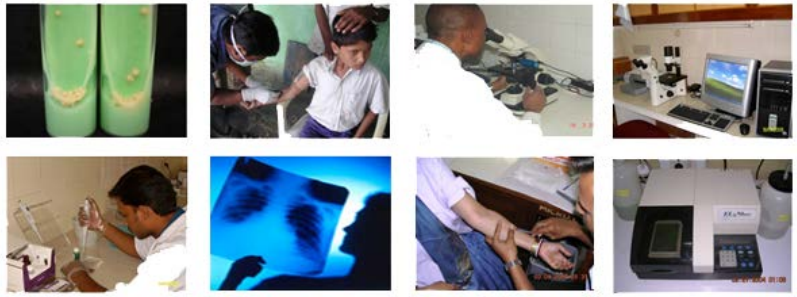
TB diagnostics: value chain, pipeline, and gaps



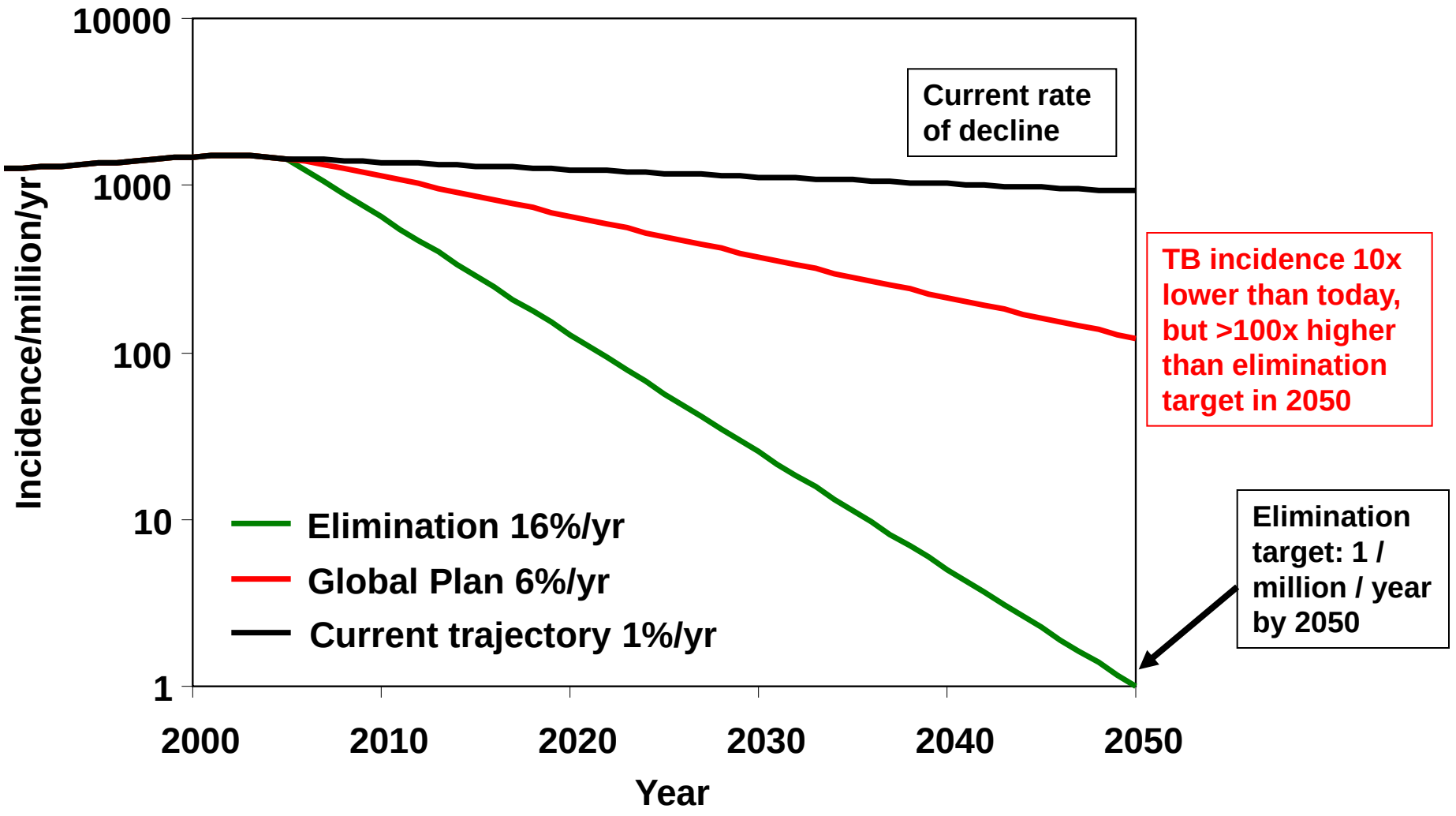
Madhukar Pai, MD, PhD

Associate Professor , McGill University, Montreal, Canada

madhukar.pai@mcgill.ca

McGill

Full implementation of Global Plan: 2015 MDG target reached but TB not eliminated by 2050



Courtesy: WHO Stop TB Department

Undiagnosed TB and mismanaged TB continues to the fuel the global TB epidemic

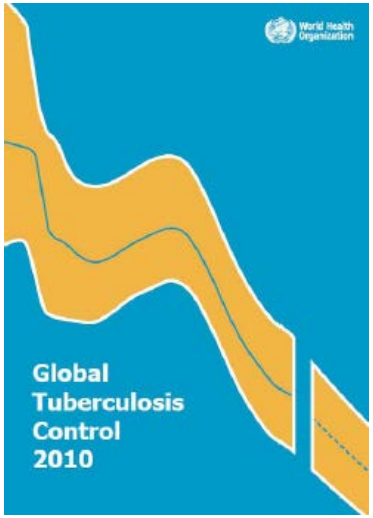
The Population Dynamics and Control of Tuberculosis

Christopher Dye[1*] and Brian G. Williams[2]

More than 36 million patients have been successfully treated via the World Health Organization's strategy for tuberculosis (TB) control since 1995. Despite predictions of a decline in global incidence, the number of new cases continues to grow, approaching 10 million in 2010. Here we review the changing relationship between the causative agent, *Mycobacterium tuberculosis*, and its human host and examine a range of factors that could explain the persistence of TB. Although there are ways to reduce susceptibility to infection and disease, and a high-efficacy vaccine would boost TB prevention, early diagnosis and drug treatment to interrupt transmission remain the top priorities for control. Whatever the technology used, success depends critically on the social, institutional, and epidemiological context in which it is applied.

"We conclude that control programs have been less effective than expected in cutting transmission mainly because patients are not diagnosed and cured quickly enough."
Dye & Williams, *Science* 2010

TB case detection continues to be poor, and diagnostic delays are common



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]

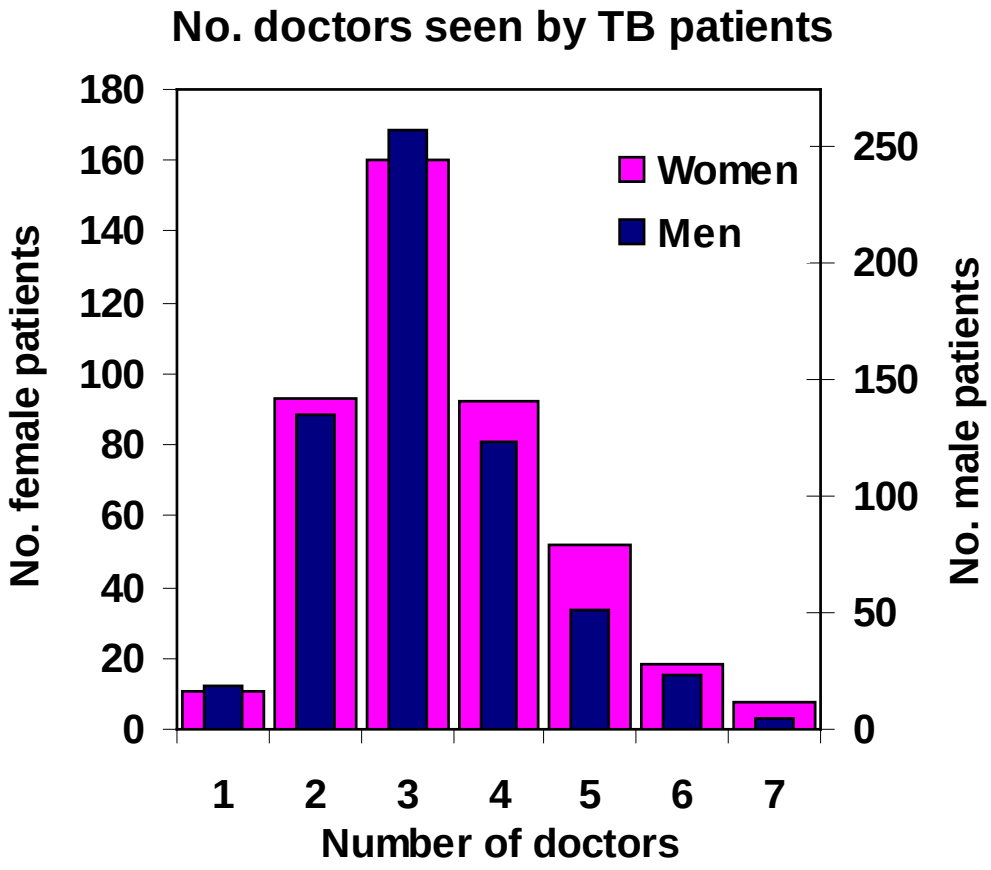
Address: [1]Department of International Health, Institute of General Practice and Community Medicine, University of Oslo, PO Box 1130 Blindern, N-0318 Oslo, Norway and [2]Competence Centre for Imported and Tropical Diseases, Ullevål University Hospital, Oslo, Norway

