Conference

8th National Conference on
Laboratory Aspects of Tuberculosis

APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES

POC TB testing: Opportunities and Challenges

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McGill

Disclosure

- No financial/industry conflicts

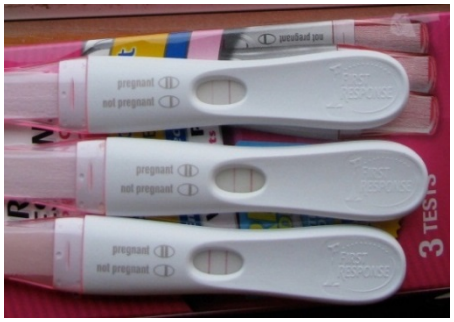
- I consult for the Bill & Melinda Gates Foundation (views expressed are my own)

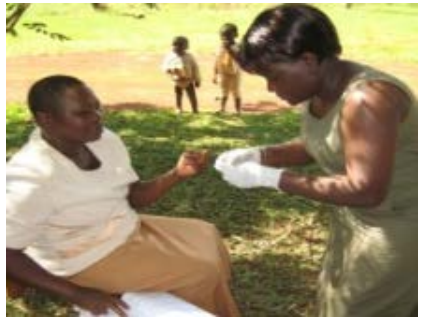
- I also receive grant funding from BMGF

BILL & MELINDA GATES *foundation*

Everyone agrees that we need POC TB testing, but we need to first agree on what POC testing is!

Popular view: product oriented





Dipstick or “pregnancy test”
Cheap
Rapid
No instrument
No lab
No trained lab personnel
Used by community health workers in remote areas

Since it is so product-oriented, the dominant view: there is no POC test for TB

TOWARDS LAB-FREE TUBERCULOSIS DIAGNOSIS

Hans-Georg Batz
Graham S Cooke
Steven D Reid

However, despite the effort and financial resources that have been invested, POC diagnostics for TB have not materialised.

This is because of the focus on product rather than what 'job needs to be done'

Point-of-care tuberculosis diagnosis: are we there yet?

"…absence of a dipstick-type point-of-care test continues to be a gaping hole in the pipeline."

Denkinger & Pai. LID 2011

Opportunities and Challenges for Cost-Efficient Implementation of New Point-of-Care Diagnostics for HIV and Tuberculosis

Marco Schito,[1] Trevor F. Peter,[2] Sean Cavanaugh,[3] Amy S. Piatek,[4] Gloria J. Young,[5] Heather Alexander,[6] William Coggin,[7] Gonzalo J. Domingo,[8] Dennis Ellenberger,[6] Eugen Ermantraut,[9] Ilesh V. Jani,[10] Achilles Katamba,[11] Kara M. Palamountain,[12] Shaffiq Essajee,[13] and David W. Dowdy[14]

"For TB, several new diagnostic tests have recently been endorsed by the WHO, but a POC test remains elusive"

A less restrictive, more realistic and goal-oriented view

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PLOS | MEDICINE

Policy Forum

Point-of-Care Testing for Infectious Diseases: Diversity, Complexity, and Barriers in Low- And Middle-Income Countries

Nitika Pant Pai[1], Caroline Vadnais[2], Claudia Denkinger[2,3], Nora Engel[4], Madhukar Pai[2,5]*

1 Division of Clinical Epidemiology, Department of Medicine, McGill University, Montreal, Canada, **2** Respiratory Epidemiology & Clinical Research Unit, Montreal Chest Institute, Montreal, Canada, **3** Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, Massachusetts, United States of America, **4** Department of Health, Ethics and Society/Caphri, Faculty of Health, Medicine and Life Sciences, Maastricht University, The Netherlands, **5** Department of Epidemiology & Biostatistics, McGill University, Montreal, Canada

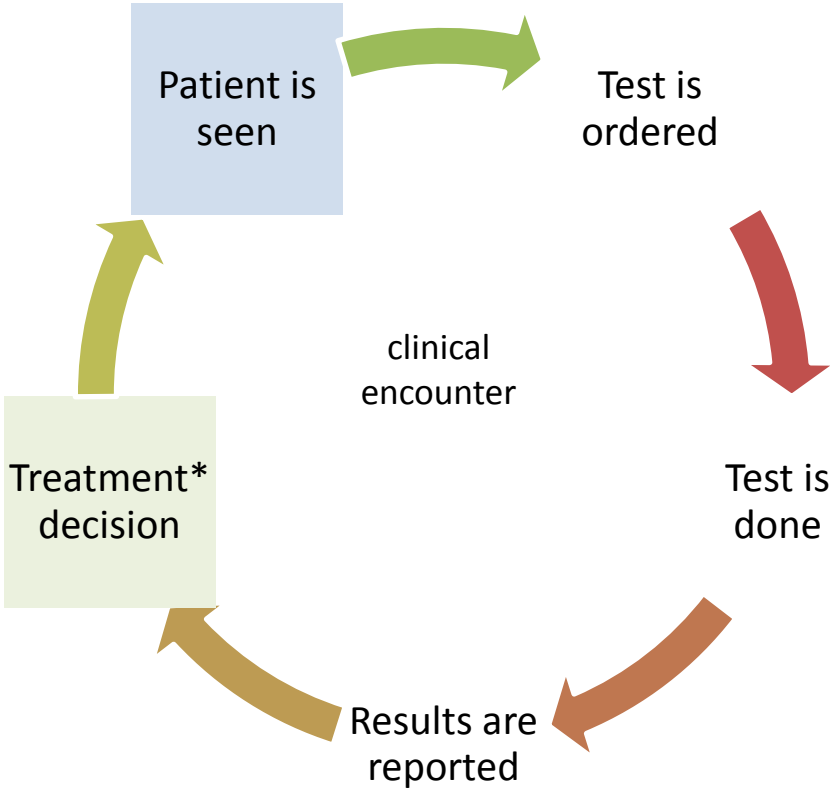
Pai NP, et al. Point-of-Care Testing for Infectious Diseases: Diversity, Complexity, and Barriers in Low- And Middle-Income Countries. PLoS Med 2012;9(9): e1001306. http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001306

Started with treatment (the goal) and worked our way backwards

Treatment is what really matters – it will have a clinical impact and hence a public health impact on reducing transmission…

on the spot; in the same clinical encounter; while the patient waits; at least on the same day

Rapid completion of the “test and treat” loop in the same clinical encounter is the ‘job-to-be-done’



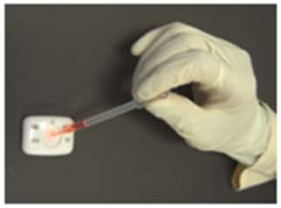
*Treatment can be: start drugs, stop drugs, modify drugs, refer, order more tests, discharge, admit, etc.

