	-8.97	HIV+, DR, EPTB
Indonesia	70,000	88	2,678,829	38.27	-2.62	HIV+, DR, Children, EPTB
Afghanistan	4,450	20	437,688	98.36	165.83	HIV+, DR α
Zimbabwe	75,570	180	224,284	2.97	394.65	HIV+, DR, Children, EPTB
DR Congo	12,800	46	2,760,000	215.63	591.11	DR



WHO: World Health Organization; TB: tuberculosis; #: Algorithm: National policy stipulating Xpert MTB/RIF as the initial diagnostic test for All: all people presumed to have TB, DR: people at risk of drug resistant TB, EPTB: extrapulmonary TB using selected specimens, HIV+: people at risk of human immunodeficiency virus associated TB, children: children presumed to have TB [5]. β: Accumulated procurement in 2015 (data from FIND). *f*: Ratio of the numbers of smears performed in high-burden countries for initial diagnosis to the numbers of Xpert cartridges procured in the same country; the annual smear volumes and the numbers of Xpert cartridges procured were collected for the year 2015. α: WHO data was not available; 2015 Afghanistan survey data used. ¶: 2014 smear/Xpert ratio for Bangladesh [3] corrected to 34.06. ##: FIND data not available; 2015 China survey data used. μ: Yangon Region is testing Xpert MTB/RIF for all registered TB cases. Extrapulmonary TB specimen is cerebrospinal fluid only. € For those countries who were not able to stratify total smears for initial diagnosis and treatment monitoring we assumed that, on average, 76% of the total sputum smears were performed for initial diagnosis (the average proportion reported by 16 countries able to stratify smears) [4]. π: Tanzania could only provide total smear positive TB cases, therefore an estimate of initial smears was based on the average proportion of total smears performed for initial diagnosis reported by Kenya and Zimbabwe, countries with a similar TB burden as Tanzania.

Cazabon D, Suresh A, Pai M, et al. ERJ (In Press)

Low utilization of new tools

RESEARCH ARTICLE

Low implementation of Xpert MTB/RIF among HIV/TB co-infected adults in the International epidemiologic Databases to Evaluate AIDS (IeDEA) program

Kate Clouse[1,2,3], Meridith Blevins[1,4], Mary Lou Lindegren[1,2], Marcel Yotebieng[5], Dung Thi Nguyen[6], Alfred Omondi[7], Denna Michael[8], Djimon Marcel Zannou[9], Gabriela Carriquiry[10], April Pettit[2,3]*, International Epidemiologic Databases to Evaluate AIDS (IeDEA) collaboration[¶]

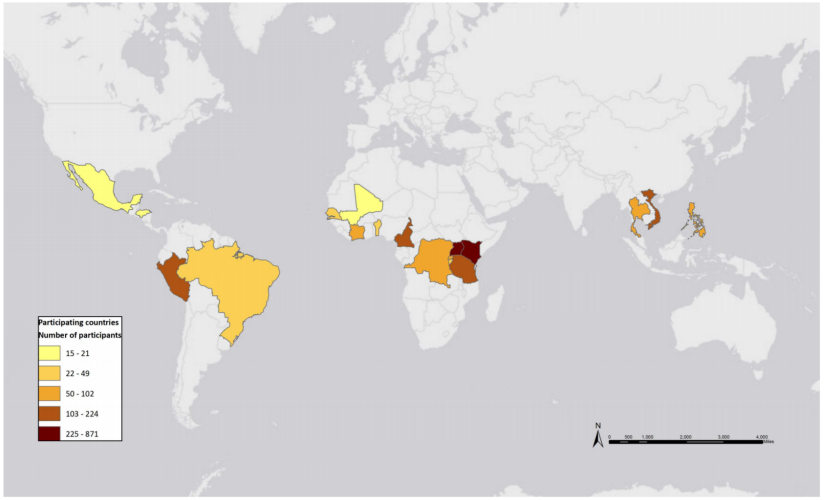


Fig 1. Participating countries (n = 18) and number of patients included by each. Map created in July 2016 by Kate Clouse using ArcMap GIS 10.3.1 (Esri, Redlands, CA).

Table 3. TB testing utilization and outcomes among 2722 adult patients.

	n (%)
TB test utilization (n = 2722)	
Received at least one TB test	2070 (76%)
Received no TB test	650 (24%)
Missing	2 (<1%)
Type of TB test performed (n = 2555)*	
AFB smear	2025 (79%)
Culture	333 (13%)
Xpert	118 (5%)
Other NAAT	79 (3%)

"Xpert utilization was low even though the majority of sites had access to the test"

Clouse K et al. PLoS ONE 2017

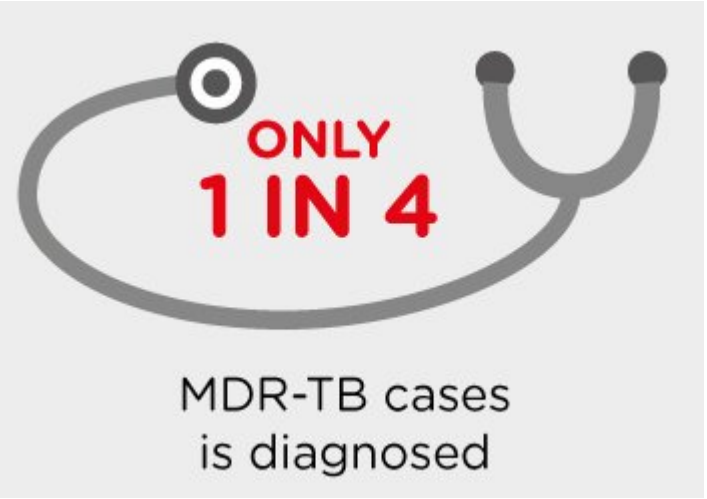
UNDIAGNOSED DRUG RESISTANCE

PLOS ONE

RESEARCH ARTICLE

Use of Xpert MTB/RIF in Decentralized Public Health Settings and Its Effect on Pulmonary TB and DR-TB Case Finding in India

Kuldeep Singh Sachdeva[1], Neeraj Raizada[2]*, Achuthan Sreenivas[3], Anna H. van't Hoog[4], Susan van den Hof[4,5], Puneet K. Dewan[3¤], Rahul Thakur[2], R. S. Gupta[1], Shubhangi Kulsange[2], Bhavin Vadera[2], Ameet Babre[2], Christen Gray[2], Malik Parmar[3], Mayank Ghedia[1], Ranjani Ramachandran[3], Umesh Alavadi[2], Nimalan Arinaminpathy[6], Claudia Denkinger[2], Catharina Boehme[2], C. N. Paramasivan[2]



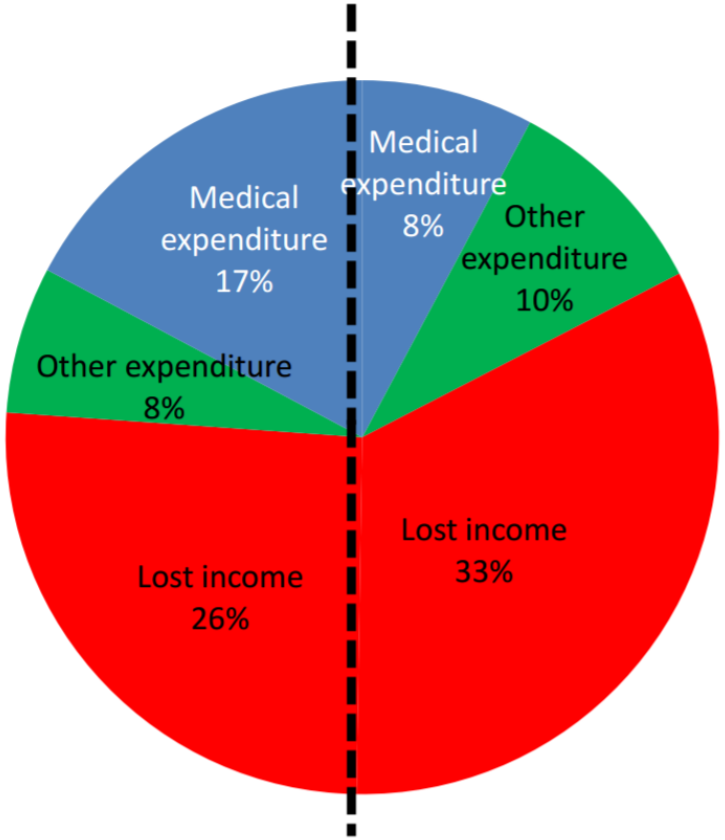
"Compared with the baseline strategy of selective DST only for PTB cases at high risk of drug-resistant TB, Xpert MTB/RIF implementation increased rifampicin resistant TB case detection by over five-fold."

Sachdeva et al. PLoS ONE 2015

On average, 50% of annual income lost:

½ before treatment

But wide country variability



½ during treatment

Higher cost among:
- People with MDR-TB
- People from low socioeconomic groups

Medical expenditure Other expenditure Lost income

Source: Tanimura T, Jaramillo E, Weil D, Raviglione M, Lönnroth K. Financial burden for tuberculosis patients in low- and middle-income countries – a systematic review. ERJ 2014

GLOBAL TB PROGRAMME

World Health Organization

HUFFPOST

CANADA LIVING

Featuring fresh takes and real-time analysis from HuffPost's signature lineup of contributors

Dr. Madhukar Pai Become a fan
Professor & Director of Global Health, McGill University

Jennifer Furin, MD., PhD Become a fan
Infectious diseases specialist and medical anthropologist
currently a lecturer at Harvard Medical School

Bridging The Gap Between Tuberculosis Innovation And Access

Posted: 05/02/2017 9:54 am EDT | Updated: 05/02/2017 10:01 am EDT

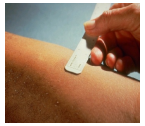
Never bring a knife to a gunfight. And yet, the global tuberculosis (TB) community has been doing precisely that for decades -- fighting a protracted battle with antiquated, inefficient tools, including an insensitive diagnostic (i.e. sputum microscopy), a low-efficacy vaccine (i.e. BCG), and drug regimens that have hardly changed for decades.

A critically ill patient, with possible drug-resistant TB being examined by his physician. Unfortunately, this patient did not have access to novel diagnostic testing or treatment and died of his disease. (Photo: Dr Jennifer Furin, with permission from the physician and the patient)

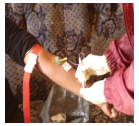
TB DX: WHAT ARE THE BIG NEEDS?

TOOLS WE HAVE TODAY?