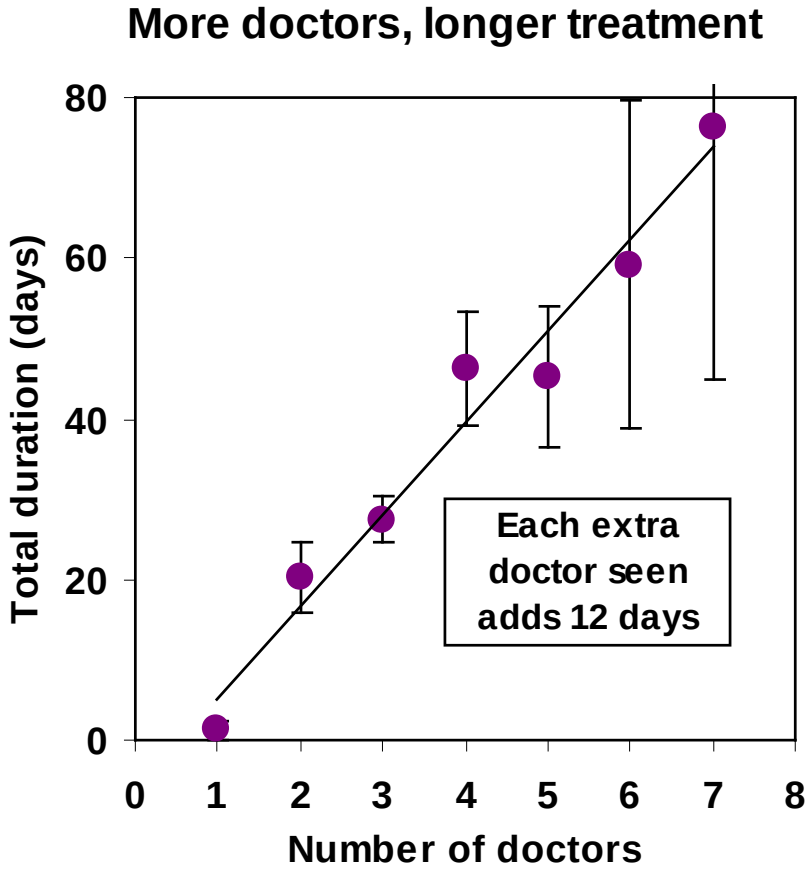
Only 63% of all forms of TB are notified

Average delays are as long as 2 – 3 months!

Doctors and delays, Bangalore

–Slide by Chris Dye

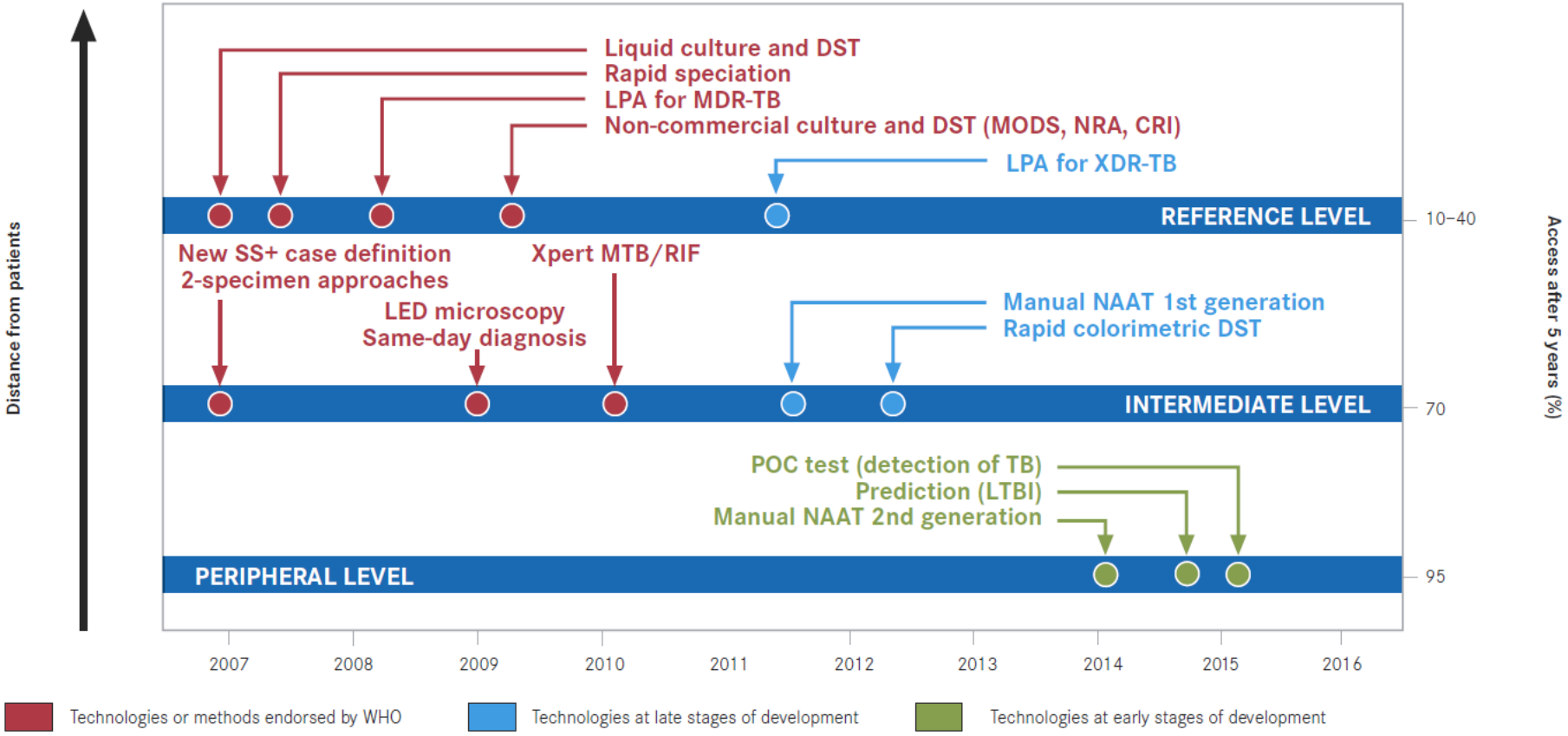




Pantoja 2009

TB diagnostics pipeline in 2011

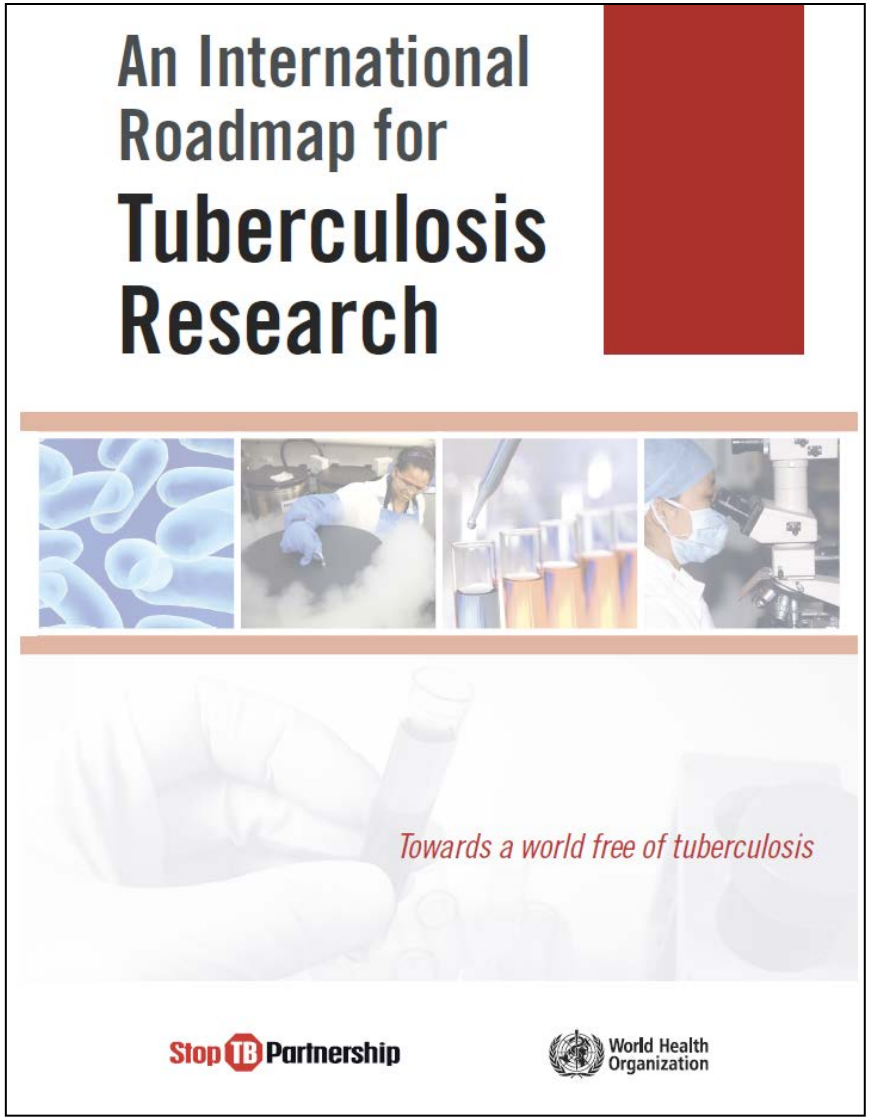
The development pipeline for new diagnostics, 2011



Abbreviations: **DST** Drug susceptibility test; **NAAT** Nucleic acid amplification test; **LTBI** Latent TB infection; **POC** Point of care; **MODS** Microscopic observation drug-susceptibility; **NRA** Nitrate reductase assay; **CRI** Colorimetric redox indicator assay; **LED** Light-emitting diode; **LPA** Line probe assay

Courtesy: WHO 2011

Gaps in the pipeline and unmet needs



Gaps in the pipeline and unmet needs

Key messages

- The highest-priority topics are:

  (i) identification of bacterial and/or host molecules that differentiate people at different stages of the disease spectrum (including predictive markers of progression from latent tuberculosis infection to active TB), and

  (ii) simplification and validation of novel tools for diagnosis at the point of care.

- A high priority is studying how to combine existing and new diagnostics to optimize the detection of various forms of TB (including drug-sensitive, drug-resistant and latent TB infection) in various population settings and at all health-care levels.