Goal-oriented definition of POC

"Testing that will result in a clear, actionable, management decision (e.g. referral, initiation of confirmatory test, start of treatment), within the same clinical encounter (e.g. day)."

TB MAC meeting Amsterdam

POCT is a "spectrum" which covers a variety of settings, users, products (i.e. TPPs)

TPP1: HOME	TPP2: COMMUNITY	TPP3: CLINIC / HEALTH POST (Out-patient)	TPP4: PERIPHERAL LAB	TPP5: HOSPITAL (In-patient)
Self-testing (home-based)	**Testing in the community by health workers** (e.g. village workers, paramedics)	**Testing in the clinic by healthcare providers** (e.g. doctors, nurses)	**Testing in the peripheral laboratory**	**Testing of in-patients in hospitals** (e.g. ER, OR, ICU)
User: Lay person	User: Minimally trained health worker	User: Clinic staff	User: Lab tech	User: Hospital staff
Device: RDT (pregnancy-type) or dipstick	Device: RDT	Device: RDT, handheld instruments	Device: RDT, molecular tests, ELISA, microscopy, etc	Device: RDT, molecular, smears, etc.
Purpose: Self assessment and referral	Purpose: Triage and referral	Purpose: Diagnosis and treatment	Purpose: Diagnosis treatment monitoring	Purpose: Diagnosis treatment monitoring
Simplest				*Relatively sophisticated*
				
HIV self-testing	Malaria, HIV, dengue	HIV, malaria, syphilis, dengue, Strep A	TB, HIV, malaria, HBV, C.diff, CD4, HCV, MRSA, flu, UTI, viral loads, etc.	TB, HIV, malaria, HBV, HCV, flu, MRSA CD4, Strep A, C.diff, etc.

Pai NP, Vadnais C, Denkinger C, Engel N, et al. (2012) Point-of-Care Testing for Infectious Diseases: Diversity, Complexity, and Barriers in Low- And Middle-Income Countries. PLoS Med 9(9): e1001306. doi:10.1371/journal.pmed.1001306
http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.1001306

To summarize

POC testing is a spectrum (dipstick in the community is just one TPP)

POCT program = technology + enabling healthcare system

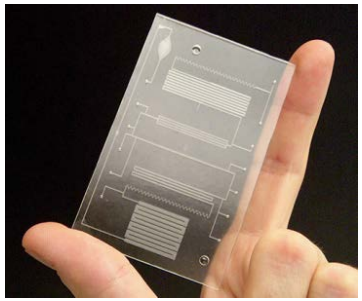
or

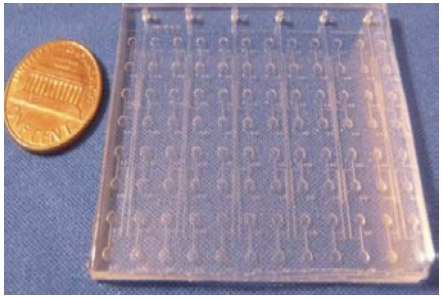
POCT program = test + business model*

- Technology does not define a POC test nor determine its use at the POC.
- It is the successful use at the point-of-care that defines a diagnostic process as POC testing.
- So, we need POC testing programs, rather than POC tests.

*courtesy: Peter Small

Test developers seem to believe that smallness of the device or portability = POC technology





Smallness/portability may help, but they do not guarantee POCT implementation

It is not the size or portability, but whether the technology can actually be implemented in a manner that allows rapid completion of the test and treat loop in any one of the 5 TPPs

Smear microscopy is not a dipstick, but is it amenable to a POCT program?

It is, but most healthcare systems are unable or unwilling to make it work as a POCT program

In India, for example, it can take 8 days before TB treatment is started after sputum smear is read +ve

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PLoS one

Factors Associated with Delays in Treatment Initiation after Tuberculosis Diagnosis in Two Districts of India

Durba Paul[1]*, Arundhathi Busireddy[2], Sharath Burugina Nagaraja[1], Srinath Satyanarayana[3], Puneet Kumar Dewan[1], Sreenivas Achutan Nair[3], Silajit Sarkar[1], Quazi Toufique Ahmed[1], Shakuntala Sarkar[4], Sreenivas Rao Motta Shamrao[5], Anthony David Harries[6,7], John Ethan Oeltmann[8]

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Abstract

Background: Excessive time between diagnosis and initiation of tuberculosis (TB) treatment contributes to ongoing TB transmission and should be minimized. In India, Revised National TB Control Programme (RNTCP) focuses on indicator start of treatment within 7 days of diagnosis for patients with sputum smear-positive PTB for monitoring DOTS implementation.

Objectives: To determine length of time between diagnosis and initiation of treatment and factors associated with delays of more than 7 days in smear-positive pulmonary TB.

Methods: Using existing programme records such as the TB Register, treatment cards, and the laboratory register, we conducted a retrospective cohort study of all patients with smear-positive pulmonary TB registered from July-September 2010 in two districts in India. A random sample of patients with pulmonary TB who experienced treatment delay of more than 7 days was interviewed using structured questionnaire.

Results: 2027 of 3411 patients registered with pulmonary TB were smear-positive. 711(35%) patients had >7 days between diagnosis and treatment and 262(13%) had delays >15 days. Mean duration between TB diagnosis and treatment initiation was 8 days (range = 0–128 days). Odds of treatment delay >7 days was 1.8 times more likely among those who had been previously treated (95% confidence interval [CI] 1.5–2.3) and 1.6 (95% CI 1.3–1.8) times more likely among those diagnosed in health facilities without microscopy centers. The main factors associated with a delay >7 days were: patient reluctance to start a re-treatment regimen, patients seeking second opinions, delay in transportation of drugs to the DOT centers and delay in initial home visits. To conclude, treatment delay >7 days was associated with a number of factors that included history of previous treatment and absence of TB diagnostic services in the local health facility. Decentralized diagnostic facilities and improved referral procedures may reduce such treatment delays.