Tuberculin



IGRAs



Conventional microscopy

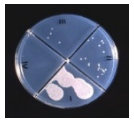
LED/FM microscopy

Urine LAM

Solid cultures

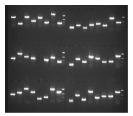
Liquid cultures

Conventional, phenotypic DST

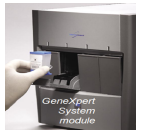


Molecular DST (LPAs)

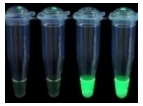
Conventional PCR



Xpert MTB/RIF & Ultra



TB LAMP



NEEDS ASSESSMENT AND TPPS

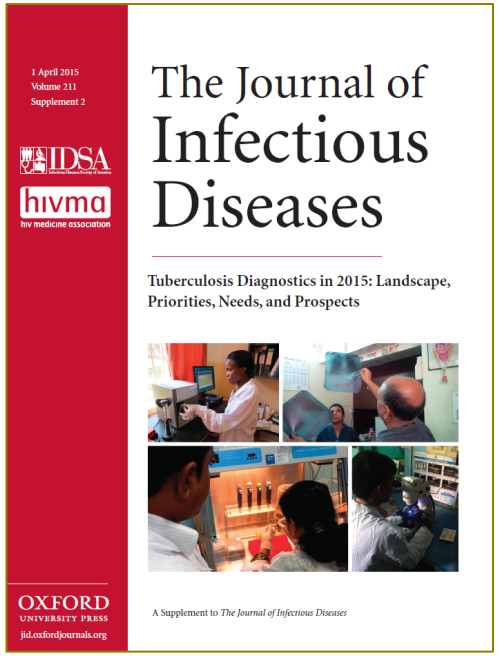
Priority needs

Tuberculosis diagnostics: which target product profiles should be prioritised?

Sandra V. Kik[1,2], Claudia M. Denkinger[1,2,3], Martina Casenghi[4], Caroline Vadnais[1,2] and Madhukar Pai[1,2]
[1]McGill International TB Centre, McGill University, Montreal, Canada. [2]Dept of Epidemiology and Biostatistics, McGill University, Montreal, Canada. [3]Division of Infectious Disease, Beth Israel Deaconess Medical Center, Boston, MA, USA. [4]Médecins Sans Frontières Access Campaign, Geneva, Switzerland.

	Target product profiles for potential new TB diagnostic tests	Prioritization by key stakeholders: Patients and community advocates	National tuberculosis programmes	Field practitioners	Researchers	Impact: Potential to reduce TB incidence	Potential to reduce TB morbidity and mortality	Market: Potential (global) market size	Potential to reach the market in the next 5 years	Implementation and scalability: Potential use as a point-of-care test	Potential to get scaled-up	Score	Priority rank
	TRIAGE, RULE OUT AND SYSTEMATIC SCREENING TEST												
A	Triage test for those seeking care	high	high	high	medium	high	medium	high	low	high	high	26	3
B	An HIV/ART clinic-based test to rule out active TB	high	high	high	high	low	high	medium	medium	high	high	26	3
C	Systematic screening test for active case finding	high	high	medium-high	medium	high	medium	medium	low	high	high	24.5	5
	RAPID TB DIAGNOSIS TEST (WITH OPTIONAL DRUG SUSCEPTIBILITY TESTING)												
D	Rapid, sputum-based, cartridge-based, molecular test for microscopy centers (with the option of add-on drug susceptibility testing cartridge)	medium-high	high	high	high	high	high	high	high	high	high	29.5	1
E	Rapid biomarker-based instrument-free test for non-sputum samples (which can also detect childhood and extrapulmonary TB)	high	high	high	high	high	high	high	low	high	high	28	2
F	Multiplexed test for TB and other infectious diseases	high	medium-high	low	medium	medium	medium-high	medium-high	low	high	medium	19	8
	NEXT-GENERATION DRUG SUSCEPTIBILITY TEST												
G	Centralized, high-throughput, drug susceptibility test (incorporating new drugs to support the roll out of new TB treatment regimens post 2014)	medium	high	medium	medium	low	medium	low	high	low	medium	18	9
	TREATMENT MONITORING TEST												
H	Treatment monitoring test (test for cure)	high	high	medium	medium	low	medium	low-medium	low	low	high	19.5	7
	PREDICTIVE TEST FOR LATENT TB INFECTION												
I	Predictive test for latent TB infection at high risk of active TB	high	high	medium	high	high	high	high	low	low	low	23	6

TPPs



Kik S et al. ERJ 2014

NEED FOR NEW TOOLS SPANS THE HEALTHCARE SYSTEM, BUT CONCENTRATED AT LOWER LEVELS OF THE SYSTEM

Community health worker | Health post | Microscopy center | District hospital | Reference center

- A: Passive & active case detection
- B: Rule out test
- D: Latent to active progression
- E: Drug susceptibility testing
- F: Treatment monitoring

eHealth and connectivity solutions

Courtesy: FIND, Geneva

TB DX: WHAT IS THE CRITICAL PATHWAY?

CHALLENGES AT BOTH ENDS OF VALUE CHAIN

TB Diagnostics Critical Pathway – work in progress

Centre international de TB McGill | McGill International TB Centre

Key Stakeholder
Milestone
Resource/link

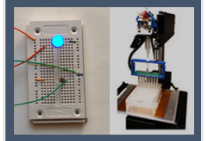
0 Identify need

- Needs assessment
- Target product profile

FIND

TBFaqs.org

1 Concept



- Feasibility
- Proof of concept

2 Development

- Prototype
- User feedback
- Optimization
- Design Lock

3 Lab & clinical validation

- Qualification
- Verification and validation
- Clinical trials

4 Regulatory submission

CE-IVD | Country of origin | FDA

5 WHO evaluation

World Health Organization

- Demo & field evaluation
- Cost-effectiveness
- Evidence synthesis / GRADE
- WHO endorsement
- Global policy / report

6 Country transition to scale

Pre-launch

- Global procurement – pricing, warranty
- In-country feasibility
- Operational research
- Cost-analysis
- User training manuals in key languages

7 Country adoption

- Country policy
- Algorithm change
- Planning / budgeting
- Mobilize advocacy
- Procure-ment
- Begin roll-out

8 Scale-up & Surveillance

- Country strategy optimization
- Monitor quality & address field issues
- Supply chain
- Scale-up monitoring

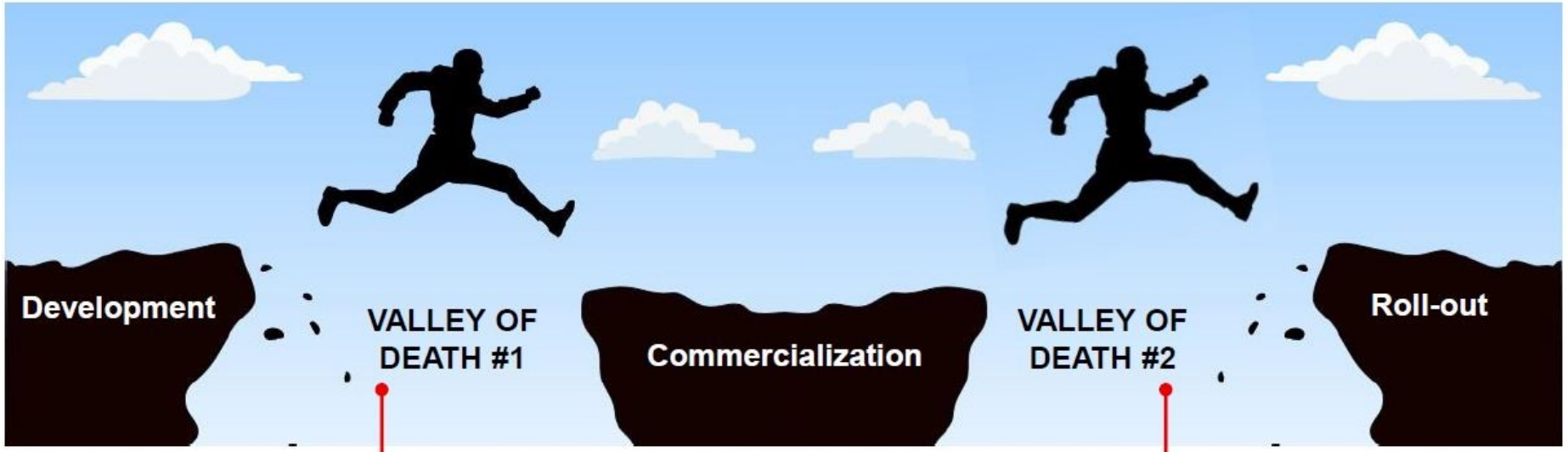
9 Impact achieved

- Impact assessment
- Increased case detection
- Lives saved / DALY
- Overall healthcare costs & benefits

Stage-gate process

Ongoing commercial activities – demand generation, market development, market planning

PRODUCT DEVELOPMENT IS STALLED FOR MANY PRODUCTS



DEVELOPMENT => COMMERCIALIZATION

- **Insufficient evaluation** in settings of intended use
- **Weak end-user involvement** in product research and development
- **Mis-alignment** in the product design and manufacturing process

COMMERCIALIZATION => ROLL-OUT

- **Lack of focus** on demand generation
- **Weak engagement** of country decision-makers and stakeholders, including civil society and community
- **Lack of planning and resources** for country adoption

Lucica Ditiu and Catharina Boehme. http://gbchealth.org/crossing-the-valleys-of-death-in-tb-from-development-to-roll-out/

UPSTREAM CHALLENGES: BIOMARKER DISCOVERY AND VALIDATION

A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Daniel E Zak, Adam Penn-Nicholson*, Thomas J Scriba*, Ethan Thompson†, Sara Suliman†, Lynn M Amon, Hassan Mahomed, Mzwandile Erasmus, Wendy Whatney, Gregory D Hussey, Deborah Abrahams, Fazlin Kafaar, Tony Hawkridge, Suzanne Verver, E Jane Hughes, Martin Ota, Jayne Sutherland, Rawleigh Howe, Hazel M Dockrell, W Henry Boom, Bonnie Thiel, Tom H M Ottenhoff, Harriet Mayanja-Kizza, Amelia C Crampin, Katrina Downing, Mark Hatherill, Joe Valvo, Smitha Shankar, Shreemanta K Parida, Stefan H E Kaufmann, Gerhard Walzl, Alan Aderem, Willem A Hanekom, for the ACS and GC6-74 cohort study groups‡*

An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis

Matthew P. R. Berry[1], Christine M. Graham[1]*, Finlay W. McNab[1]*, Zhaohui Xu[6], Susannah A. A. Bloch[3], Tolu Oni[4,5], Katalin A. Wilkinson[2,4], Romain Banchereau[9], Jason Skinner[6], Robert J. Wilkinson[2,4,5], Charles Quinn[6], Derek Blankenship[7], Ranju Dhawan[8], John J. Cush[6], Asuncion Mejias[10], Octavio Ramilo[10], Onn M. Kon[3], Virginia Pascual[6], Jacques Banchereau[6], Damien Chaussabel[6] & Anne O'Garra[1]