- Of great importance are definition and evaluation of the performance of new diagnostic tests in terms of feasibility, cost-effectiveness, reduced diagnostic delay and impact on clinical decision-making and patient benefit.

- Particular reference is made to the need to identify combinations of methods for collecting useful specimens from children.

- Another high priority is development of a systemic marker of bacterial load in TB with various samples and methods.

- The automated nucleic acid amplification test is potentially revolutionary for TB control, but it must be decentralized to points of treatment, and its use would have to be scaled up rapidly in order to achieve an impact at population level, particularly in resource-limited settings.

Value chain or pathways for TB dx
e.g. Optimized smears

INT J TUBERC LUNG DIS 15(10):1283–1293

http://dx.doi.org/10.5588/ijtld.11.0297

STATE OF THE ART

STATE OF THE ART SERIES
Operational Research, *Edited by* Donald A. Enarson
NUMBER 10 IN THE SERIES

Translating tuberculosis research into global policies: the example of an international collaboration on diagnostics

A. Ramsay,* K. R. Steingart,† J. Cunningham,* M. Pai‡

Table 3 Timeline of key events

Date	Event
2004–2005	TDR and Diagnostics SAC assess TB diagnostics policy and practice; sputum smear microscopy identified as a neglected research area
May 2005	TDR commissions systematic reviews on smear microscopy
September 2005	TDR, FIND and STB convene an Expert Consultation Meeting in Geneva to consider the policy and research implications of the SRs; prioritised research agenda agreed
From late 2005	Informal collaborations begin work on optimised smear microscopy informed by the Expert Consultation Meeting
Late 2005	USAID and BMGF agree to the use of funds for the prioritised research
Late 2005	Improved microscopy included in the diagnostics research agenda of the Global Plan to Stop TB 2006–2015
2006	RTF created by Stop TB Partnership
August 2006	TDR calls for applications to provide study sites for optimised smear microscopy research commissioned by TDR
Late 2006/early 2007	Short-listed study sites visited prior to final selection
March 2007	TDR convenes a series of research planning meetings in Geneva with potential investigators and international advisors
June 2007	STAG-TB approves new definition of a positive smear and a smear-positive case, reduces number of specimens from 3 to 2
June 2007	RTF recognises that the lack of a defined WHO policy-making process is an obstacle to adoption of new tools by NTPs
November 2007	Retooling Forum at Union Conference in Cape Town calls upon the RTF to work with WHO STB on defining a process for translating evidence into policy
2007	TDR issues research contracts around pragmatic RCT and linked-in operational research
Jan 2008	Multicountry pragmatic RCT begins
March 2008	FIND convenes international research meeting in Geneva on LED-FM
Mid-2008	WHO STB publishes its policy-making process on its website
Jan 2009	Last patients recruited to multicountry pragmatic RCT
May 2009	STB commissions SRs on optimised microscopy approaches
Sept 2009	TDR and STB convene Expert Group Meeting on optimised smear microscopy; recommendations made to STAG-TB
October 2009	STAG-TB approves front-loaded (or 'same-day') microscopy and LED-FM
June 2010	WHO Policy Statements on same-day microscopy and LED-FM issued

TDR = Special Programme for Research and Training in Tropical Diseases; SAC = Scientific Advisory Committee; TB = tuberculosis; FIND = Foundation for Innovative New Diagnostics; STB = Stop TB; SR = systematic review; USAID = United States Agency for International Development; BMGF = Bill & Melinda Gates Foundation; RTF = Retooling Task Force; STAG-TB = Strategic and Technical Advisory Group for Tuberculosis; WHO = World Health Organization; NTP = National TB Programme; RCT = randomised controlled trial; LED-FM = light emitting diode-fluorescence microscopy.

Value chain
e.g. Xpert MTB/RIF


The NEW ENGLAND JOURNAL of MEDICINE

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study

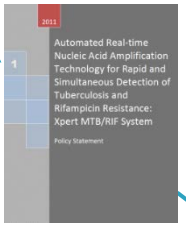
WHO Expert Group meeting on Xpert Sept 1 & 2, 2010

World Health Organization

Implementation and scale-up of the Xpert MTB/RIF system for rapid diagnosis of tuberculosis and multidrug-resistance

GLOBAL CONSULTATION

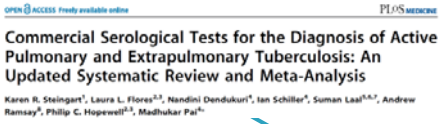
Date and time: 30 November - 2 December 2010
Venue: Centre International de Conférences de Genève (CICG)
17, Rue de Varembé, Geneva, Switzerland



Scale-up at the country level & impact

Value chain
e.g. Serological TB tests

Advocacy and evidence

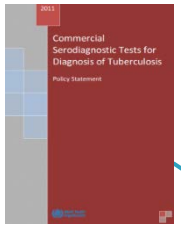


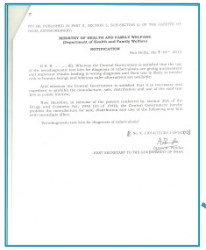
Commercial Serological Tests for the Diagnosis of Active Pulmonary and Extrapulmonary Tuberculosis: An Updated Systematic Review and Meta-Analysis

Serological Testing Versus Other Strategies for Diagnosis of Active Tuberculosis in India: A Cost-Effectiveness Analysis

David W. Dowdy[1], Karen R. Steingart[2], Madhukar Pai[3]*

WHO Expert Group meeting in 2010





Ban and scale-down at the country level & replacement of serology with WHO-approved tools

Scale-up of new tools

- Although many tools have been WHO endorsed, scale-up has been slow
- Global value chain was envisioned in a linear way
  - Too many versions of value chain with no clear consensus on each step
  - Evidence needed at each stage is not quite clear
    - Even terms like “demonstration studies” and “impact” are confusing and inconsistent
  - WHO policy process using GRADE has limitations
    - GRADE itself has limitations, and TB diagnostics literature has serious limitations
- Unclear pathways for adoption and scale-up at the country level
  - What evidence is needed for scale-up? Currently, is that part of the WHO policy process?
  - How do countries make judgements? What do policy makers need?
  - If a tool is scaled up, how do we measure “impact”?

IJTLD – State of the Art series on new tools

New TB technologies: challenges for retooling and scale-up

Madhukar Pai, MD, PhD[1]

Kara M. Palamountain, MBA[2]

Several barriers to national adoption and scale-up of new technologies:

- global policies that do not provide sufficient information for scale-up
- complex decision-making processes and weak political commitment at country-level
- limited engagement of and support to NTP managers
- high cost of tools and poor fit with user needs
- unregulated markets and inadequate business models
- limited capacity for laboratory strengthening and implementation research
- insufficient advocacy and donor support.

Pai et al. IJTLD 2012 (in press)

Variations in diagnostics value chain/pathways

Phased evaluation of medical tests

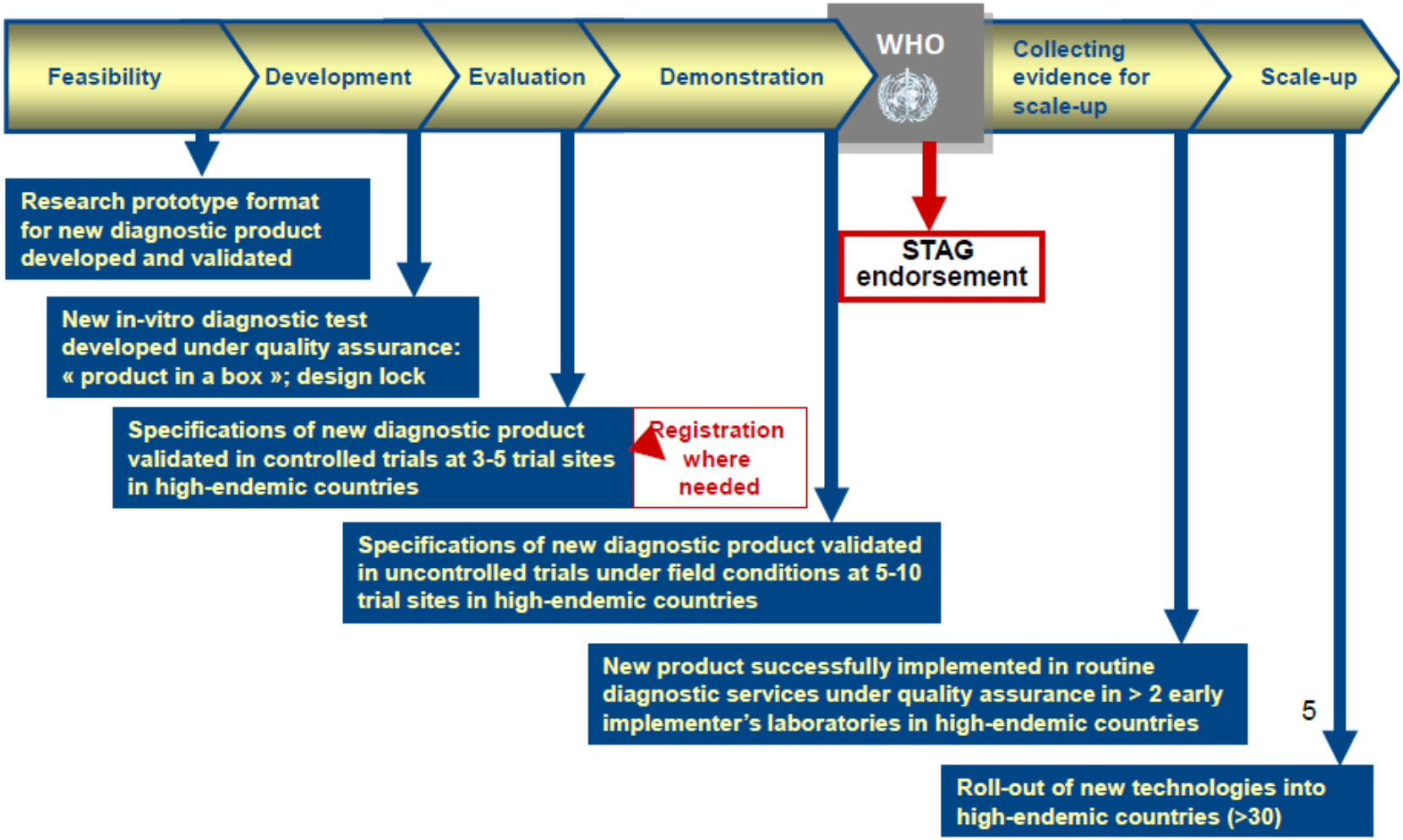
Levels/Phases
Technical efficacy
Intended use
Diagnostic accuracy
Usual range
Subgroups
Clinical population
Diagnostic thinking efficacy
Therapeutic efficacy
Patient outcome efficacy
Societal efficacy