Citation: Paul D, Busireddy A, Nagaraja SB, Satyanarayana S, Dewan PK, et al. (2012) Factors Associated with Delays in Treatment Initiation after Tuberculosis Diagnosis in Two Districts of India. PLoS ONE 7(7): e39040. doi:10.1371/journal.pone.0039040

In S Africa, one in four smear-positive TB patients were not started on treatment within 1 month of diagnosis…

INT J TUBERC LUNG DIS 17(5):603–607

http://dx.doi.org/10.5588/ijtld.12.0505

Tuberculosis patients in primary care do not start treatment. What role do health system delays play?

M. M. Claassens,*† E. du Toit,* R. Dunbar,* C. Lombard,‡ D. A. Enarson,§ N. Beyers,* M. W. Borgdorff†

*Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Cape Town, South Africa; †University of Amsterdam, Amsterdam, The Netherlands; ‡Biostatistics Unit, Medical Research Council, Cape Town, South Africa; §International Union Against Tuberculosis and Lung Disease, Paris, France

SUMMARY

SETTING: Primary health care facilities in five provinces of South Africa.

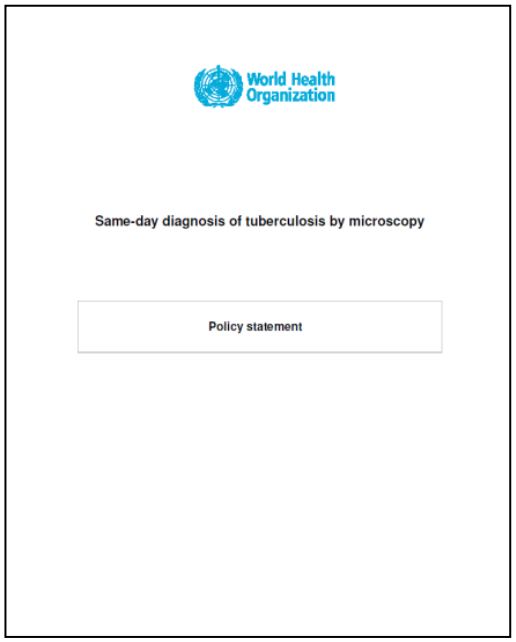
OBJECTIVE: To investigate the association between the proportion of sputum results with a prolonged smear turnaround time and the proportion of smear-positive tuberculosis (TB) cases initially lost to follow-up.

DESIGN: The unit of investigation was a primary health care facility and the outcome was the initial loss to follow-up rate per facility, which was calculated by comparing the sputum register with the TB treatment register. A prolonged turnaround time was defined as more than 48 h from when the sputum sample was documented in the sputum register to receipt of the result at the facility.

RESULTS: The mean initial loss to follow-up rate was 25% (95%CI 22–28). Smear turnaround time overall was inversely associated with initial loss to follow-up ($P = 0.008$), when comparing Category 2 (33–66% turnaround time within 48 h) with Category 1 (0–32%) (OR 0.73, 95%CI 0.48–1.13, $P = 0.163$) and when comparing Category 3 (67–100%) with Category 1 (OR 0.62, 95%CI 0.39–0.99, $P = 0.045$). The population preventable fraction of initial loss to follow-up (when turnaround time was <48 h in ⩾67% of smear results) was 21%.

CONCLUSION: Initial loss to follow-up should be reported as part of the TB programme to ensure that patients are initiated on treatment to prevent transmission within communities.

KEY WORDS: tuberculosis; initial loss to follow-up; turnaround time



Test and Treat: A New Standard for Smear-Positive Tuberculosis

J. Lucian Davis, MD, MAS*†
David W. Dowdy, MD, PhD, ScM‡
Saskia den Boon, MSc, PhD†
Nicholas D. Walter, MD†§
Achilles Katamba, MBChB, PhD†‖
Adithya Cattamanchi, MD, MAS*†

JAIDS 2012

Diagnostic accuracy of same-day microscopy versus standard microscopy for pulmonary tuberculosis: a systematic review and meta-analysis

J Lucian Davis, Adithya Cattamanchi, Luis E Cuevas, Philip C Hopewell, Karen R Steingart

OPEN ACCESS Freely available online PLoS MEDICINE

A Multi-Country Non-Inferiority Cluster Randomized Trial of Frontloaded Smear Microscopy for the Diagnosis of Pulmonary Tuberculosis

Luis Eduardo Cuevas[1,2]*, Mohammed Ahmed Yassin[1], Najla Al-Sonboli[3], Lovett Lawson[4], Isabel Arbide[5], Nasher Al-Aghbari[6], Jeevan Bahadur Sherchand[7], Amin Al-Absi[6], Emmanuel Nnamdi Emenyonu[4], Yared Merid[8], Mosis Ifenyi Okobi[9], Juliana Olubunmi Onuoha[4], Melkamsew Aschalew[8], Abraham Aseffa[10], Greg Harper[1], Rachel Mary Anderson de Cuevas[1], Kristin Kremer[11], Dick van Soolingen[11], Carl-Michael Nathanson[2], Jean Joly[2], Brian Faragher[1], Stephen Bertel Squire[1], Andrew Ramsay[2]

"same-day reporting of results is more likely to result in successful treatment initiation than either same-day or 2-day collection with delayed reporting"

Can GeneXpert work as a POCT program for TB?

South Africa

INT J TUBERC LUNG DIS 16(5):701–710

Correspondence

Location of Xpert® MTB/RIF in centralised laboratories in South Africa undermines potential impact

"Ultimately, the diagnosis-treatment gap will only be closed by rapid point-of-care diagnostic assays that can be used during the patient's first clinic visit to permit immediate treatment decisions…"

Lawn S et al.