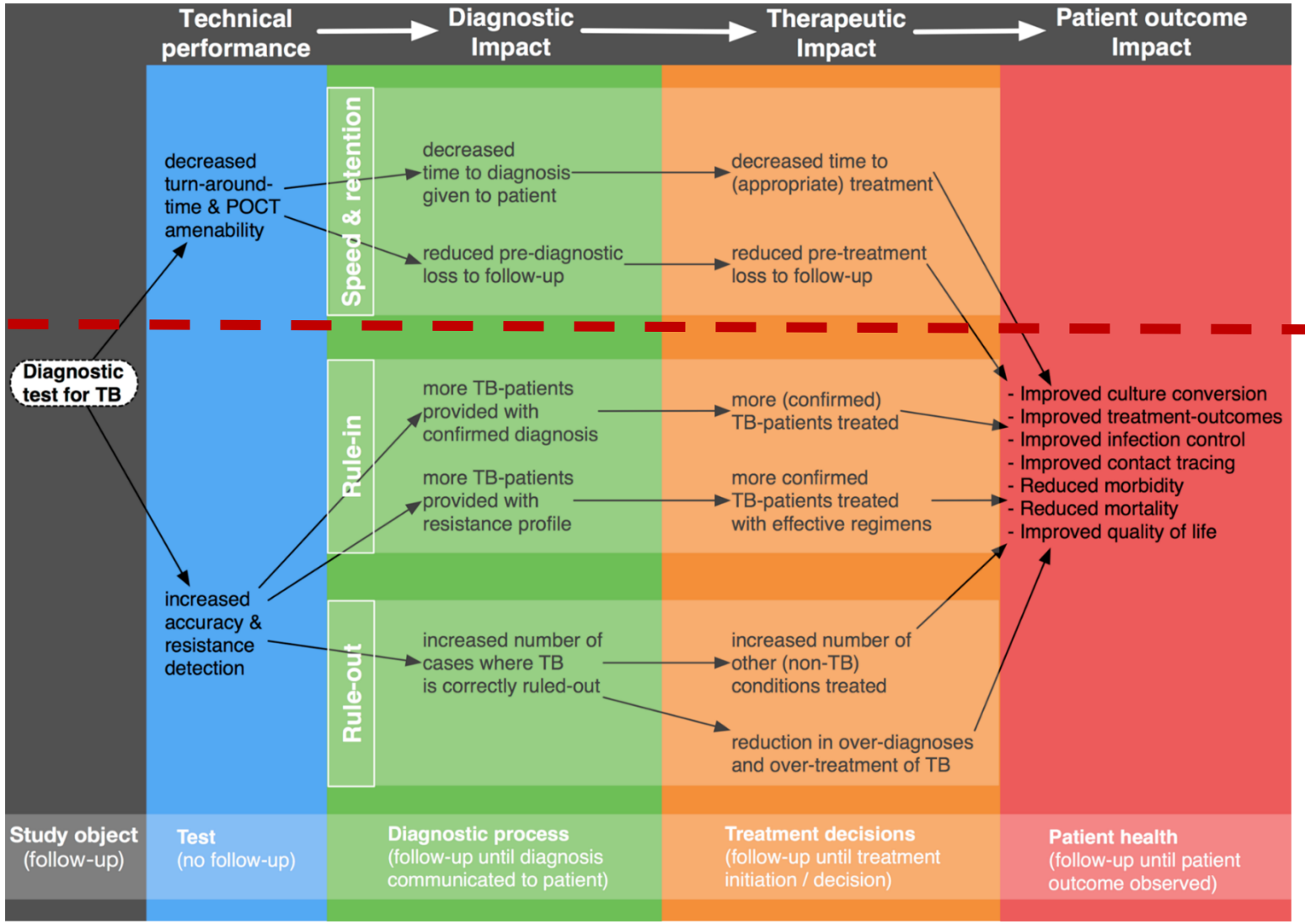
Rapid, comprehensive, and affordable mycobacterial diagnosis with whole-genome sequencing: a prospective study

Louise J Pankhurst, Carlos del Ojo Elias*, Antonina A Votintseva*, Timothy M Walker*, Kevin Cole, Jim Davies, Jilles M Fermont, Deborah M Gascoyne-Binzi, Thomas A Kohl, Clare Kong, Nadine Lemaitre, Stefan Niemann, John Paul, Thomas R Rogers, Emma Roycroft, E Grace Smith, Philip Supply, Patrick Tang, Mark H Wilcox, Sarah Wordsworth, David Wyllie, Li Xu, Derrick W Crook, for the COMPASS-TB Study Group†*

Genome-wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis

Timothy E Sweeney, Lindsay Braviak, Cristina M Tato, Purvesh Khatri

DOWNSTREAM CHALLENGES: PRODUCTS TO IMPACT



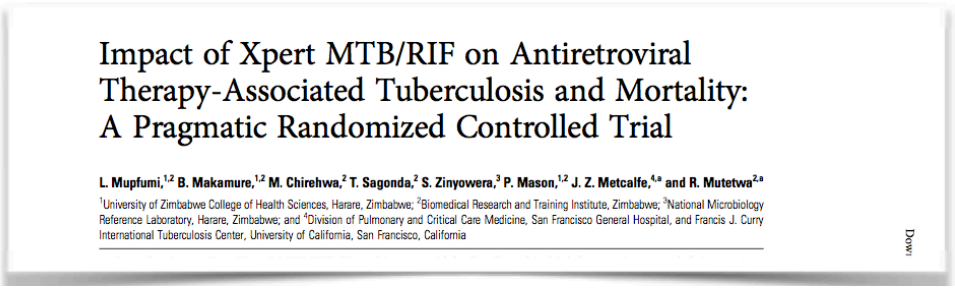
IMPROVED HEALTH OUTCOMES

Schumacher S et al. PLOS ONE 2016.
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0151073

PRAGMATIC TRIALS OF XPERT: IMPACT BLUNTED BY HEALTH SYSTEM ISSUES

Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial

*Grant Theron, Lynn Zijenah, Duncan Chanda, Petra Clowes, Andrea Rachow, Maia Lesosky, Wilbert Bara, Stanley Mungofa, Madhukar Pai, Michael Hoelscher, David Dowdy, Alex Pym, Peter Mwaba, Peter Mason, Jonny Peter, Keertan Dheda, for the TB-NEAT team**



Impact of Xpert MTB/RIF on Antiretroviral Therapy-Associated Tuberculosis and Mortality: A Pragmatic Randomized Controlled Trial

L. Mupfumi,[1,2] B. Makamure,[1,2] M. Chirehwa,[2] T. Sagonda,[2] S. Zinyowera,[3] P. Mason,[1,2] J. Z. Metcalfe,[4,a] and R. Mutetwa[2,a]

[1]University of Zimbabwe College of Health Sciences, Harare, Zimbabwe; [2]Biomedical Research and Training Institute, Zimbabwe; [3]National Microbiology Reference Laboratory, Harare, Zimbabwe; and [4]Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, and Francis J. Curry International Tuberculosis Center, University of California, San Francisco, California

Impact of Replacing Smear Microscopy with Xpert MTB/RIF for Diagnosing Tuberculosis in Brazil: A Stepped-Wedge Cluster-Randomized Trial

Betina Durovni[1,2], Valeria Saraceni[1,3], Susan van den Hof[4,5], Anete Trajman[2,6]*, Marcelo Cordeiro-Santos[3,7], Solange Cavalcante[1,8], Alexandre Menezes[9], Frank Cobelens[4,5]

Xpert MTB/RIF versus sputum microscopy as the initial diagnostic test for tuberculosis: a cluster-randomised trial embedded in South African roll-out of Xpert MTB/RIF

Gavin J Churchyard, Wendy S Stevens, Lerole D Mametja, Kerrigan M McCarthy, Violet Chihota, Mark P Nicol, Linda K Erasmus, Norbert O Ndjeka, Lindiwe Mvusi, Anna Vassall, Edina Sinanovic, Helen S Cox, Christopher Dye, Alison D Grant, Katherine L Fielding

Note: not all trials were powered to look at long-term outcomes; most were pragmatic, and treatment issues were not addressed

MISSED OPPORTUNITIES FOR TB TESTING

Engel *et al. BMC Health Services Research* (2015) 15:550
DOI 10.1186/s12913-015-1223-3

BMC Health Services Research

RESEARCH ARTICLE Open Access

Point-of-care testing in India: missed opportunities to realize the true potential of point-of-care testing programs

Nora Engel[1*], Gayatri Ganesh[2], Mamata Patil[2], Vijayashree Yellappa[2], Caroline Vadnais[3], Nitika Pant and Madhukar Pai[3]

PLOS | ONE

Use of standardised patients to assess quality of tuberculosis care: a pilot, cross-sectional study

Jishnu Das, Ada Kwan, Benjamin Daniels, Srinath Satyanarayana, Ramnath Subbaraman, Sofi Bergkvist, Ranendra K Das, Veena Das, Madhukar Pai

Summary

Background Existing studies of the quality of tuberculosis care have relied on recall-based patient surveys, questionnaire surveys of knowledge, and prescription or medical record analysis, and the results mostly show the health-care provider's knowledge rather than actual practice. No study has used standardised patients to assess clinical practice. Therefore we aimed to assess quality of care for tuberculosis using such patients.