Proposals for a Phased Evaluation of Medical Tests

Jeroen G. Lijmer, MD, PhD, Mariska Leeflang, PhD, Patrick M. M. Bossuyt, PhD

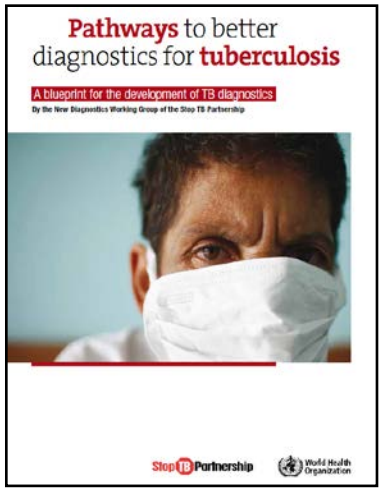
Med Desic Making 2009

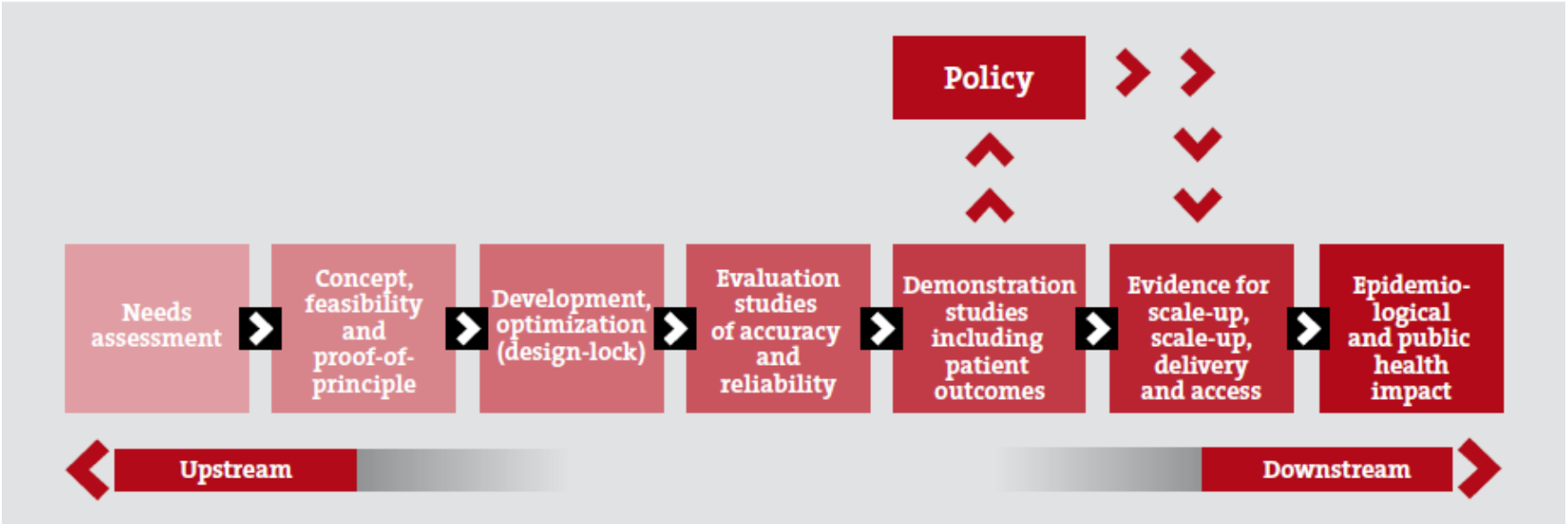
WHO process (newly revised)



Source: Dr Karin Weyer, WHO

NDWG blueprint (original)





STP NDWG 2009

Challenges in converting evidence into policy

Challenges for translating evidence into policy

Table 5 Challenges and limitations in formulating tuberculosis diagnostic policies

Challenge or limitation	Description and examples
Limitations of the existing evidence base	Majority of TB diagnostic studies are focused on test accuracy (sensitivity and specificity); therefore, systematic reviews are also focused on accuracy
	Test accuracy studies are often poorly designed, executed, and reported.
	Impact of tests on patient-important outcomes is rarely available.
	Accuracy studies are downgraded by GRADE for 'directness' and can never receive a rating of 'high-quality' evidence.
	Ease of implementation, resources required, cost-effectiveness, biosafety, and programmatic issues are critical for policy, but systematic reviews may not provide such data.
Evidence vs. expert opinion	Existing evidence does not meet the needs of policy makers.
	Outcomes that experts want and GRADE requires are often not available.
	In such situations, expert opinion tends to dominate and experts do not always agree; expert opinions are often based on their own unique experiences and anecdotes, which may not necessarily be generalizable or valid.
Difficulties in learning and using the GRADE system	Systematic reviewers, policy makers, and TB experts are not necessarily trained in GRADE.
	Grading may be done inconsistently across tests by different systematic reviewers; same evidence can be interpreted and rated differently; GRADE ratings may be revised *posthoc*, depending on which tests the experts want to recommend.
	Some tests are actively 'championed', whereas others are not and this can result in uneven decisions
Conflicts of interest and involvement of test developers	Participation of test developers and industry representatives in the policy process introduces conflicts of interest.
	There is no consensus on whether test developers and those invested in specific technologies be allowed to do systematic reviews and participate in guideline panel meetings.
	There can be tension between commercial and noncommercial tests; type and quality of evidence might differ for commercial vs. noncommercial tests, and commercial products might be more actively championed by those with industry involvement.
Patient-important outcomes	Patient outcomes may not reflect the accuracy or benefit of a diagnostic test/approach in settings with weak overall health infrastructure (e.g. rapid or improved microscopy in facilities where stock-outs of anti-TB drugs occur frequently).
	The possible tension (for TB diagnosis and control) between the importance of individual patient outcomes and public health outcomes (e.g. the notion that false-negative sputum smear results may pose a greater public health risk than false-positive results).
	For tests used at the central/reference laboratory level, patient-outcome data may not be a good index of a test's impact; the test's impact is confounded by several other factors such as specimen transport, time to get results back to the clinicians, weak healthcare systems, etc.
	Impact on patient outcomes is affected not just by the test, but the whole package, including treatment, healthcare system efficiency, etc. It can be difficult to separate out the test's impact, and hard/expensive to study the whole package or strategy (which can be time-consuming and expensive).
	Diagnostic RCTs are rarely available and very hard to do (ethics, cost, etc.)
	In addition to patient values and preferences, need to acknowledge preferences and values of laboratory technologists and test users.
	If RCTs and patient-important outcomes are required for noncommercial tests, this will be severely limited by access to funds required to perform these large-scale evaluations.
Systematic review methods	No standardized methodology to search for and objectively synthesize evidence on operational implementation issues, costs to health services, costs to patients, and patient perspectives on new diagnostic tests and approaches.
	Narrative evidence on the above issues may be excluded from search strategies during systematic reviews of studies on diagnostic accuracy.
	Results from qualitative and socio-economic studies may not have been captured in the systematic reviews on diagnostic accuracy of the different approaches.
	Systematic reviews can make an effort to look for, include, and describe outcomes other than sensitivity and specificity, but often do not because they choose to focus instead on easily meta-analyzable outcomes.
	Policy makers should have a thorough understanding of all the important outcomes (including outcomes that are important to patients) they hope to include in their policy deliberations before commissioning systematic reviews. By explicitly outlining the test characteristics that will influence their decisions in advance, guideline panels can ensure evidence is as complete and objective as possible. This approach will minimize evidence gaps, making the process less susceptible to expert opinion. Weighting the importance of test characteristics in advance can also help to avoid redefining and reinterpreting evidence *posthoc* to suit individual desires to recommend or not recommend.

GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; TB, tuberculosis.

Pai, Minion, Steingart & Ramsay. Curr Op Pulm Med 2010

RATING QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

GRADE: grading quality of evidence and strength of recommendations for diagnostic tests and strategies

The GRADE system can be used to grade the quality of evidence and strength of recommendations for diagnostic tests or strategies. This article explains how patient-important outcomes are taken into account in this process

SUMMARY POINTS

As for other interventions, the GRADE approach to grading the quality of evidence and strength of recommendations for diagnostic tests or strategies provides a comprehensive and transparent approach for developing recommendations

Cross sectional or cohort studies can provide high quality evidence of test accuracy

However, test accuracy is a surrogate for patient-important outcomes, so such studies often provide low quality evidence for recommendations about diagnostic tests, even when the studies do not have serious limitations

Inferring from data on accuracy that a diagnostic test or strategy improves patient-important outcomes will require the availability of effective treatment, reduction of test related adverse effects or anxiety, or improvement of patients' wellbeing from prognostic information

Judgments are thus needed to assess the directness of test results in relation to consequences of diagnostic recommendations that are important to patients

Mapping The Landscape Of Tuberculosis Diagnostic Research

L. Brunet[1], J. Minion[2], C. Lienhardt[3], M. Pai[1]

[1]McGill University, Montreal, Canada, [2]Montreal Chest Institute, McGill University Health Centre, Montreal, Canada, [3]World Health Organization, Geneva, Switzerland

AJRCCM 2010

- About 15% of all TB papers are mainly focused on TB diagnosis.
- Of these, about 85% are evaluation studies of tests and markers.
- Of these evaluation studies, about 85% are early phase studies of test accuracy; there are very little data on impact on patient outcomes.

Even accuracy studies are not well conducted and reported...