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

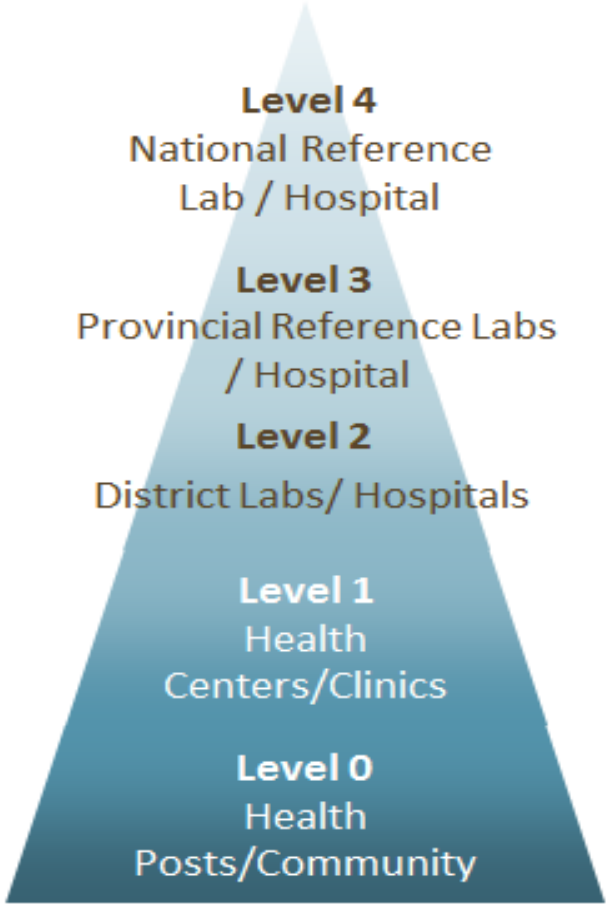
A. Van Rie,* L. Page-Shipp,† C. F. Hanrahan,* K. Schnippel,† H. Dansey,‡ J. Bassett,‡ K. Clouse,*§ L. Scott,¶ W. Stevens,¶# I. Sanne†§

"Providing Xpert at point of care had important advantages. Results were available the day of the clinic visit, allowing immediate treatment initiation and eliminating the need for a return visit. This reduced the cost borne by patients…" [Van Rie et al. IJTLD 2013]

India

Xpert implemented in upgraded microscopy centers (CB-NAAT demonstration study)
But a system is currently not in place that allows providers to start TB Rx on the same day

Even if Xpert can be made to work as a POCT program, it was designed for district/sub-district labs



?

Microscopy centers
- More decentralized
- Closer to patients
- May help detect TB earlier

Why are microscopy centers important?

Country	Number of microscopy centres	Annual smear volumes in public sector (millions)
Afghanistan	Pending	0.46
Bangladesh	1059	4.00
Brazil	Pending	Pending
Cambodia	214	0.55
China	Pending	Pending
Congo (DRC)	1,522	0.89
Ethiopia	2,497	6.04
India	13,000	7.87
Indonesia	5,566	2.04
Kenya	1818	4.85
Mozambique	300	0.25
Myanmar	Pending	Pending
Nigeria	1,341	1.90
Pakistan	1,171	1.78
Philippines	Pending	1.81
Russia	Pending	Pending
South Africa	240	4.56
Tanzania	830	0.55
Thailand	1,081	0.56
Uganda	1,030	0.24
Vietnam	818	2.46
Zimbabwe	220	0.06
Total	**32,707**	**40.9**

Millions of patients are tested at this level

TB drugs are usually available

This is the most decentralized level where Rx can be initiated

Sputum smear volumes in 22 highest TB burden countries: Preliminary results of ongoing survey
Sandra Kik, Madhukar Pai et al.

Enter “POC NAATs” [‘fast-followers’]

EXPERT REVIEWS

Nucleic acid testing for tuberculosis at the point-of-care in high-burden countries

Expert Rev. Mol. Diagn. 12(7), 687–701 (2012)

Angelika Niemz*[1] and David S Boyle[2]

Early diagnosis of tuberculosis (TB) facilitates appropriate treatment initiation and can limit the spread of this highly contagious disease. However, commonly used TB diagnostic methods are

Commercialization of microfluidic point-of-care diagnostic devices†

Curtis D. Chin,[a] Vincent Linder*[b] and Samuel K. Sia*[a]

Received 5th December 2011, Accepted 25th January 2012
DOI: 10.1039/c2lc21204h

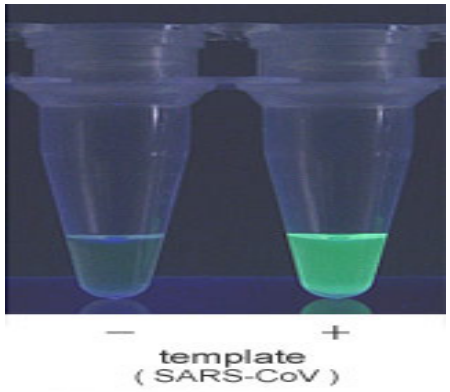
A large part of the excitement behind microfluidics is in its potential for producing practical devices, but surprisingly few lab-on-a-chip based technologies have been successfully introduced into the market. Here, we review current work in commercializing microfluidic technologies, with a focus on point-of-care diagnostics applications. We will also identify challenges to commercialization, including lessons drawn from our experience in Claros Diagnostics. Moving forward, we discuss the need to strike a balance between achieving real-world impact with integrated devices *versus* design of novel single microfluidic components.

Alere to Develop Simple, Affordable Point-of-Care Nucleic Acid Test for Tuberculosis & Expand Manufacturing for POC HIV Viral Load Platform

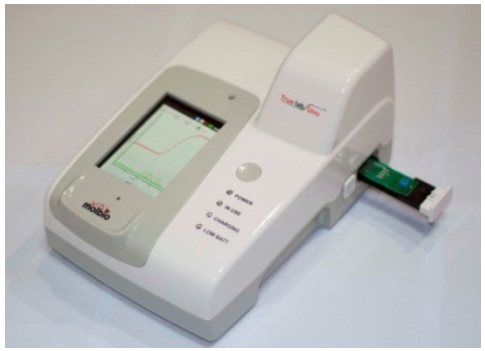
Waltham, MA – March 1, 2013 – Alere Inc. (NYSE: ALR) announced today that it has been awarded a grant of up to $21.6 million and debt financing of up to $20.6 million from the Bill & Melinda Gates Foundation. The $21.6 million grant will fund the development of a tuberculosis assay, which will be designed for use in both resource-constrained and well-resourced settings. It will also support the company’s efforts to incorporate one of its isothermal amplification technologies for TB detection onto the Alere™ Q, a compact, portable, and robust device intended for molecular testing at the point of care. In addition, the Gates Foundation will provide below-market loans of up to $20.6 million for the expansion and scale up of Alere’s manufacturing facilities in Jena, Germany for both the POC TB Nucleic Acid Test and the POC HIV Viral Load Test currently in the final stages of development. The Gates Foundation will provide these loans in exchange for commitments from Alere to make these diagnostics available at an affordable price to people in need in developing countries.

“POC NAATs” for TB

Can they be deployed at microscopy centers?
Will manual sample prep be a challenge?
Will health systems allow them to be implemented for same-day Rx?