Lancet Infect Dis 2015
Published Online
August 10, 2015
http://dx.doi.org/10.1016/S1473-3099(15)00077-8

Tropical Medicine and International Health

VOLUME 20 NO 4 PP 493–500 APRIL 2015

Compounding diagnostic delays: a qualitative study of point-of-care testing in South Africa

Nora Engel[1]*, Malika Davids[2]*, Nadine Blankvoort[1], Nitika Pant Pai[3], Keertan Dheda[2] and Madhukar Pai[4]

1 *Department of Health, Ethics & Society, Research School for Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands*
2 *Lung Infection and Division of Pulmonology and UCT Lung Institute, University of Cape Town, Cape Town, South Africa*
3 *Division of Clinical Epidemiology, McGill University and McGill University Health Centre, Montreal, QC, Canada*
4 *McGill International TB Centre, McGill University, Montreal, QC, Canada*

RESEARCH ARTICLE

Missed Opportunities for TB Investigation in Primary Care Clinics in South Africa: Experience from the XTEND Trial

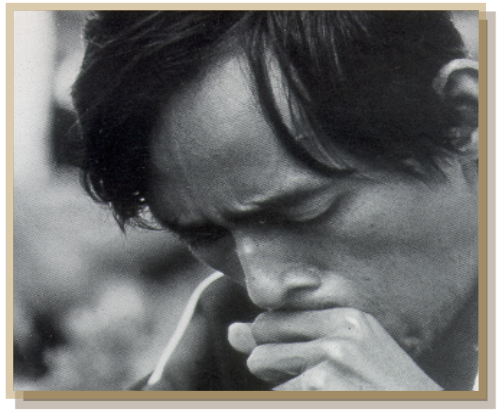
Violet N. Chihota[1,2]*, Sibuse Ginindza[1], Kerrigan McCarthy[1,2], Alison D. Grant[2,3], Gavin Churchyard[1,2,3], Katherine Fielding[3]

1 The Aurum Institute, Johannesburg, South Africa, **2** School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, **3** London School of Hygiene & Tropical Medicine, London, United Kingdom

RESEARCH ARTICLE

Barriers to Point-of-Care Testing in India: Results from Qualitative Research across Different Settings, Users and Major Diseases

Nora Engel[1]*, Gayatri Ganesh[2], Mamata Patil[2], Vijayashree Yellappa[2], Nitika Pant Pai[3], Caroline Vadnais[4], Madhukar Pai[4]

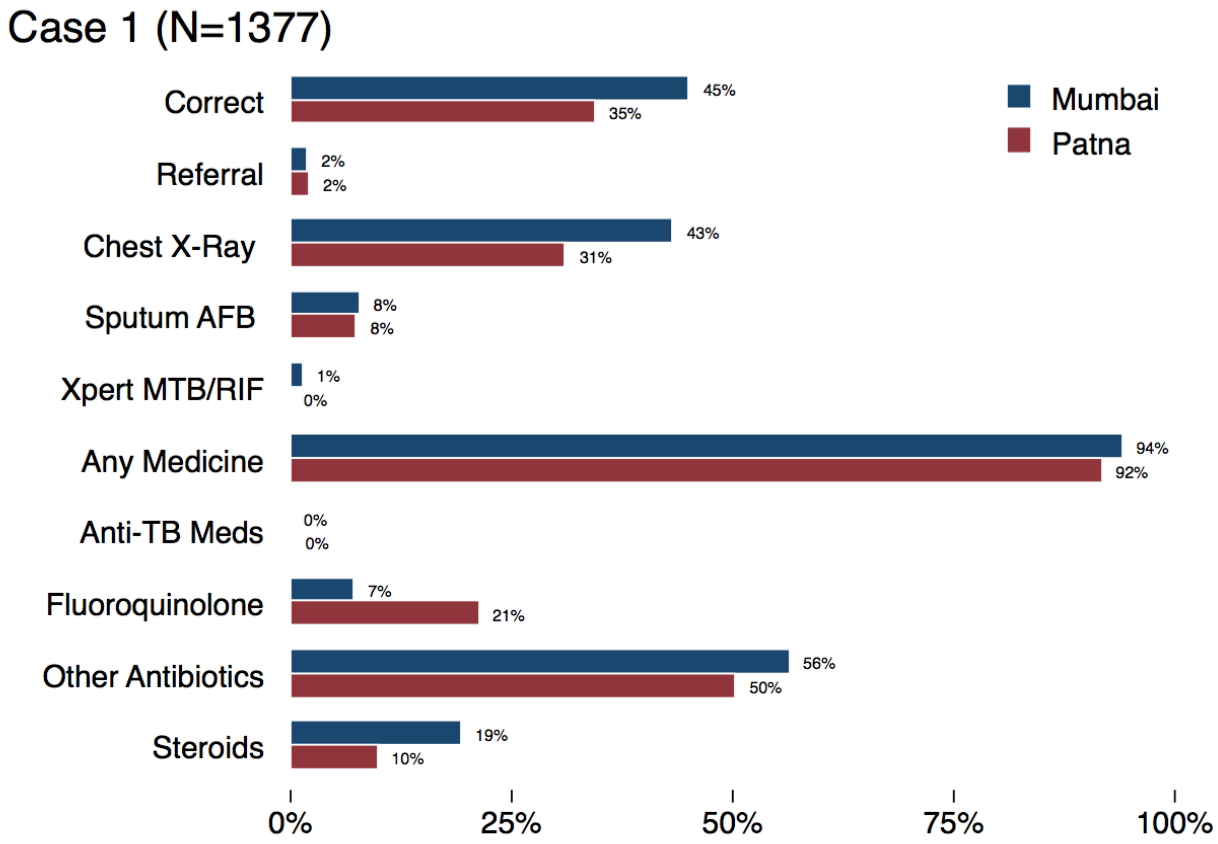


SIMULATED PATIENT STUDY IN INDIA: CLASSIC CASE OF SUSPECTED TB (2-3 WEEKS OF PRODUCTIVE COUGH, FEVER, WEIGHT LOSS – “PRESUMED TB”)

Das J et al. Lancet Infect Dis 2015

DATA FROM 2 CITIES: MUMBAI & PATNA

SP1: Classic case of suspected TB (2-3 weeks of productive cough, fever, weight loss – “presumed TB”)



Das J, Pai M, QuTUB team, unpublished

EMPIRICAL TREATMENT IS WIDESPREAD

INT J TUBERC LUNG DIS 20(4):536–543
© 2016 The Union
http://dx.doi.org/10.5588/ijtld.15.0562

Treatment as diagnosis and diagnosis as treatment: empirical management of presumptive tuberculosis in India

A. McDowell, M. Pai

McGill International TB Centre & Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

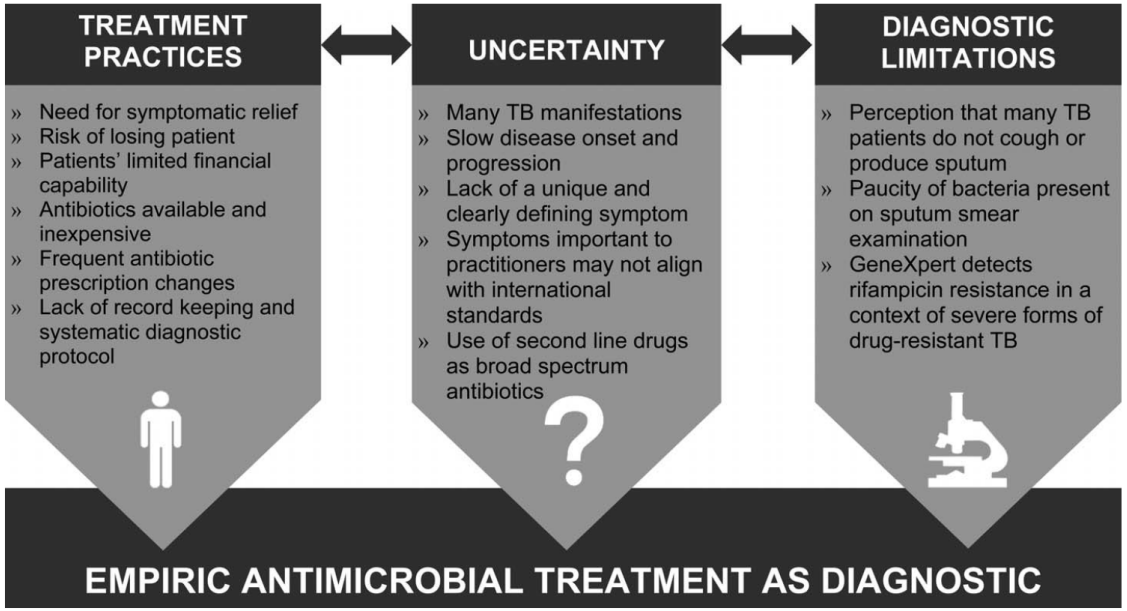


Figure Key drivers of empirical treatment. TB = tuberculosis.

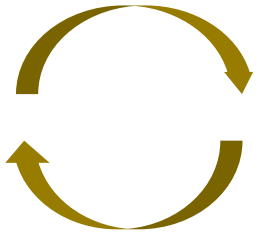
Do high rates of empirical treatment undermine the potential effect of new diagnostic tests for tuberculosis in high-burden settings?

Grant Theron, Jonny Peter, David Dowdy, Ivor Langley, S Bertel Squire, Keertan Dheda

DIAGNOSTIC ECOSYSTEMS ARE WEAK

SOUTH AFRICA:

Samples and results have to move, with delays and drop-offs



Courtesy: Nora Engel

Time to MDR-TB Rx = ~2 months

Implementation of GenoType MTBDR*plus* Reduces Time to Multidrug-Resistant Tuberculosis Therapy Initiation in South Africa

Karen R. Jacobson,[1,5] Danie Theron,[7] Emily A. Kendall,[2] Molly F. Franke,[3] Marinus Barnard,[5,6] Paul D. van Helden,[5] Tommie C. Victor,[5] Elizabeth M. Streicher,[5] Megan B. Murray,[3,4] and Robin M. Warren[5]

[1]Division of Infectious Diseases, and [2]Department of Medicine, Massachusetts General Hospital, [3]Division of Global Health Equity, Brigham and Women's Hospital, and [4]Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts; [5]Department of Science and Technology/National Research Foundation Centre of Excellence for Biomedical Tuberculosis Research/Medical Research Council Centre for Molecular and Cellular Biology, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, and [6]National Health Laboratory Service, Cape Town, and [7]Brewelskloof Hospital, Worcester, South Africa

Background. Diagnosis of drug resistance and timely initiation of multidrug-resistant (MDR) tuberculosis therapy are essential to reduce transmission and improve patient outcomes. We sought to determine whether implementation of the rapid MTBDR*plus* diagnostic shortened the time from specimen collection to patient MDR tuberculosis therapy initiation.

Methods. We conducted a retrospective cohort analysis of 197 MDR tuberculosis patients treated at Brewelskloof, a rural tuberculosis hospital in Western Cape Province, South Africa, between 2007 and 2011.

Results. Eighty-nine patients (45%) were tested using conventional liquid culture and drug susceptibility testing (DST) on solid medium and 108 (55%) were tested using the MTBDR*plus* assay after positive acid-fast bacilli or culture. Median time from sample taken to therapy initiation was reduced from 80 days (interquartile range [IQR] 62–100) for conventional DST to 55 days (IQR 37.5–78) with the MTBDR*plus*. Although the laboratory processing time declined significantly, operational delays persisted both in the laboratory and the clinical infrastructure for getting patients started on treatment. In multivariate analysis, patients tested using the MTBDR*plus* test had a reduced risk of starting treatment 60 days or more after sputum collection of 0.52 ($P < .0001$) compared with patients tested with culture-based DST, after adjustment for smear status and site of disease.