OPEN ACCESS Freely available online

PLoS one

Quality and Reporting of Diagnostic Accuracy Studies in TB, HIV and Malaria: Evaluation Using QUADAS and STARD Standards

Patricia Scolari Fontela[1], Nitika Pant Pai[2], Ian Schiller[2], Nandini Dendukuri[2], Andrew Ramsay[3], Madhukar Pai[1,4]*

1 Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada, **2** Department of Medicine, Division of Clinical Epidemiology, McGill University, Montreal, Canada, **3** Special Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland, **4** Respiratory Epidemiology and Clinical Research Unit, Montreal Chest Institute, Montreal, Canada

Abstract

Background: Poor methodological quality and reporting are known concerns with diagnostic accuracy studies. In 2003, the QUADAS tool and the STARD standards were published for evaluating the quality and improving the reporting of diagnostic studies, respectively. However, it is unclear whether these tools have been applied to diagnostic studies of infectious diseases. We performed a systematic review on the methodological and reporting quality of diagnostic studies in TB, malaria and HIV.

Methods: We identified diagnostic accuracy studies of commercial tests for TB, malaria and HIV through a systematic search of the literature using PubMed and EMBASE (2004–2006). Original studies that reported sensitivity and specificity data were included. Two reviewers independently extracted data on study characteristics and diagnostic accuracy, and used QUADAS and STARD to evaluate the quality of methods and reporting, respectively.

Findings: Ninety (38%) of 238 articles met inclusion criteria. All studies had design deficiencies. Study quality indicators that were met in less than 25% of the studies included adequate description of withdrawals (6%) and reference test execution (10%), absence of index test review bias (19%) and reference test review bias (24%), and report of uninterpretable results (22%). In terms of quality of reporting, 9 STARD indicators were reported in less than 25% of the studies: methods for calculation and estimates of reproducibility (0%), adverse effects of the diagnostic tests (1%), estimates of diagnostic accuracy between subgroups (10%), distribution of severity of disease/other diagnoses (11%), number of eligible patients who did not participate in the study (14%), blinding of the test readers (16%), and description of the team executing the test and management of indeterminate/outlier results (both 17%). The use of STARD was not explicitly mentioned in any study. Only 22% of 46 journals that published the studies included in this review required authors to use STARD.

Conclusion: Recently published diagnostic accuracy studies on commercial tests for TB, malaria and HIV have moderate to low quality and are poorly reported. The more frequent use of tools such as QUADAS and STARD may be necessary to improve the methodological and reporting quality of future diagnostic accuracy studies in infectious diseases.

PLoS One 2009

In TB, since we have mostly low-quality accuracy studies:

example of GRADE profile from WHO EGM on tests for drug-resistant TB

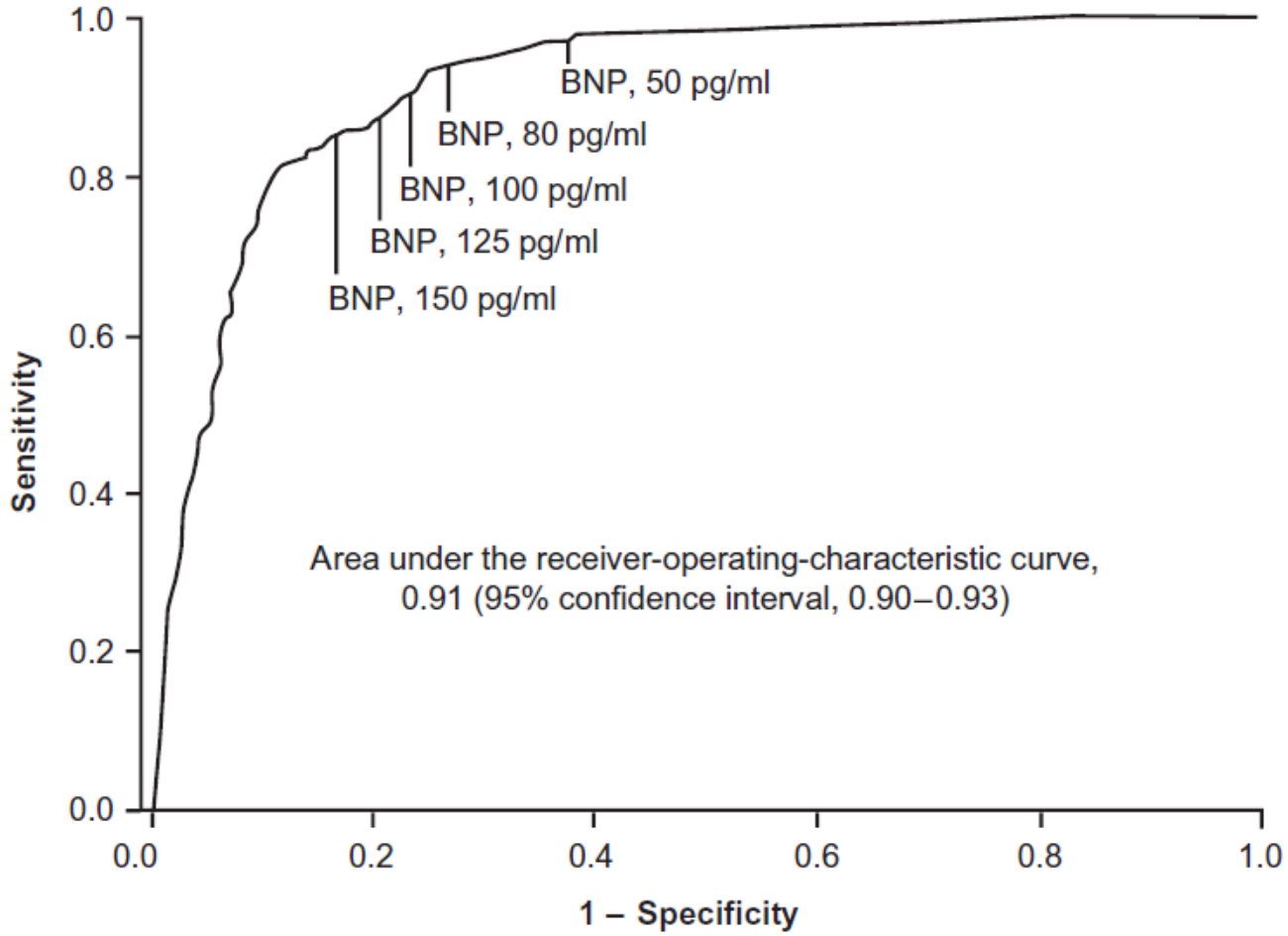
Test, # Studies (participants)	Design	Limitations	Directness	Inconsistency	Imprecise or sparse data	Publication Bias	Evidence Quality
MODS, 9 (1474)	CS & CC	Low	No evidence **-1**	Low	Low	Possible	Moderate
NRA, 19 (2304)	CS & CC	Low	No evidence **-1**	Low	Low	Possible	Moderate
CRI, 31 (2498)	CS & CC	Low	No evidence **-1**	Low	Low	Possible	Moderate
TLA, 3 (439)	CS & CC	Low	No evidence **-1**	Low	High -1	Possible	Low
Phage, 12 (2935)	CS & CC	Moderate/High -1	No evidence **-1**	Moderate/High -1	Low	Probable	Very low
LPA, 12 (4937)	CS & CC	Low	No evidence **-1**	Low	Low	Possible	Moderate

- Regardless of study quality, precision, consistency … accuracy studies will never lead to High Quality Evidence

Clinical impact of test results on diagnostic and treatment decisions, and eventually, patient outcomes

"Improved accuracy is not always a necessary prerequisite for improving patient health, nor does it guarantee other downstream improvements"
[di Ruffano et al. *BMJ* 2012;344:e686]

Accuracy vs Impact:
Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure



Maisel et al, *N Engl J Med*. 2002 Jul 18;**347**(3):

Annals of Internal Medicine | ARTICLE

B-Type Natriuretic Peptide Testing, Clinical Outcomes, and Health Services Use in Emergency Department Patients With Dyspnea

A Randomized Trial

Hans-Gerhard Schneider, MBBS, MD; Louisa Lam, MPH; Amaali Lokuge, MBBS; Henry Krum, MBBS, PhD; Matthew T. Naughton, MBBS; Pieter De Villiers Smit, MBBS; Adam Bystrzycki, MBBS; David Eccleston, MBBS, PhD; Jacob Federman, MBBS; Genevieve Flannery, MBBS; and Peter Cameron, MBBS, MD

Background: B-type natriuretic peptide (BNP) is used to diagnose heart failure, but the effects of using the test on all dyspneic patients is uncertain.

Objective: To assess whether BNP testing alters clinical outcomes and health services use of acutely dyspneic patients.

Design: Randomized, single-blind study. Patients were assigned to a treatment group through randomized numbers in a sealed envelope. Patients were blinded to the intervention, but clinicians and those who assessed trial outcomes were not.

Setting: 2 Australian teaching hospital emergency departments.

Patients: 612 consecutive patients who presented with acute severe dyspnea from August 2005 to March 2007.

Intervention: BNP testing ($n = 306$) or no testing ($n = 306$).

Measurements: Admission rates, length of stay, and emergency department medications (primary outcomes); mortality and readmission rates (secondary outcomes).

Results: There were no between-group differences in hospital admission rates (85.6% [BNP group] vs. 86.6% [control group]; difference, −1.0 percentage point [95% CI, −6.5 to 4.5 percentage points]; $P = 0.73$), length of admission (median, 4.4 days [interquartile range, 2 to 9 days] vs. 5.0 days [interquartile range, 2 to 9 days]; $P = 0.94$), or management of patients in the emergency department. Test discrimination was good (area under the receiver-operating characteristic curve, 0.87 [CI, 0.83 to 0.91]). Adverse events were not measured.

Limitation: Most patients were very short of breath and required hospitalization; the findings might not apply for evaluating patients with milder degrees of breathlessness.

Conclusion: Measurement of BNP in all emergency department patients with severe shortness of breath had no apparent effects on clinical outcomes or use of health services. The findings do not support routine use of BNP testing in all severely dyspneic patients in the emergency department.