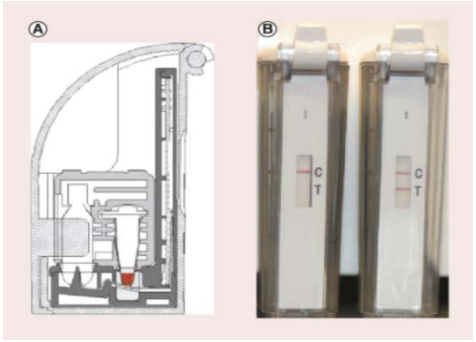


Loopamp® by Eiken, Japan



TrueLab® by Molbio, India

GeneDrive® by Epistem, UK



NATeasy® by Ustar, China

Courtesy: A. Ramsay, Kenya; Lucian Davis and Adithya Cattamanchi, Uganda; Madhu Pai, India

Eur Respir J 2013; 42: 542–544 | DOI: 10.1183/09031936.00201012 | Copyright ©ERS 2013

Are peripheral microscopy centres ready for next generation molecular tuberculosis diagnostics?

Claudia M. Denkinger[1,2], Ioana Nicolau[2], Andrew Ramsay[3], Pamela Chedore[4] and Madhukar Pai[2,4]
[1]Division of Infectious Disease, Beth Israel Deaconess Medical Center, Boston, MA, USA. [2]McGill International TB Centre and Dept of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, and [4]Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, Montreal, Montreal, QC, Canada.[3]Bute School of Medicine, St Andrews University, Fife, UK.

Characteristics of peripheral microscopy centers in 22 HBCs

	Country	Environment	
		Temp*	Humidity
Non-BRICS	Congo		
	Zimbabwe		
	Mozambique		
	Ethiopia		
	Afghanistan		
	Myanmar		
	Uganda		
	Tanzania		
	Kenya		
	Bangladesh		
	Cambodia		
	Nigeria		
	Pakistan		
	Vietnam		
	Philippines		
	Indonesia		
	Thailand		
BRICS	India		
	China		
	South Africa		
	Brazil		
	Russia		

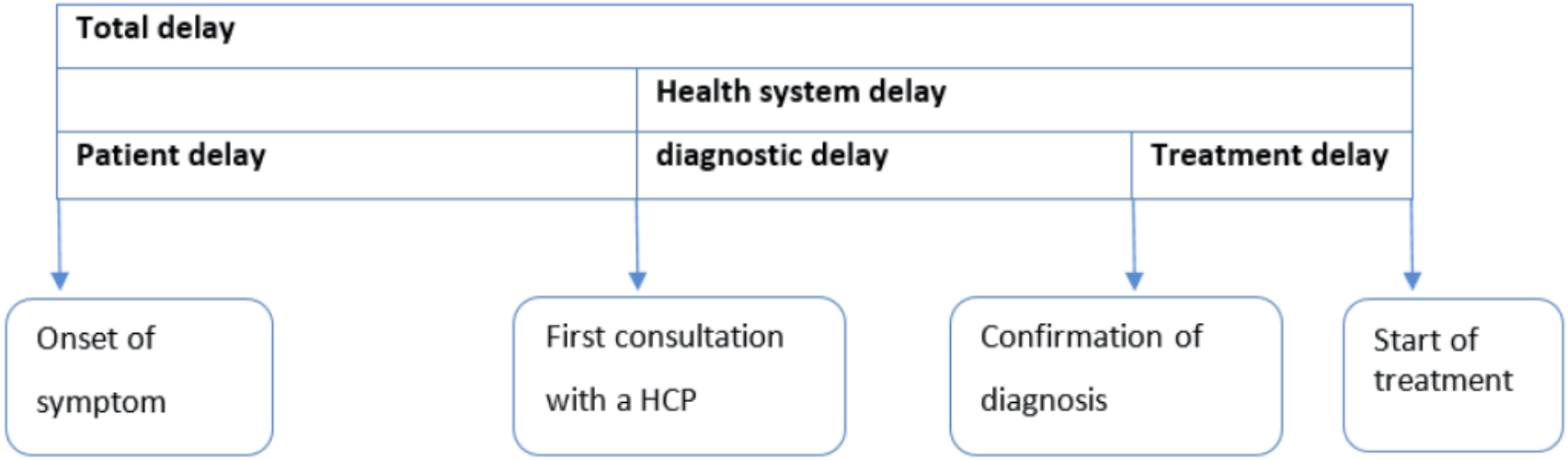
LEGEND

BAD | GOOD | MAYBE | UNSURE/ no answer

Characteristics continued

	Country	Skills		
		Pipetting	PCR tests	Computer
Non-BRICS	Congo			
	Zimbabwe			
	Mozambique			
	Ethiopia			
	Afghanistan			
	Myanmar			
	Uganda			
	Tanzania			
	Kenya			
	Bangladesh			
	Cambodia			
	Nigeria			
	Pakistan			
	Vietnam			
	Philippines			
	Indonesia			
	Thailand			
BRICS	India			
	China			
	South Africa			
	Brazil			
	Russia			

Even if we can deploy NAATs in microscopy centers, which problem will it fix?



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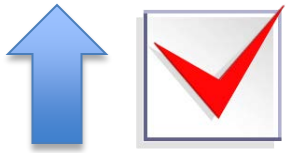


Health system delay can be reduced via POCT

Patient delays can be considerable, as shown by systematic reviews

Research article

Open Access

Time delays in diagnosis of pulmonary tuberculosis: a systematic review of literature

Chandrashekhar T Sreeramareddy*[1,5], Kishore V Panduru[2,6], Joris Menten[3] and J Van den Ende[4]