Conclusions. Use of MTBDR*plus* significantly reduced time to MDR tuberculosis treatment initiation. However, DST reporting to clinics was delayed by more than 1 week due, in part, to laboratory operational delays, including dependence on smear and culture positivity prior to MTBDR*plus* performance. In addition, once MDR tuberculosis was reported, delays in contacting patients and initiating therapy require improvements in clinical infrastructure.

OPEN ACCESS Freely available online PLOS ONE

The Impact of Expanded Testing for Multidrug Resistant Tuberculosis Using Geontype MTBDR*plus* in South Africa: An Observational Cohort Study

Colleen F. Hanrahan[1,2*], Susan E. Dorman[3], Linda Erasmus[4], Hendrik Koornhof[4], Gerrit Coetzee[4], Jonathan E. Golub[2,3]

1 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, United States of America, **2** Department of Epidemiology, UNC Gilling School of Global Public Health, Chapel Hill, North Carolina, United States of America, **3** Department of Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland, United States of America, **4** National TB Reference Laboratory, National Health Laboratory Services, Johannesburg, South Africa

Abstract

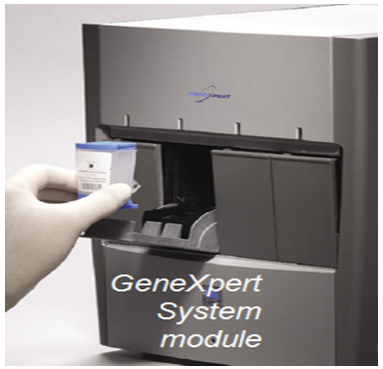
Introduction: Globally, multidrug resistant tuberculosis (MDR-TB) remains underdiagnosed. The Genotype MTBDR*plus*®, a rapid drug susceptibility testing (DST) assay used to detect resistance to isoniazid and rifampicin in the diagnosis of MDR-TB, has good diagnostic accuracy, but its impact on patient outcomes in routine practice is unproven. We assessed the clinical impact of routine DST using MTBDR*plus* in a single health district in South Africa.

Methods: Data were collected on all adult pulmonary TB patients registered at 25 public health clinics in the periods before and after introduction of an expanded DST algorithm using MTBDR*plus* version 1.0.

Results: We collected data on 1176 TB patients before implementation and 1177 patients afterwards. In the before period, measured MDR-TB prevalence among new cases was 0.7% (95% CI1.4–3.1%), and among retreatment cases 6.2% (95% CI:3.5–8.8%), *versus* 3.7% (95% CI:2.4–5.0, p<0.01) and 6.6% (95% CI:3.8–9.4%, p = 0.83) respectively after MTBDR*plus* introduction. The median times from sputum collection to MDR treatment in the before and after periods were 78 days (IQR:52–93) and 62 days (IQR:32–86, p = 0.05), respectively. Among MDR-TB cases, 27% (95%CI:10–44) in the before period converted sputum cultures to negative by 8 months following treatment initiation, while 52% (95%CI:38–66) converted in the intervention period (p = 0.04).

Conclusions: The expanded use of MTBDR*plus* DST resulted in a substantial increase in the proportion of new cases identified as MDR-TB; though time to MDR treatment was reduced, it was still over two months. Culture conversion for MDR-TB patients improved after introduction of MTBDR*plus*. This work illustrates the mixture of successes and challenges resulting from increased access to rapid DST in a setting with a high TB burden.

Time to Rx = ~2 weeks



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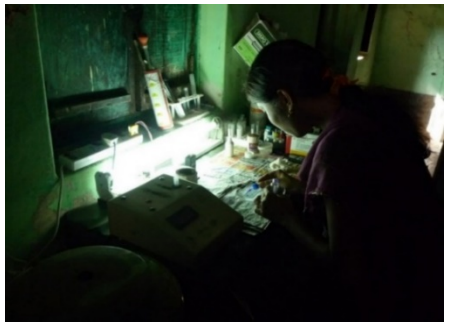
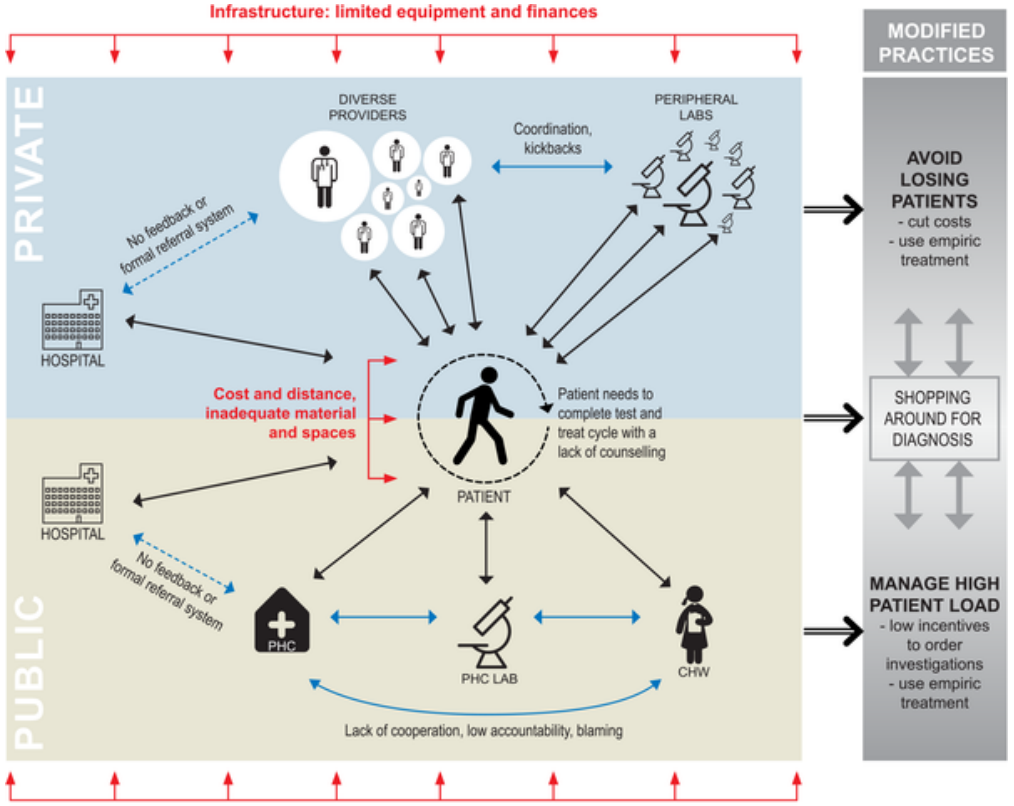
A Comparison of Multidrug-Resistant Tuberculosis Treatment Commencement Times in MDRTBPlus Line Probe Assay and Xpert® MTB/RIF-Based Algorithms in a Routine Operational Setting in Cape Town

Pren Naidoo[1]*, Elizabeth du Toit[1], Rory Dunbar[1], Carl Lombard[2], Judy Caldwell[3], Anne Detjen[4], S. Bertel Squire[5], Donald A. Enarson[4], Nulda Beyers[1]

INDIA:

Patients run around,
get tested,
carry results,
and
go back to providers





Engel N, PLoS ONE 10(8): e0135112. doi:10.1371/journal.pone.0135112
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0135112

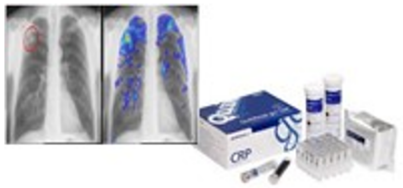
TB DX PIPELINE: PROMISE VS REALITY

	Early development	Late or completed development	On pathway to WHO evaluation
High complexity assays	**Molecular - Detection/DST**		
	New TruArray MDR-TB (Akkoni) COBAS TaqMan MTB + DST(Roche) Hydra 1K (Insilixa) Mycobacterium Real-time MDR (CapitalBio) MTB Detect (Great Basin Scientific)	TRC Rapid MTB (Tosoh) VereMTB (Veredus Laboratories) LiPA Pyrazinamide (Nipro) Fluorotype MTBDR (Hain) TBMDx (Abbott) Meltpro (Zeesan) Mycobacteria RT PCR (CapitalBio) REBA MTB-XDR (YD Diagnostics) EasyNAT TB (Ustar) BD Max (BD) Anyplex series (Seegene, Korea) AccuPower TB&MDR (Bioneer)	REBA MTB-Rifa (YD Diagnostics)
	Culture-based - Detection/DST		
	BNP Middlebrook (NanoLogix) MYCOLOR TK BNP (Salubris, USA)	TREK Sensitive MYCOTB (Thermo Fisher) Sensititre System (Thermo Fisher)	
Moderate complexity assays	**Molecular Detection/DST**		
	Xtend XDR (Cepheid) Alere Q (Alere) Enigma ML (Enigma Diagnostics) Q-POC (QuantuMDx) EOSCAPE (Wave80) TBDx system (KGI) X1 (Xagenic) MTB Detection (Tangen Biosciences) TB POC (Qiagen) Savanna (NWGHF/Quidel)	Genedrive MTB/RIF (Epistem) Truelab/Truenat MTB (Molbio)	Xpert Ultra platform (Cepheid)
	Cellular Response - Detection/Latent and latent to active progression		
	ESAT-6/CFP-10 skin test (SSI)	QuantiFERON-TB PLUS (Qiagen) Diaskin (Generium)	
	Breath biomarker - Detection		
	BreathLink (Menssana) TB Breathalyser (Rapid Biosensor Systems) Aeonose (The eNose Company) Breath analysis instrument (Avisa) Breath analysis instrument (Technion)		
	Automated Microscopy & Imaging - Detection		
	Fluorescent microscopy (ID-FISH Tech.) Automatic TB Screener (Fluorobot) Cellscope (UCSF) TBDx (Applied Visual Sciences)	CAD4TB (Delft Imaging Systems)	
Low complexity assays	**Antigen, Antibody and Biomarker detection- Detection**		
	LAM in urine (Fujifilm, Global Goods, and others) IRISA-TB -pleural/pericardial/ascitic fluid (Antrum Biotec) Host marker (several groups)		