Primary Funding Source: Janssen-Cilag.

Ann Intern Med. 2009;150:365-371. www.annals.org
For author affiliations, see end of text.
ClinicalTrials.gov registration number: NCT00163709.

Example: malaria RDTs

Accuracy

Nkrumah *et al. BMC Infectious Diseases* 2011, **11**:143
http://www.biomedcentral.com/1471-2334/11/143

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Comparative evaluation of two rapid field tests for malaria diagnosis: Partec Rapid Malaria Test® and Binax Now® Malaria Rapid Diagnostic Test

Bernard Nkrumah[1*], Samuel EK Acquah[1], Lukeman Ibrahim[1], Juergen May[2], Norbert Brattig[2], Egbert Tannich[2], Samuel Blay Nguah[3], Yaw Adu-Sarkodie[4] and Frank Huenger[1,5]

Abstract

Background: About 90% of all malaria deaths in sub-Saharan Africa occur in children under five years. Fast and reliable diagnosis of malaria requires confirmation of the presence of malaria parasites in the blood of patients with fever or history suggestive of malaria; hence a prompt and accurate diagnosis of malaria is the key to effective disease management. Confirmation of malaria infection requires the availability of a rapid, sensitive, and specific testing at an affordable cost. We compared two recent methods (the novel Partec Rapid Malaria Test® (PT) and the Binax Now® Malaria Rapid Diagnostic Test (BN RDT) with the conventional Giemsa stain microscopy (GM) for the diagnosis of malaria among children in a clinical laboratory of a hospital in a rural endemic area of Ghana.

Methods: Blood samples were collected from 263 children admitted with fever or a history of fever to the pediatric clinic of the Agogo Presbyterian Hospital. The three different test methods PT, BN RDT and GM were performed independently by well trained and competent laboratory staff to assess the presence of malaria parasites. Results were analyzed and compared using GM as the reference standard.

Results: In 107 (40.7%) of 263 study participants, *Plasmodium sp.* was detected by GM. PT and BN RDT showed positive results in 111 (42.2%) and 114 (43.4%), respectively. Compared to GM reference standard, the sensitivities of the PT and BN RDT were 100% (95% CI: 96.6-100) and 97.2% (95% CI: 92.0-99.4), respectively, specificities were 97.4% (95% CI: 93.6-99.3) and 93.6% (95% CI: 88.5-96.9), respectively. There was a strong agreement (kappa) between the applied test methods (GM vs PT: 0.97; $p < 0.001$ and GM vs BN RDT: 0.90; $p < 0.001$). The average turnaround time per tests was 17 minutes.

Conclusion: In this study two rapid malaria tests, PT and BN RDT, demonstrated a good quality of their performance compared to conventional GM. Both methods require little training, have short turnaround times, are applicable as well as affordable and can therefore be considered as alternative diagnostic tools in malaria endemic areas. The species of *Plasmodium* cannot be identified.

Example: malaria RDTs

Clinical impact

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Influence of Rapid Malaria Diagnostic Tests on Treatment and Health Outcome in Fever Patients, Zanzibar—A Crossover Validation Study

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Abstract

Background: The use of rapid diagnostic tests (RDTs) for *Plasmodium falciparum* malaria is being suggested to improve diagnostic efficiency in peripheral health care settings in Africa. Such improved diagnostics are critical to minimize overuse and thereby delay development of resistance to artemisinin-based combination therapies (ACTs). Our objective was to study the influence of RDT-aided malaria diagnosis on drug prescriptions, health outcomes, and costs in primary health care settings.

Methods and Findings: We conducted a cross-over validation clinical trial in four primary health care units in Zanzibar. Patients of all ages with reported fever in the previous 48 hours were eligible and allocated alternate weeks to RDT-aided malaria diagnosis or symptom-based clinical diagnosis (CD) alone. Follow-up was 14 days. ACT was to be prescribed to patients diagnosed with malaria in both groups. Statistical analyses with multilevel modelling were performed. A total of 1,887 patients were enrolled February through August 2005. RDT was associated with lower prescription rates of antimalarial treatment than CD alone, 361/1005 (36%) compared with 752/882 (85%) (odds ratio [OR] 0.04, 95% confidence interval [CI] 0.03–0.05, $p<0.001$). Prescriptions of antibiotics were higher after RDT than CD alone, i.e., 372/1005 (37%) and 235/882 (27%) (OR 1.8, 95%CI 1.5–2.2, $p<0.001$), respectively. Reattendance due to perceived unsuccessful clinical cure was lower after RDT 25/1005 (2.5%), than CD alone 43/882 (4.9%) (OR 0.5, 95% CI 0.3–0.9, $p=0.005$). Total average cost per patient was similar: USD 2.47 and 2.37 after RDT and CD alone, respectively.

Conclusions: RDTs resulted in improved adequate treatment and health outcomes without increased cost per patient. RDTs may represent a tool for improved management of patients with fever in peripheral health care settings.

Trial Registration: Clinicaltrials.gov NCT00549003

Please see later in the article for the Editors' Summary.

Citation: Msellem MI, Mårtensson A, Rotllant G, Bhattarai A, Strömberg J, et al. (2009) Influence of Rapid Malaria Diagnostic Tests on Treatment and Health Outcome in Fever Patients, Zanzibar—A Crossover Validation Study. PLoS Med 6(4): e1000070. doi:10.1371/journal.pmed.1000070

Example: RIDTs for influenza

Accuracy

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PLoS one

Diagnostic Accuracy of a Rapid Influenza Test for Pandemic Influenza A H1N1

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Abstract

Background: With the current influenza A H1N1 pandemic (H1N1pdm), it is extremely important that clinicians can quickly and accurately identify influenza cases.

Methodology/Principal Findings: To investigate the performance of the QuickVue Influenza A+B rapid test, we conducted a prospective study of the diagnostic accuracy of the QuickVue Influenza A+B test compared to real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for influenza A H1N1pdm in Nicaraguan children aged 2 to 14 years. Rapid test sensitivity and specificity compared to real-time RT-PCR were 64.1% (95% CI 53.5, 73.9) and 98.3% (95.0, 99.6), respectively. Agreement between the two tests was 86.4% (95% CI 81.7, 90.3), and kappa was calculated to be 0.67 (95% CI 0.56, 0.76). Performance of the rapid test varied by day of presentation, with a sensitivity of 41.7% (95% CI 22.1, 63.4) for samples from children presenting on the day of symptom onset and a sensitivity of 72.1% (95% CI 59.9, 82.3) for samples from children presenting one or more days post-symptom onset.

Conclusions/Significance: We found that the rapid test performed with moderate sensitivity and high specificity. Test performance varied by day of onset, with lower sensitivity on the day of symptom onset.

Citation: Gordon A, Videa E, Saborío S, López R, Kuan G, et al. (2010) Diagnostic Accuracy of a Rapid Influenza Test for Pandemic Influenza A H1N1. PLoS ONE 5(4): e10364. doi:10.1371/journal.pone.0010364

Rapid tests for influenza: Clinical impact

Impact of the Rapid Diagnosis of Influenza on Physician Decision-Making and Patient Management in the Pediatric Emergency Department: Results of a Randomized, Prospective, Controlled Trial

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ABSTRACT. *Objective.* To determine the impact of the rapid diagnosis of influenza on physician decision-making and patient management, including laboratory tests and radiographs ordered, patient charges associated with these tests, antibiotics/antivirals prescribed, and length of time to patient discharge from the emergency department.

Methods. Patients aged 2 months to 21 years presenting to an urban children's teaching hospital emergency department were screened for fever and cough, coryza, myalgias, headache, and/or malaise. After obtaining informed consent, patients were randomized to 1 of 2 groups: 1) physician receives (physician aware of) the rapid influenza test result; or 2) physician does not receive (physician unaware of) the result. For patients in the physician aware group, nasopharyngeal swabs were obtained, immediately tested with the FluOIA test for influenza A and B, and the result was placed on the chart before patient evaluation by the attending physician. For the physician unaware group, nasopharyngeal swabs were obtained, stored according to manufacturer's directions, and tested within 24 hours. Results for the physician unaware group were not disclosed to the treating physicians at any time. The 2 resultant influenza-positive groups (aware and unaware) were compared for laboratory and radiograph studies and their associated patient charges, antibiotic/antiviral prescriptions, and length of stay in the emergency department.

Results. A total of 418 patients were enrolled, and 391 completed the study. Of these, 202 tested positive for influenza. Comparison of the 96 influenza-positive patients whose physician was aware of the result with the 106 influenza-positive patients whose physician was unaware of the result revealed significant reductions among the former group in: 1) numbers of complete blood counts, blood cultures, urinalyses, urine cultures, and chest radiographs performed; 2) charges associated with these tests; 3) antibiotics prescribed; and 4) length of stay in the emergency department. The number of influenza-positive patients who received prescriptions for antiviral drugs was significantly higher among those whose physician was aware of the result.

Conclusions. Physician awareness of a rapid diagnosis of influenza in the pediatric emergency department significantly reduced the number of laboratory tests and radiographs ordered and their associated charges, decreased antibiotic use, increased antiviral use, and decreased length of time to discharge. *Pediatrics* 2003;112: 363–367; *pediatric, influenza, physician decision-making, patient management.*

Influenza virus types A and B are common respiratory pathogens in the pediatric population. Depending on age, attack rates may be 1.5 to 3 times higher than for adults, with school-aged children having the highest attack rates.[1,2] A retrospective cohort study of children under 15 years of age demonstrated outpatient visits attributable to influenza ranging from 6 to 15 per 100 children.[3] Infection with influenza virus leads to a significant increase in primary care visits, and also increases in emergency department utilization during wintertime epidemics.[2]

Rapid diagnostic test kits for influenza types A and B are currently available for outpatient use and have proven to be both sensitive and specific.[4–7] Few studies have been performed which analyze the impact of rapid diagnostic testing for influenza and subsequent effect on patient management.[8–11] To date, there are no prospective, randomized studies analyzing use of rapid influenza testing and effect on patient management in the pediatric emergency department. Rapid diagnostic tests are not currently routinely incorporated in the work-up of infants and children with fever and vague symptoms, or with fever and no documented source.[12] Use of rapid tests in the pediatric emergency department which are sensitive and specific for influenza could potentially decrease performance of other more invasive tests, thereby reducing associated patient charges, reducing patient length of stay in the emergency depart-

Pediatrics 2003;112;363-367

Impact of Rapid Diagnosis on Management of Adults Hospitalized With Influenza

ARCHIVES EXPRESS

Ann R. Falsey, MD; Yoshihiko Murata, MD, PhD; Edward E. Walsh, MD

Background: Rapid influenza testing decreases antibiotic and ancillary test use in febrile children, yet its effect on the care of hospitalized adults is unexplored. We compared the clinical management of patients with influenza whose rapid antigen test result was positive (Ag+) with the management of those whose rapid antigen test result was negative or the test was not performed (Ag0).