Research article

Open Access

A systematic review of delay in the diagnosis and treatment of tuberculosis

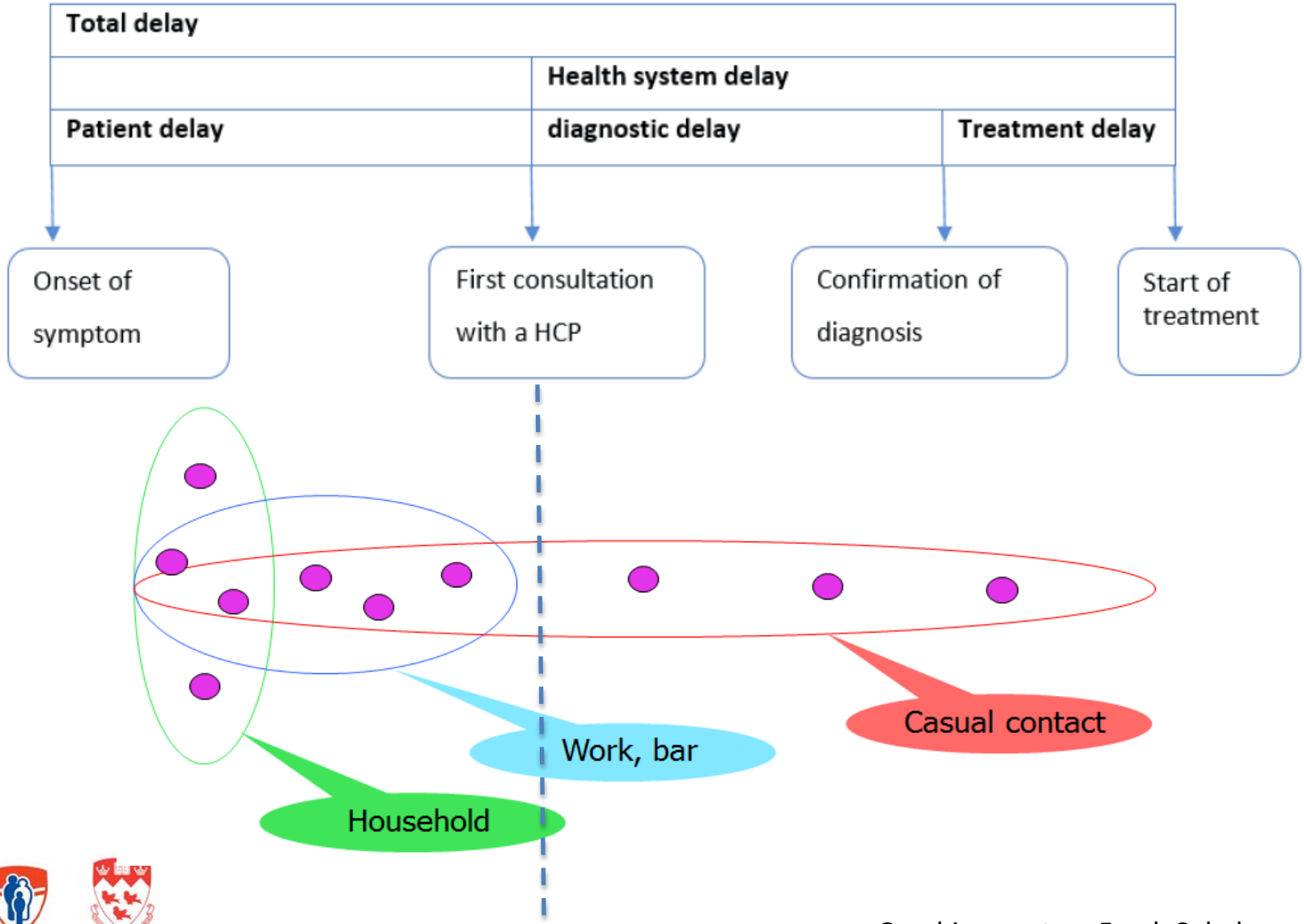
Dag Gundersen Storla*[1,2], Solomon Yimer[1] and Gunnar Aksel Bjune[1]

Address: [1]Department of International Health, Institute of General Practice and Community Medicine, University of Oslo, PO Box 1130 Blindern, N-0318 Oslo, Norway and [2]Competence Centre for Imported and Tropical Diseases, Ullevål University Hospital, Oslo, Norway

Average patient delay ~ 1 month

Total delay of 2 – 3 months

If much of the transmission occurs early, then new POCT diagnostics may have little impact on TB incidence…



Graphic: courtesy Frank Cobelens

Are patients not seeking care, or are they seeking care from informal, 'invisible' sectors?

In many developing countries, there are huge numbers of:

- Unqualified healthcare providers
- Less than qualified providers
- Traditional healers
- Chemists and pharmacists
- Alternative health system practitioners

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PLOS ONE

What Is the Role of Informal Healthcare Providers in Developing Countries? A Systematic Review

May Sudhinaraset[1]*, Matthew Ingram[2], Heather Kinlaw Lofthouse[3], Dominic Montagu[1]

1 Global Health Sciences, University of California San Francisco, San Francisco, California, United States of America, 2 Metta Fund, Corte Madera, California, United States of America, 3 Absolute Return for Kids US, New York, New York, United States of America

"Informal providers make up a significant portion of the healthcare sector globally... Utilization estimates from 24 studies for healthcare services ranged from 9% to 90% of all healthcare interactions…."

PLoS ONE 2013

'First we go to the small doctor': First contact for curative health care sought by rural communities in Andhra Pradesh & Orissa, India

Meenakshi Gautham*, Erika Binnendijk*, Ruth Koren** & David. M. Dror*,†

A large number of people with TB are not seeking first-contact care in NTPs

India: TB patients often seek care from informal providers and chemists in the private sector