Problems
Solutions

TEST, TREAT AND TRACK: WE NEED COMPLETE SOLUTIONS

Symptomatic



Rapid Triage Test

Rapid Molecular Dx & Upfront DST

Culture/ sequencing confirmation at referral labs

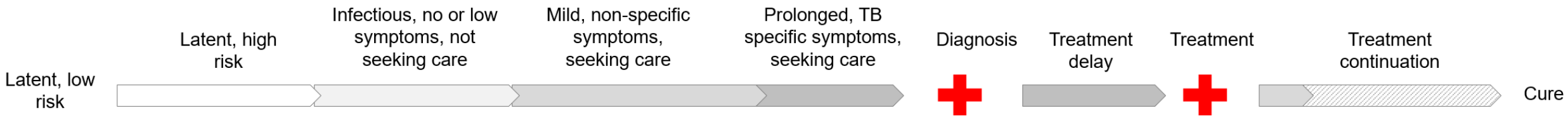
eTB ICT system

Electronic notification & tracking

Adherence monitoring tools

Shorter drug regimens

Solutions are required across the entire pathway



UNMET NEEDS	**Screen high risk populations for TB and risk of progression** to TB as they link for other causes, and ensure they are put on preventative treatment Consider active case finding	Get providers to **screen for rare TB occurrences** either with multi-disease or TB-only test	Get providers to know TB signs & symptoms and **screen for TB**	Increase **performance** of case detection at **lower levels** in health system, and **test non-pulmonary, non-sputum cases**	**Accelerate referral** of patients, samples and information to and from lab back to provider or patient	Get provider to **test for sensitivity to Rif, other drugs, and to shorter term regimen** at **lower levels** in health systems	Test **adherence** and **response** to treatment	
DELIVERY SOLUTIONS	**Intensive case finding in specific populations (e.g. ART clinics)** **LTBI treatment in high-risk populations (e.g. PLHIV)**	**Level 0/1 provider training & incentives for referrals** **Increased use of chest X-ray**		**Omni / Ultra uptake support; Ustar or Molbio in specific countries** **ICT-enabled sample referral to L3 for DST**	**ICT-enabled sample, patient and result referral**	**Omni/Ultra** **NAAT uptake support**	**Test for Rx response**	

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IN THE NEXT 5Y, WHAT MUST SCALE-UP THESE SOLUTIONS

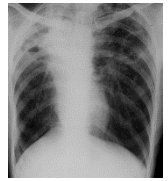
L0

Triage options

Organized community health workers or pharmacists to refer presumed TB, or collect and send sample to L1

L1

Triage with CXR
Case detection options
CD + RIF options

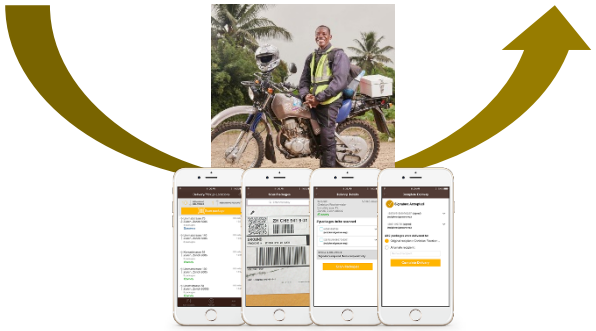


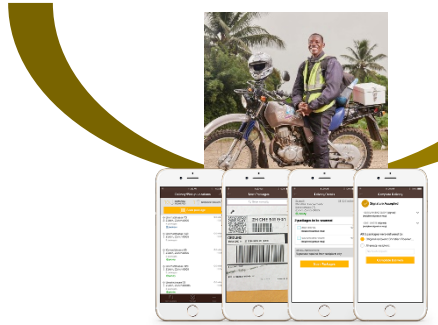
L2

CD + RIF option
CD + RIF/FQ option

L3

CD + Full DST options





Sample transportation system, supported by ICT

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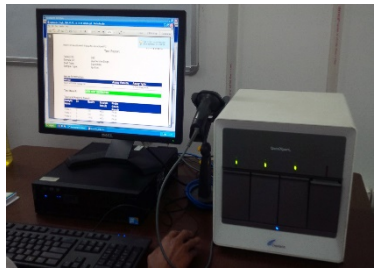
WE WILL NEED OPTIMIZE ALL OPTIONS ACROSS THE VALUE CHAIN

Move the test lower, and move the sample higher

L1: Primary care

GeneXpert Omni system with
Xpert MTB/RIF Ultra, TB LAMP,
TrueNAT MTB, EasyNAT TB

L2: District level



Xpert MTB/RIF, and Xpert XDR
for detecting resistance to quinolones
and second-line injectable drugs

L3: Reference lab

First and second line LPAs
High throughput NAATs
Next-generation sequencing

Sample transportation system, supported by ICT

MacLean E, Huddart S, Pai M. Exp Rev Mol Diag 2016

HOW CAN WE GET MORE IMPACT FROM DX?

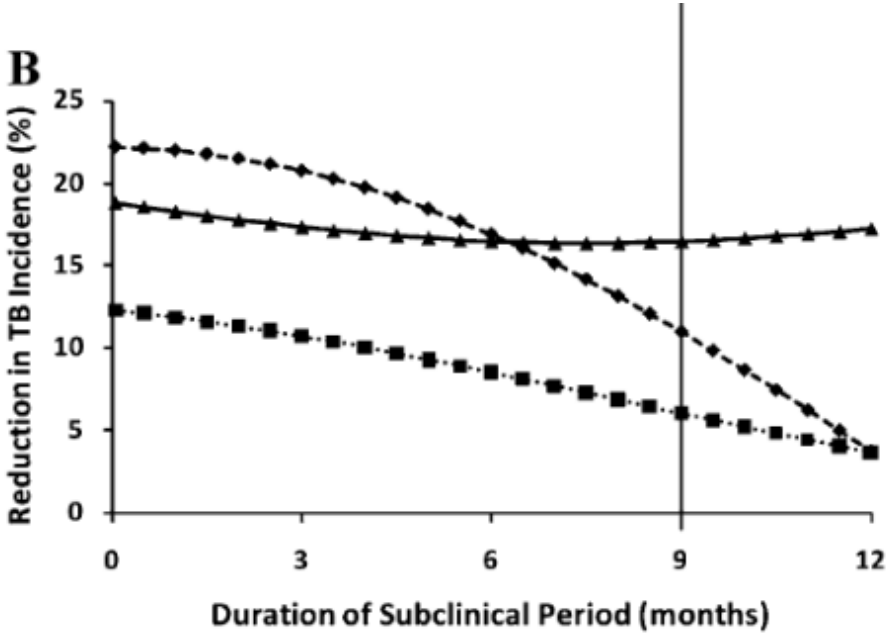
MODELS ARE GENERALLY OPTIMISTIC, WITH FAIRLY CONSISTENT ESTIMATES OF IMPACT

Author (Journal, Year)	Reduction in Incidence	Reduction in Mortality
Dowdy (AIDS 2006)	9%	19-22%
Abu-Raddad (PNAS 2009)	12-24%	23%
Lin (Bull WHO 2012)	3%	9%
Menzies (PLOS Med 2012)	6%	21%
Sun (Am J Epidemiol 2013)	7-9%	20-22%
Langley (Lancet GH 2014)	~5%	~20%

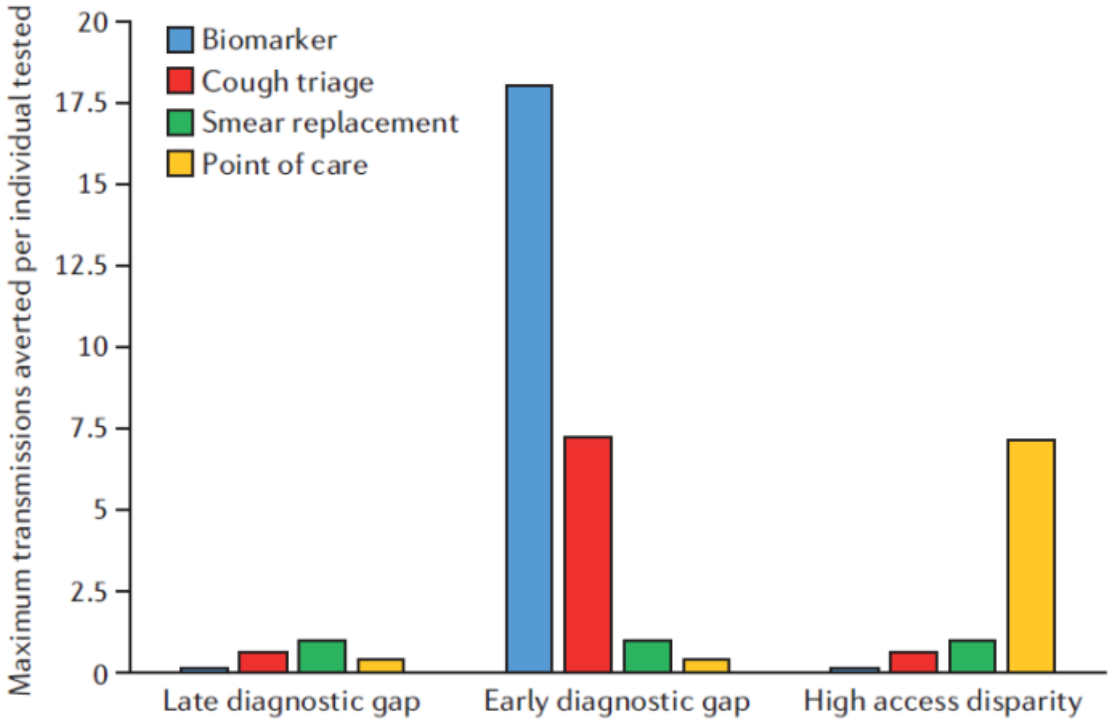
Most models of scaling up novel diagnostic tests project:

- **5-10% reduction in incidence**
- **~20% reduction in mortality**
- **over a ~10-year time frame.**

BUT THE IMPACT OF A NEW DIAGNOSTIC DEPENDS ON WHEN TRANSMISSION OCCURS RELATIVE TO DIAGNOSIS…



If TB has a long subclinical phase (and diagnostics not used for ACF), projected impact can fall by 75%.

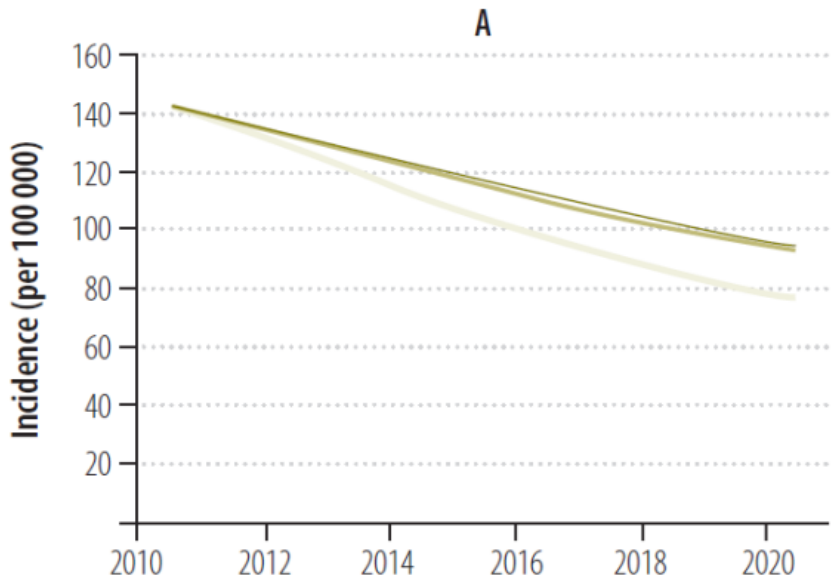


If most transmission occurs before people have classic TB symptoms, tests to predict progression or triage coughers will have greater relative impact vs. smear replacement or POC passive diagnostics for TB.