Methods: Medical record review was performed on patients with influenza hospitalized during 4 winters (1999-2003). Hospital policy mandated influenza testing (antigen or culture) for all patients with acute cardiopulmonary diseases admitted from November 15 through April 15. A subset of patients participated in an epidemiological study and had reverse-transcriptase polymerase chain reaction or serologic testing performed. Clinical data from Ag+ and Ag0 patients were compared.

Results: Of 166 patients with available records, 86 were Ag+ and 80 were Ag0. Antibiotic use (74 [86%] of 86 patients vs 79 [99%] of 80 patients; $P=.002$) was less and antibiotic discontinuance (12 [14%] of 86 patients vs 2 [2%] of 80 patients; $P=.01$) was greater in Ag+ compared with Ag0 patients. No significant differences in antibiotic days, length of hospital stay, or antibiotic complications were noted. Antiviral use (63 [73%] of 86 patients vs 6 [8%] of 80 patients; $P<.001$) was greater in Ag+ than Ag0 patients. Antigen status was independently associated with withholding or discontinuing antibiotics in multivariate analysis. Of 44 Ag+ patients deemed low risk for bacterial infection, 27 continued to receive antibiotics despite positive influenza test results. These patients more commonly had pulmonary disease and had significantly more abnormal lung examination results ($P=.005$) compared with those in whom antibiotics were withheld or discontinued.

Conclusions: Rapid influenza testing leads to reductions in antibiotic use in hospitalized adults. Better tools to rule out concomitant bacterial infection are needed to optimize the impact of viral testing.

Arch Intern Med. 2007;167:354-360

"Impact" outcomes include:

- Change in clinical decisions
- Reduction in antibiotic use
- Increased antiviral use
- Decreased length of time to discharge
- Reduction in lab investigations, etc

Example: POC CD4 counts

Accuracy

Evaluation of the PIMA Point-of-Care CD4 Analyzer in VCT Clinics in Zimbabwe

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Abstract: Point-of-care (POC) CD4 testing was implemented at a stand-alone HIV voluntary testing and counseling centre in Harare, Zimbabwe. To validate the use of this new technology, paired blood samples were collected from 165 patients either by a nurse or a laboratory technician and tested using POC and conventional laboratory CD4 machines. Finger prick (capillary) blood was collected directly into the PIMA POC CD4 Analyzer cartridges and tested immediately, whereas venous blood collected into evacuated tubes was used for CD4 enumeration on a Becton Dickinson FACSCalibur. There was no significant difference in mean absolute CD4 counts between the POC PIMA and Becton Dickinson FACSCalibur platforms (+7.6 cells/μL; $P = 0.72$). Additionally, there was no significant difference in CD4 counts between the platforms when run by either a nurse (+18.0 cells/μL; $P = 0.49$), or a laboratory technicians (−3.1 cells/μL; $P = 0.93$). This study demonstrates that POC CD4 testing can be conducted in a voluntary testing and counseling setting for staging HIV-positive clients. Both nurses and laboratory technicians performed the test accurately, thereby increasing the human resources available for POC CD4 testing. By producing same-day results, POC CD4 facilitates immediate decision-making, patient management and referral and may help improve patient care and retention. POC CD4 may also alleviate testing burdens at traditional central CD4 laboratories, hence improving test access in both rural and urban environments.

Key Words: CD4, HIV, diagnosis, client-initiated testing, laboratory, PIMA, point-of-care, voluntary counseling and testing, VCT

(*J Acquir Immune Defic Syndr* 2010;55:1–7)

BACKGROUND

CD4 T-lymphocyte count is an important qualifying test for antiretroviral treatment (ART) in HIV-positive individuals and is also used to monitor treatment efficacy.[1–7] The scale up of public ART programs globally[8] has led to an increased demand for CD4 count tests, especially to assess treatment eligibility. Despite expansion of laboratory infrastructure and services, access to CD4 testing remains a bottleneck to ART scale-up. In Zimbabwe, an estimated 380,000 adults are in need of ART[9] and, by the end of 2009, an estimated 215,000 were on ART within the public sector.[10] There is clearly a need to increase access to ART services and improving CD4 access may help.

In Zimbabwe, the "New Start" voluntary testing and counseling (VCT) centers (also known as client-initiated testing and counselling centers) are established by the Ministry of Health and Child Welfare in partnership with Population Services International (PSI) and provide free rapid HIV testing services to more than 360,000 clients nationwide on an annual basis. Clients testing positive at VCT centers are then referred to Opportunistic Infection (OI) clinics for HIV care and ART if eligible. After enrollment at the OI clinics, patients are scheduled for a CD4 count test. Due to high demand, delays in CD4 testing can occur for 2–3 weeks on average. There is substantial loss-to-follow-up of patients between HIV diagnosis and registration at the OI clinics and delays in CD4 testing can result in further loss of patients who do not return or who die before initiating treatment. The situation is exacerbated in rural areas where more limited CD4 access creates a significant bottleneck to the scale up of ART.

Example: POC CD4 counts

Clinical impact

Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: an observational cohort study

Ilesh V Jani, Nádia E Sitoe, Eunice R Alfai, Patrina L Chongo, Jorge I Quevedo, Beatriz M Rocha, Jonathan D Lehe, Trevor F Peter

Background Loss to follow-up of HIV-positive patients before initiation of antiretroviral therapy can exceed 50% in low-income settings and is a challenge to the scale-up of treatment. We implemented point-of-care counting of CD4 cells in Mozambique and assessed the effect on loss to follow-up before immunological staging and treatment initiation.

Methods In this observational cohort study, data for enrolment into HIV management and initiation of antiretroviral therapy were extracted retrospectively from patients' records at four primary health clinics providing HIV treatment and point-of-care CD4 services. Loss to follow-up and the duration of each preparatory step before treatment initiation were measured and compared with baseline data from before the introduction of point-of-care CD4 testing.

Findings After the introduction of point-of-care CD4 the proportion of patients lost to follow-up before completion of CD4 staging dropped from 57% (278 of 492) to 21% (92 of 437) (adjusted odds ratio [OR] 0·2, 95% CI 0·15–0·27). Total loss to follow-up before initiation of antiretroviral treatment fell from 64% (314 of 492) to 33% (142 of 437) (OR 0·27, 95% CI 0·21–0·36) and the proportion of enrolled patients initiating antiretroviral therapy increased from 12% (57 of 492) to 22% (94 of 437) (OR 2·05, 95% CI 1·42–2·96). The median time from enrolment to antiretroviral therapy initiation reduced from 48 days to 20 days ($p<0·0001$), primarily because of a reduction in the median time taken to complete CD4 staging, which decreased from 32 days to 3 days ($p<0·0001$). Loss to follow-up between staging and antiretroviral therapy initiation did not change significantly (OR 0·84, 95% CI 0·49–1·45).

Interpretation Point-of-care CD4 testing enabled clinics to stage patients rapidly on-site after enrolment, which reduced opportunities for pretreatment loss to follow-up. As a result, more patients were identified as eligible for and initiated antiretroviral treatment. Point-of-care testing might therefore be an effective intervention to reduce pretreatment loss to follow-up.

Published Online September 26, 2011 DOI:10.1016/S0140-6736(11)61052-0

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Clinical versus epidemiological impact

- Clinical impact of a test result on individual patient outcome
  - This is what GRADE needs
  - Ideally, needed before policy (but currently not happening much)
  - Collected at the individual level (as in a clinical trial)
  - E.g. If Xpert is used instead of smear microscopy, will help initiate TB treatment quicker and ensure cure?

- Epidemiological (public health) impact of introducing a test on disease control
  - Public health or "societal" impact
  - Collected after policy and scale-up
  - Collected at the ecological/population level
  - E.g. Will scale-up of Xpert in S Africa, will it help reduce TB transmission and cut TB incidence rates?

So,

- Test accuracy studies need to be done better and reported better
- Need to go beyond test accuracy and generate evidence on:
  - Impact of test on diagnostic thinking and decision making
  - Incremental or added value beyond what is already in place
  - Time to diagnosis and treatment
  - Impact of test on patient important outcomes
  - Cost-effectiveness
  - Population level impact of scale-up

These topics will be covered in this course!

Post-policy challenges for scaling up tests

Poor scale-up at the country level

- Unclear pathways for adoption and scale-up at the country level
  - What information do country level policy makers need to make decisions?