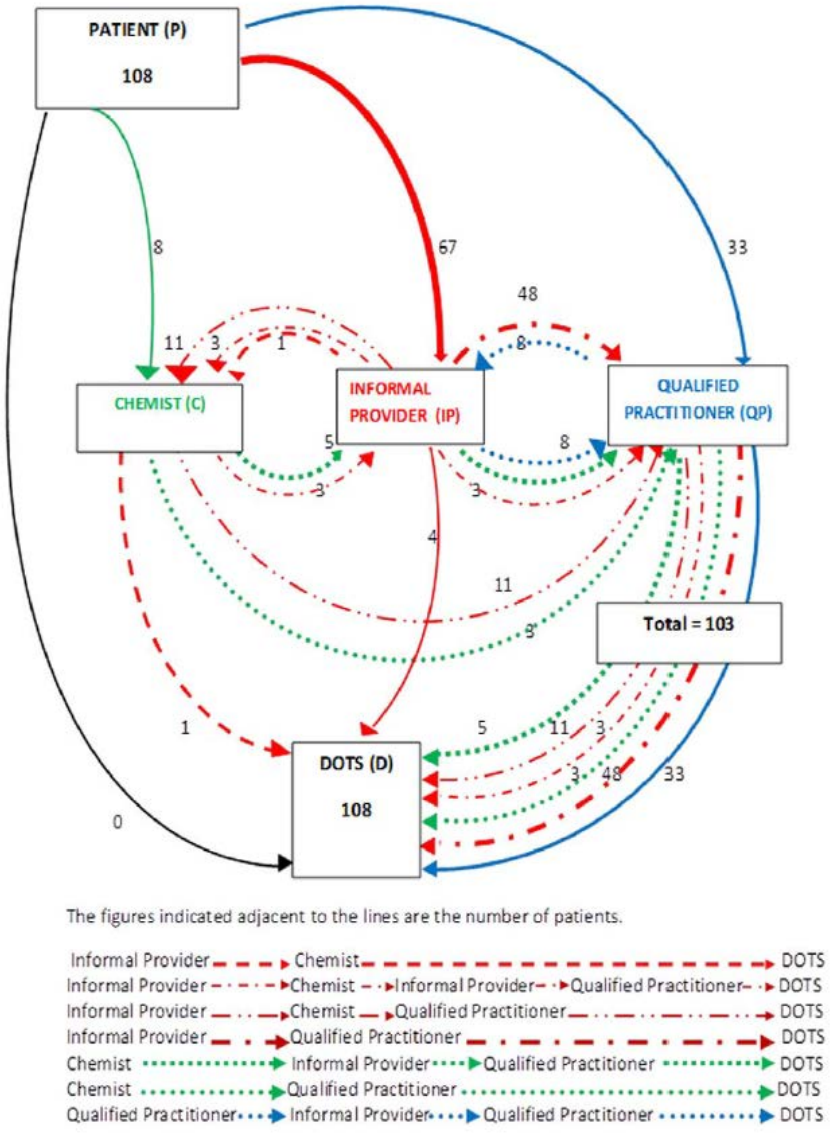

Figure 1. Pathways undertaken by the patients to reach the RNTCP (DOTS) Facilities, Delhi, India.
doi:10.1371/journal.pone.0042458.g001

Long, broken pathway to care

On average, 3 providers are seen before TB diagnosis and treatment

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How Did the TB Patients Reach DOTS Services in Delhi? A Study of Patient Treatment Seeking Behavior

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So, to diagnose TB early, we need a strategy to engage providers who see TB patients first

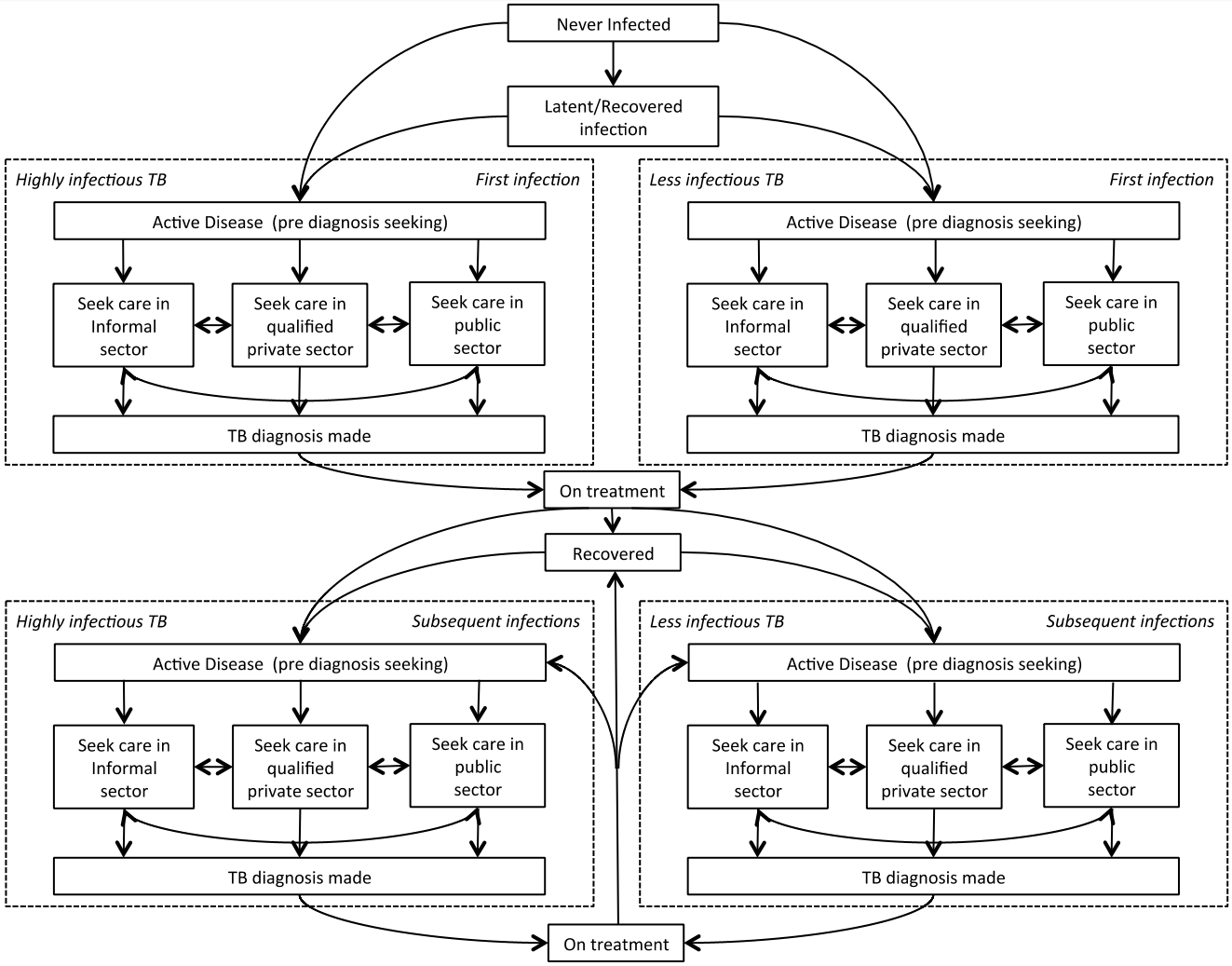
Does deployment strategy matter? Modeling the scale-up of novel tuberculosis diagnostics in the Indian healthcare system

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

We modeled the population-level impact and resource implications of scaling-up a molecular diagnostic test (Xpert MTB/RIF) in different healthcare sectors over five years.