Dowdy, Basu, Andrews AJRCCM 2013

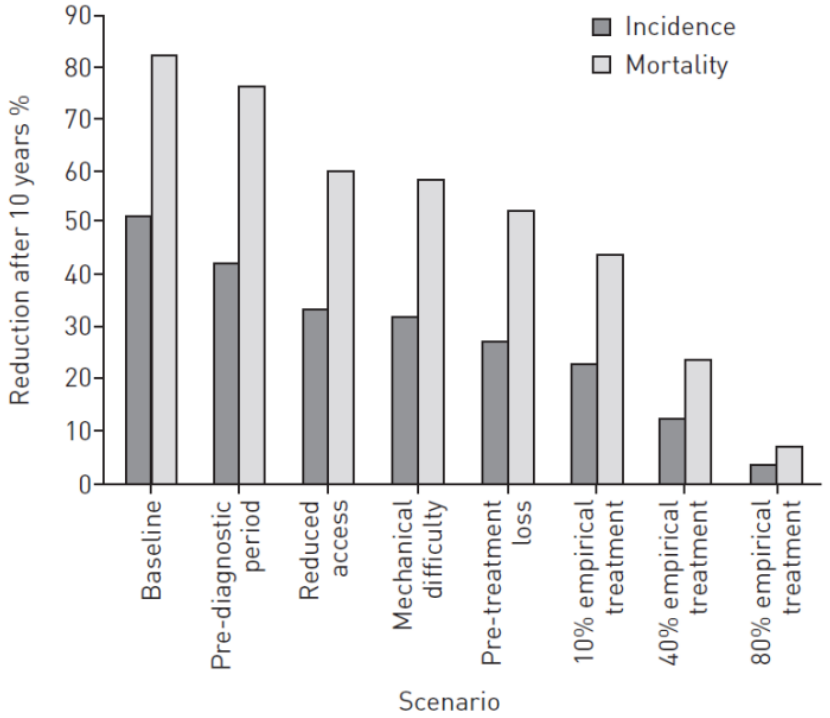
Arinaminpathy & Dowdy, Nature 2015

…AND ON HOW DX ARE IMPLEMENTED IN A HEALTH SYSTEM



Impact of a new diagnostic can be greatly augmented by combining it with shortened patient delay, increased access to care, and better treatment success.

Lin et al, Bull WHO 2012



Alternatively, the impact of a new diagnostic test can be greatly attenuated by reduced access, pre-treatment loss to follow-up, and high rates of empiric therapy.

Sun et al, Eur Respir J 2014

WE CAN GET BETTER IMPACT BY OPTIMIZING IMPLEMENTATION

IN MONTREAL, XPERT MTB/RIF HAD LITTLE IMPACT

Xpert MTB/RIF Testing in a Low Tuberculosis Incidence, High-Resource Setting: Limitations in Accuracy and Clinical Impact

Hojoon Sohn,[1,2] Abebech D. Aero,[1,2] Dick Menzies,[1,2] Marcel Behr,[1,2] Kevin Schwartzman,[1,2] Gonzalo G. Alvarez,[1,3] Andrei Dan,[1] Fiona McIntosh,[1,2] Madhukar Pai,[1,2,a] and Claudia M. Denkinger[1,4,a]

[1]McGill International Tuberculosis Centre and Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, [2]Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, and [3]Ottawa Hospital Research Institute, University of Ottawa, Canada; and [4]Division of Infectious Disease, Beth Israel Deaconess Medical Center, Boston, Massachusetts

"Limited potential impact of Xpert testing in high-resource, low-incidence ambulatory settings due to lower sensitivity in the context of less extensive disease, and limited potential to expedite diagnosis beyond what is achieved with the existing, well-performing diagnostic algorithm."

CID 2014:58 (1 April)

IN IQALUIT, XPERT MTB/RIF HAD A POSITIVE IMPACT

[Original Research **Chest Infections**]

CHEST

The Feasibility, Accuracy, and Impact of Xpert MTB/RIF Testing in a Remote Aboriginal Community in Canada

Gonzalo G. Alvarez, MD; Deborah D. Van Dyk, MScN; Marc Desjardins, PhD; Abdool S. Yasseen III, MSc; Shawn D. Aaron, MD; D. William Cameron, MD; Natan Obed, BA; Maureen Baikie, MD; Smita Pakhale, MD; Claudia M. Denkinger, MD; Hojoon Sohn, MSc; and Madhukar Pai, MD

"In a predominantly Inuit population …where the burden of TB is high and no TB testing facilities are available, on-site Xpert was feasible, accurate and shortened time to TB treatment initiation."

Alvarez G et al. CHEST 2015

IN KHAYELITSHA, XPERT MTB/RIF HAD A POSITIVE IMPACT

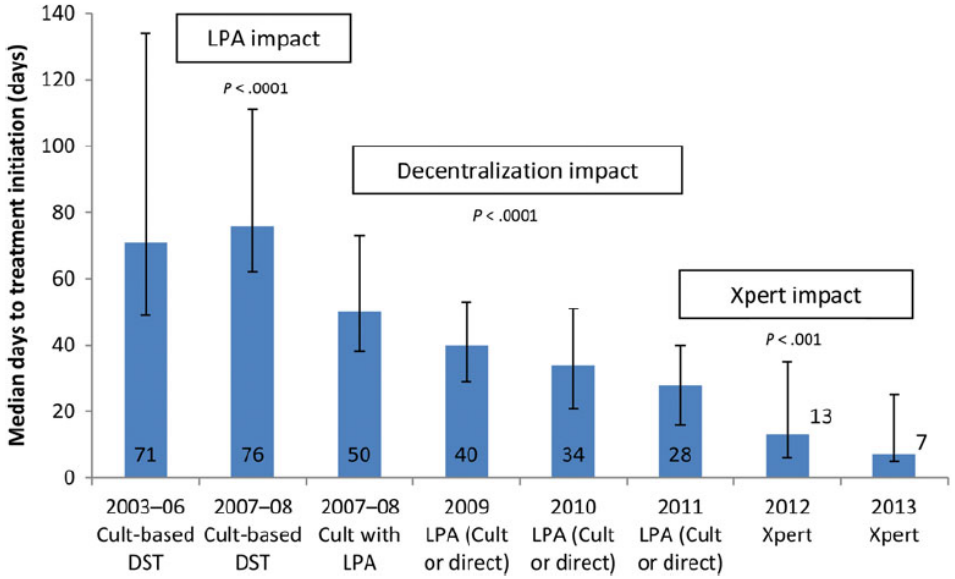
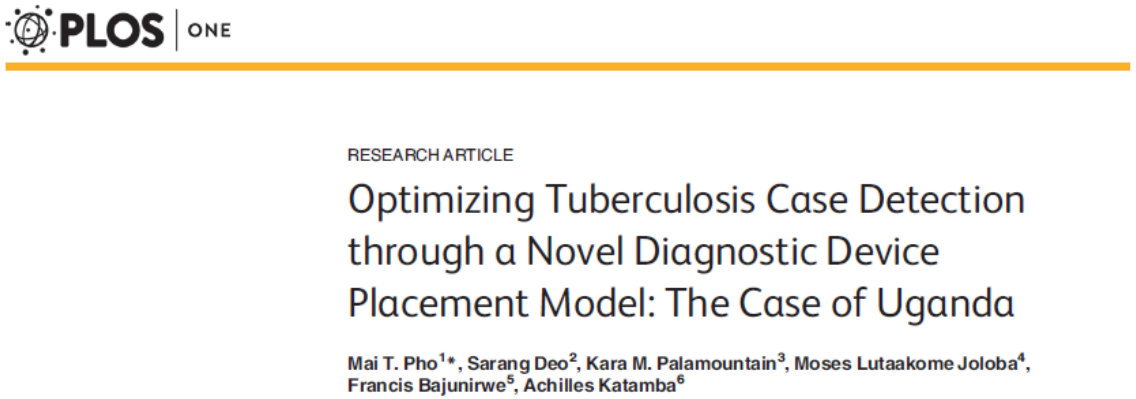


Figure 1. Median time to treatment (days) by year and diagnostic method (error bars represent interquartile range). Abbreviations: DST, drug susceptibility testing; LPA, line probe assay.

Cox et al. Open Forum Infect 2015

SO, OUR MONTREAL GENEXPERT MACHINE IS NOW SERVING PATIENTS IN RURAL INDIA!

WE NEED TO GET SMARTER ABOUT WHERE AND HOW WE PLACE TECH


PLOS ONE

RESEARCH ARTICLE

Optimizing Tuberculosis Case Detection through a Novel Diagnostic Device Placement Model: The Case of Uganda

Mai T. Pho[1]*, Sarang Deo[2], Kara M. Palamountain[3], Moses Lutaakome Joloba[4], Francis Bajunirwe[5], Achilles Katamba[6]

"In Uganda, placement of Xpert devices in sites with high TB prevalence yielded the highest TB CDR at the lowest cost per additional case diagnosed. These results represent novel use of program level data to inform the optimal placement of new technology in resource-constrained settings."