Salje H et al. Under review [confidential]

Transmission model that accounts for private/informal sector, movement between the sectors, and diagnostic delays



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Key findings: it is not just the technology, but how it is deployed that matters

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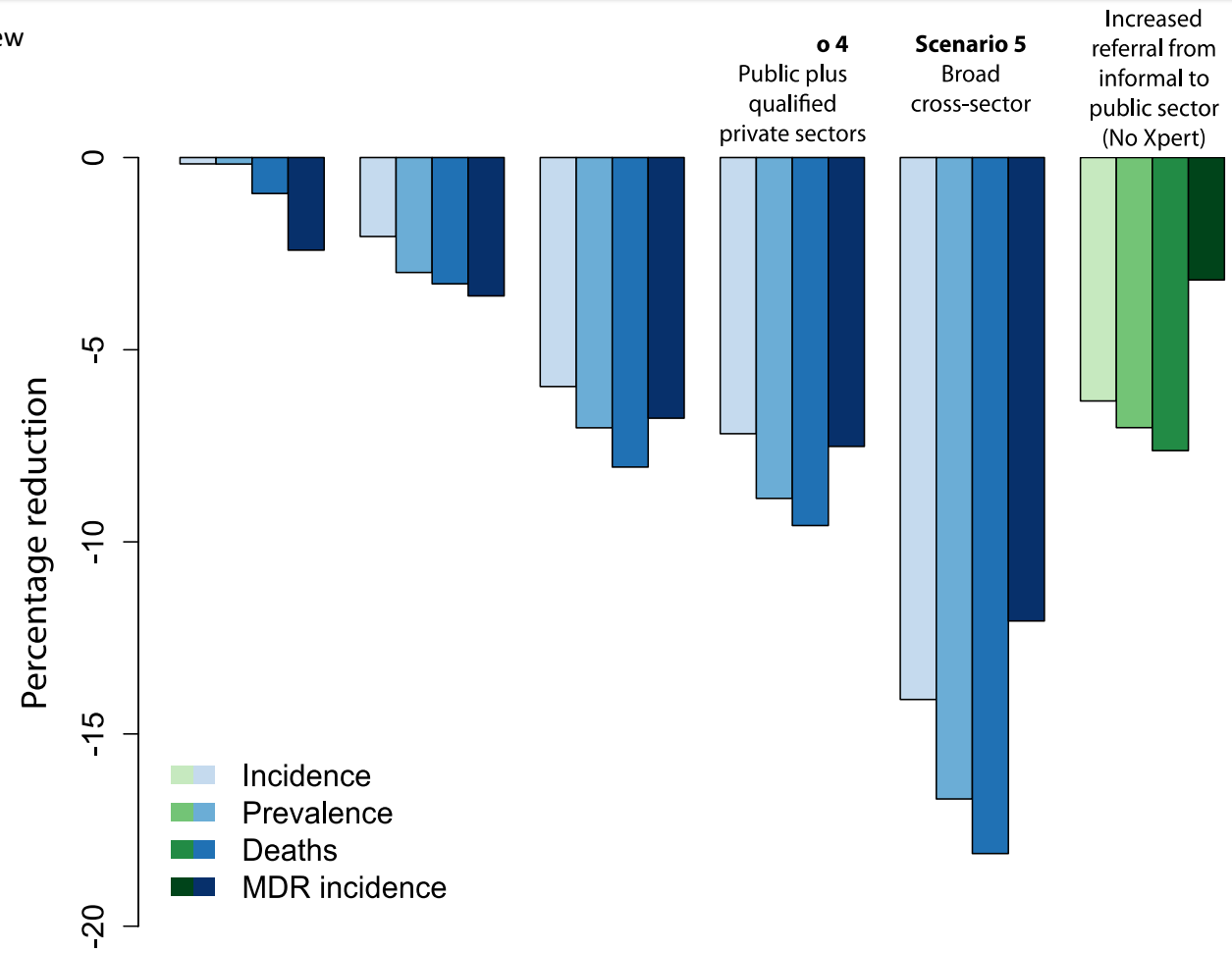

Transformative strategies require private/informal sector engagement, improved quality of care, and substantial resources.

Final thoughts…

- DOTS has saved lives, but has not reduced incidence as expected

- *Early diagnosis* will require two approaches:

  - New technologies, designed for decentralized settings

  - New delivery strategies
    - POCT programs to reduce health system delays
    - Large-scale engagement of informal, private and first-contact providers to reduce patient pathways to care

Both approaches are being pursued!

NAATs for microscopy centers

Innovative private-sector initiatives

Engaging the private sector to increase tuberculosis case detection: an impact evaluation study

Aamir J Khan, Saira Khowaja, Faisal S Khan, Fahad Qazi, Ismat Lotia, Ali Habib, Shama Mohammed, Uzma Khan, Farhana Amanullah, Hamidah Hussain, Mercedes C Becerra, Jacob Creswell, Salmaan Keshavjee

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See Comment page 579

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Summary

Background In many countries with a high burden of tuberculosis, most patients receive treatment in the private sector. We evaluated a multifaceted case-detection strategy in Karachi, Pakistan, targeting the private sector.

Methods A year-long communications campaign advised people with 2 weeks or more of productive cough to seek care at one of 54 private family medical clinics or a private hospital that was also a national tuberculosis programme (NTP) reporting centre. Community laypeople participated as screeners, using an interactive algorithm on mobile phones to assess patients and visitors in family-clinic waiting areas and the hospital's outpatient department. Screeners received cash incentives for case detection. Patients with suspected tuberculosis also came directly to the hospital's tuberculosis clinic (self-referrals) or were referred there (referrals). The primary outcome was the change (from 2010 to 2011) in tuberculosis notifications to the NTP in the intervention area compared with that in an adjacent control area.

Findings Screeners assessed 388 196 individuals at family clinics and 81 700 at Indus Hospital's outpatient department from January–December, 2011. A total of 2416 tuberculosis cases were detected and notified via the NTP reporting centre at Indus Hospital: 603 through family clinics, 273 through the outpatient department, 1020 from self-referrals, and 520 from referrals. In the intervention area overall, tuberculosis case notification to the NTP increased two times (from 1569 to 3140 cases) from 2010 to 2011—a 2·21 times increase (95% CI 1·93–2·53) relative to the change in number of case notifications in the control area. From 2010 to 2011, pulmonary tuberculosis notifications at Indus Hospital increased by 3·77 times for adults and 7·32 times for children.

Interpretation Novel approaches to tuberculosis case-finding involving the private sector and using laypeople, mobile phone software and incentives, and communication campaigns can substantially increase case notification in dense urban settings.

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- Henrik Salje

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