Pho et al. PLoS ONE 2015

POCT IMPLEMENTATION IS FEASIBLE, BUT MORE EXPENSIVE BECAUSE OF PROCESS INNOVATIONS

INT J TUBERC LUNG DIS e-publication ahead of print 30 June 2015
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http://dx.doi.org/10.5588/ijtld.15.0120

Impact of point-of-care implementation of Xpert® MTB/RIF: product vs. process innovation

S. G. Schumacher,*† B. Thangakunam,‡ C. M. Denkinger,*†§ A. A. Oliver,‡ K. B. Shakti,‡ Z. Z. Qin,*† J. S. Michael,¶ R. Luo,# M. Pai,*† D. J. Christopher‡

INT J TUBERC LUNG DIS 17(3):368–372
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http://dx.doi.org/10.5588/ijtld.12.0392

Point-of-care Xpert® MTB/RIF for smear-negative tuberculosis suspects at a primary care clinic in South Africa

A. Van Rie,* L. Page-Shipp,† C. F. Hanrahan,* K. Schnippel,† H. Dansey,‡ J. Bassett,‡ K. Clouse,*§ L. Scott,¶ W. Stevens,¶# I. Sanne†§

*Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA; †Right to Care, Johannesburg, ‡Witkoppen Health and Welfare Centre, Johannesburg, §Clinical HIV Research Unit, Johannesburg, ¶Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, #National Health Laboratory Service, Johannesburg, South Africa

Tropical Medicine and International Health doi:10.1111/j.1365-3156.2012.03028.x
VOLUME 00 NO 00

Scaling up Xpert MTB/RIF technology: the costs of laboratory- *vs.* clinic-based roll-out in South Africa

Kathryn Schnippel[1], Gesine Meyer-Rath[1,2], Lawrence Long[1], William MacLeod[1,2], Ian Sanne[1,2], Wendy S. Stevens[3,4] and Sydney Rosen[1,2]

1 *Health Economics and Epidemiology Research Office, Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*
2 *Center for Global Health and Development, Boston University, Boston, MA, USA*
3 *Department of Molecular Medicine and Haematology, University of the Witwatersrand, Johannesburg, South Africa*
4 *National Health Laboratory Service, Johannesburg, South Africa*

INT J TUBERC LUNG DIS 19(7):811–816
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http://dx.doi.org/10.5588/ijtld.15.0013

The patient impact of point-of-care vs. laboratory placement of Xpert® MTB/RIF

C. F. Hanrahan,* K. Clouse,† J. Bassett,‡ L. Mutunga,‡ K. Selibas,§ W. Stevens,¶# L. Scott,# I. Sanne,§ A. Van Rie*

*Department of Epidemiology, University of North Carolina Gillings School of Global Public Health, Chapel Hill, North Carolina, †Vanderbilt Institute for Global Health, Vanderbilt University, Nashville, Tennessee, USA; ‡Witkoppen Health and Welfare Centre, Johannesburg, §Clinical HIV Research Unit, Johannesburg, ¶Department of Molecular Medicine and Haematology, University of the Witwatersrand, Johannesburg, #The National Health Laboratory Service, Johannesburg, South Africa

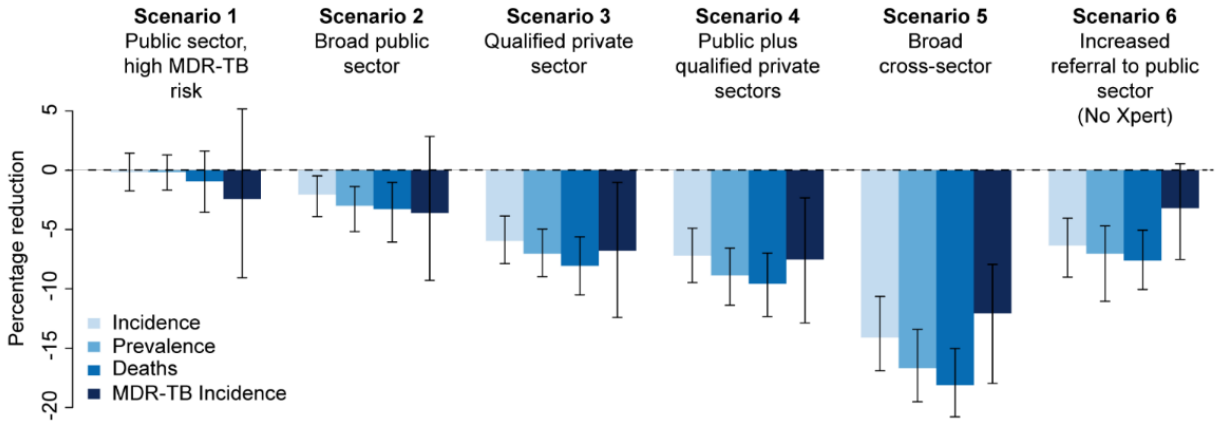
WHO GETS ACCESS ALSO MATTERS: E.G. PRIVATE SECTOR IN INDIA

OPEN ACCESS Freely available online

PLOS | MEDICINE

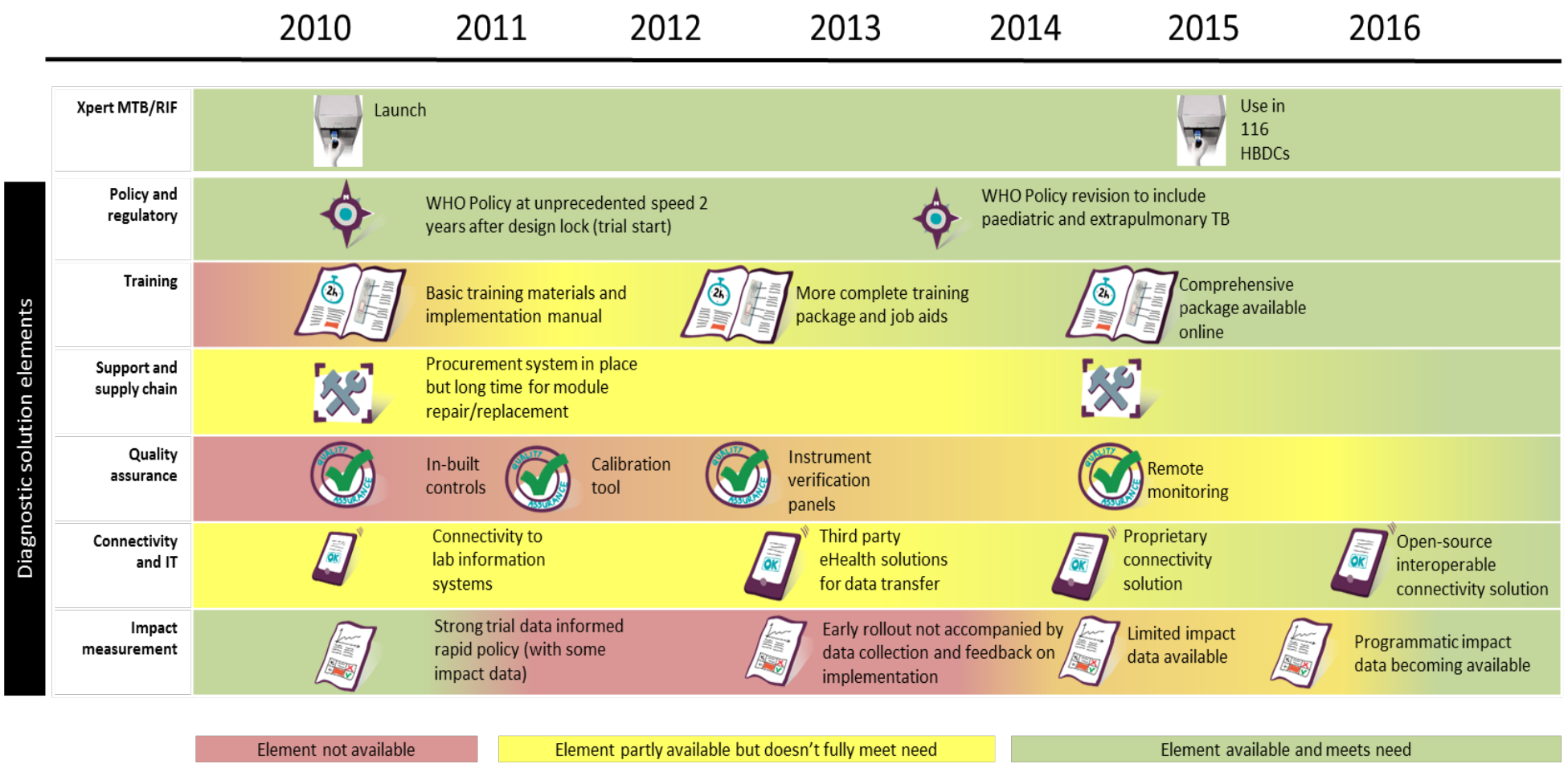
The Importance of Implementation Strategy in Scaling Up Xpert MTB/RIF for Diagnosis of Tuberculosis in the Indian Health-Care System: A Transmission Model

Henrik Salje[1], Jason R. Andrews[2¤], Sarang Deo[3], Srinath Satyanarayana[4,5], Amanda Y. Sun[6], Madhukar Pai[4,5,7¶], David W. Dowdy[1,8*¶]



PLoS Med 2014

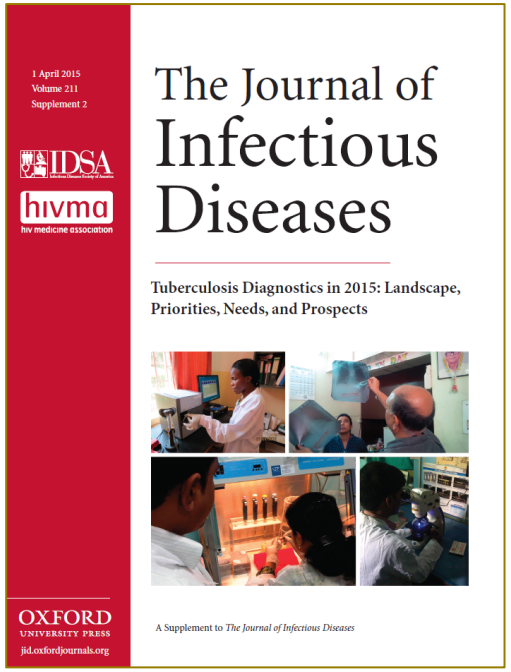
WE HAVE LEARNT A LOT WITH ROLL-OUT OF NEW TOOLS, AND NEED TO APPLY THEM FOR BETTER IMPACT!

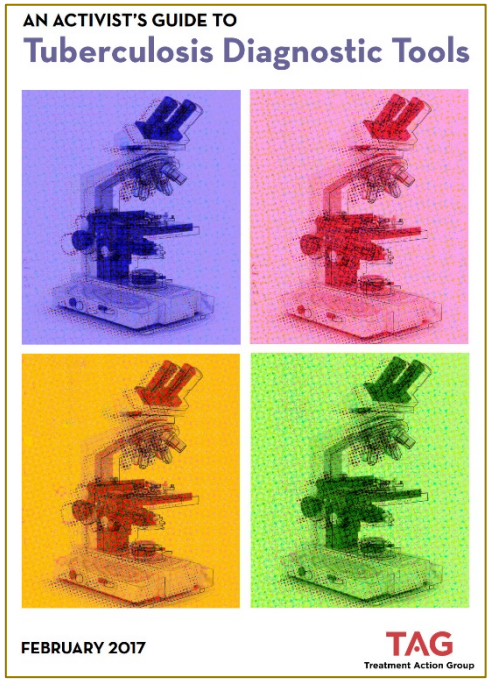


Albert H et al. ERJ 2016

FOR MORE RESOURCES, PLEASE SEE

OPEN ACCESS





Thank you!!