- How can new tools get scaled up in a messy ecosystem?
  - Lab capacity is weak in many high burden countries
  - Quality assurance is a big concern
  - Regulatory systems are very weak
  - Widespread abuse of suboptimal diagnostics in many high burden countries
  - Systematic market failures throughout value chain for diagnostics – doctors receiving payments/incentives for tests ordered, over-reliance on useless tests, and under-use of good diagnostics

Information needed for adoption and scale-up at country level

Michael Kimerling
Madhu Pai

We did a quick survey of the 4 BASIC countries

	China	India	Brazil	S Africa
Who approves new tests?	MoH	MoH	MoH	DoH
Any new test implemented?	No	LPA	MGIT	LPA
Registration needed?	Yes	Yes	Yes	Yes
WHO/STAG approval necessary?	No	No (but helps)	No	No (but important)
After WHO approval, further studies needed?	Yes	Not specified, but helps	Not necessarily, but preferable	Depends on cost implications
What type of country level data needed?	Effectiveness, feasibility, cost-effectiveness	Demonstration in public sector	Economic impact for health system	Feasibility, cost-effectiveness

Main findings

	China	India	Brazil	S Africa
Data on impact on patient outcomes needed?	No	Not (but helps)	Yes	No, but could inform CEA
After country approval, is evidence for scale-up needed?	Yes, feasibility in several settings before scale-up	No, but valuable	Yes	Moving target
What type of evidence for scale up?	Feasibility and effectiveness	Performance, feasibility, operational	CEA and economic impact for health system	CEA, feasibility
Can private sector introduce new tests without NTP approval?	Not applicable (private sector does not manage TB)	Yes	Yes, but drugs only via public	Yes
Can ethical concerns re access to treatment delay implementation?	Yes	Yes	No	Unlikely
Most critical step?	?	Outside: WHO approval Inside: Local endorsement	Cost for the health system	Cost-effectiveness

Some observations

- The global and local value chains are not well aligned
  - Global value chain needs to be clear and efficient, so that country-level uptake can be facilitated
  - But the local value chain does not appear to be well defined or linear/sequential in most countries
    - Confusion on which test to scale up and when
      - If newer/cheaper/better tools are coming, why scale up now?
    - The push to adopt new diagnostics may be forcing countries to set up the local pathway
      - Experience with MGIT and LPA may be the first such examples; now Xpert
      - Pathways may vary for different diagnostics (India experience)
- WHO/STAG approval not mandatory, but might help for NTP adoption
  - Private sector can adopt new tools with fewer barriers
- Even if WHO approved, local studies needed
  - On feasibility, cost-effectiveness, fit with algorithms, HR and lab implications, delivery models, willingness to pay, price point analysis, etc.
- Access to treatment is an ethical concern for some countries
- Local economic (health system) and CEA issues may be more relevant (what will it cost us and who will pay?) than accuracy or clinical impact of the test

Adoption and scale-up issues in India (for example)

- LED:
  - Not enthusiastic –they had recently purchased a large number of light microscopes
  - LED will replace light microscopes in a phase manner (over several years)
  - FM EQA still under development
- Xpert MTB/RIF:
  - Because LPA/MGIT is being slowly scaled up, enthusiasm for Xpert is less
    - "if a better test comes along, what do we do with Xpert?"
    - High cost of Xpert (but no effort has been made to look at CEA)
  - Lack of SLD and cost of MDR Rx is a major barrier
    - Although WHO-endorsed, and 3 published studies have Xpert data from India, demonstration study is now ongoing
    - Little clarity on where to position Xpert in the health system
      - If placed in 43 culture/DST labs, might do nothing to reduce TB transmission in the community!
      - If restricted to MDR suspects or HIV+, again, might have limited impact

Challenge for China… universal DST?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

National Survey of Drug-Resistant Tuberculosis in China

Yanlin Zhao, Ph.D., Shaofa Xu, M.D., Lixia Wang, M.S., Daniel P. Chin, M.D., Shengfen Wang, Ph.D., Guanglu Jiang, B.S., Hui Xia, M.S., Yang Zhou, M.S., Qiang Li, M.S., Xichao Ou, M.S., Yu Pang, Ph.D., Yuanyuan Song, B.S., Bing Zhao, B.S., Hongtao Zhang, Ph.D., Guangxue He, B.S., Jing Guo, Ph.D., and Yu Wang, M.D.

Most cases of MDR and XDR tuberculosis resulted from primary transmission.
--- Therefore, prompt diagnosis is critical (systems issue)

Among all patients with TB, approximately 1 of 4 had disease that was resistant to isoniazid, rifampin, or both, and 1 of 10 had MDR tuberculosis.
--- Universal DST is now considered necessary (technology issue)

Scale-up issues in SA

‘Bazooka’ against TB launched

25.03.2011 Dipuo Sedibe and Kerry Cullinan

The health department has bought 30 multi-million rand machines that can diagnose drug-resistant tuberculosis within two hours rather than the usual four weeks.

Health Minister Dr Aaron Motsoaledi unveiled the biggest of these GeneXpert machines, which can process 48 TB tests in a two-hour session, at Prince Mshiyeni Hospital in Durban during a World TB Day function yesterday.

South Africa is the first African country to get these machines and only the fourth outside of the USA. USAID assisted government to pay for the machines, which cost a total of R53-million.

KwaZulu-Natal MEC Dr Sibongiseni Dhlomo and Health Minister Dr Aaron Motsoaledi testing the GenXpert machine

Photo credit: Lettie Ferreira

Nine smaller GeneXpert machines that can process 16 tests at a time, have been sent to each province and installed in their TB “hot spots”, said Motsoaledi.

A further 20 machines that can do four tests at once are going to used in hot spots around the country, including at Tugela Ferry where the deadly extensively drug-resistant (XDR) TB was first discovered.

Dr Motsoaled described the machines as a “revolution”, saying that these were the “bazookas” in the war against TB.

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PLoS one

The Impact and Cost of Scaling up GeneXpert MTB/RIF in South Africa

Gesine Meyer-Rath[1,2]*, Kathryn Schnippel[1], Lawrence Long[1], William MacLeod[1,2], Ian Sanne[1,2], Wendy Stevens[3,4,5], Sagie Pillay[3,4], Yogan Pillay[6], Sydney Rosen[1,2]

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Abstract

Objective: We estimated the incremental cost and impact on diagnosis and treatment uptake of national rollout of Xpert MTB/RIF technology (Xpert) for the diagnosis of pulmonary TB above the cost of current guidelines for the years 2011 to 2016 in South Africa.

Methods: We parameterised a population-level decision model with data from national-level TB databases (n = 199,511) and implementation studies. The model follows cohorts of TB suspects from diagnosis to treatment under current diagnostic guidelines or an algorithm that includes Xpert. Assumptions include the number of TB suspects, symptom prevalence of 5.5%, annual suspect growth rate of 10%, and 2010 public-sector salaries and drug and service delivery costs. Xpert test costs are based on data from an in-country pilot evaluation and assumptions about when global volumes allowing cartridge discounts will be reached.

Results: At full scale, Xpert will increase the number of TB cases diagnosed per year by 30%–37% and the number of MDR-TB cases diagnosed by 69%–71%. It will diagnose 81% of patients after the first visit, compared to 46% currently. The cost of TB diagnosis per suspect will increase by 55% to USD 60–61 and the cost of diagnosis and treatment per TB case treated by 8% to USD 797–873. The incremental capital cost of the Xpert scale-up will be USD 22 million and the incremental recurrent cost USD 287–316 million over six years.

Conclusion: Xpert will increase both the number of TB cases diagnosed and treated and the cost of TB diagnosis. These results do not include savings due to reduced transmission of TB as a result of earlier diagnosis and treatment initiation.

Citation: Meyer-Rath G, Schnippel K, Long L, MacLeod W, Sanne I, et al. (2012) The Impact and Cost of Scaling up GeneXpert MTB/RIF in South Africa. PLoS ONE 7(5): e36966. doi:10.1371/journal.pone.0036966

Challenges for scale-up of Xpert

INT J TUBERC LUNG DIS e-publication ahead of print 13 October 2011

http://dx.doi.org/10.5588/ijtld.11.0392

PERSPECTIVES

Xpert® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how?

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SUMMARY

Xpert® MTB/RIF offers new and important possibilities for the diagnosis of sputum smear-negative tuberculosis (TB) and/or rifampicin (RMP) resistance, and many are encouraging rapid and widespread implementation. This simple test can be implemented almost everywhere, and it provides results within a few hours. In low-income countries (LICs), however, its cost, environmental limitations (stable and regular electricity, adequate room temperature) and difficulties involved in supply and maintenance are major obstacles. While it may be suitable for major reference hospitals, operational research is needed to evaluate the test and its additional yield above high-quality smear microscopy and clinical algorithms before its use at the peripheral level. In the meantime, direct microscopy should remain the initial diagnostic test for TB suspects. In most LICs, the prevalence of RMP resistance among new TB patients is very low; an Xpert MTB/RIF result indicating RMP resistance will thus always need confirmation by another test. In a population at high risk of RMP resistance (>15%), however, the positive predictive value for RMP resistance by Xpert MTB/RIF is high, and identification of RMP resistance is an excellent proxy for multidrug-resistant TB (MDR-TB). The assay should be widely used for this purpose if, and only if, excellent MDR-TB management is available, both for ethical reasons and to reduce the risk of extensively drug-resistant TB.

KEY WORDS: tuberculosis; diagnostics; GeneXpert; low-income countries; Xpert® MTB/RIF

INT J TUBERC LUNG DIS 15(12):1563

http://dx.doi.org/10.5588/ijtld.11.0728

EDITORIAL

The ethics of national tuberculosis programmes in low-income countries not rolling out Xpert® MTB/RIF

IN THIS ISSUE of the *Journal*, Trébucq et al. posit a provocative position: Xpert® MTB/RIF should not be rolled out in low-income settings if no effective second-line treatment is available, as doing so would be ethically indefensible.[1] This is in contrast to the recent position taken by the World Health Organization (WHO) Task Force on Addressing Ethical Issues in TB Care and Control Programmes, which states 'while countries are in the process of scaling up treatment, the use of drug susceptibility testing can be appropriate as an interim measure even when no second- or third-line drug treatment is available, or when the only available treatment is substandard'.[2]

Detecting more tuberculosis (TB) will put moral pressure on governments to provide and enhance universal access to first- and second-line TB regimens. By extension, it also places moral pressure on drug and diagnostics manufacturers to lower the prices of their products and to develop novel ones. Further, increased demand for drugs as a result of sensitive case detection in and of itself creates scale and, accordingly, ultimately lowers prices, thus facilitating treatment accessibility. The human immunodeficiency virus (HIV) field provides precedence here: in most low-income settings, HIV testing is rising, despite inadequate treatment facilities.[3] The progressive scale-up of HIV treatment programs globally has resulted in increased drug demand, which, coupled with generic competition and more efficient manufacturing of the active ingredients, has contributed to drastic reductions of the cost of HIV drugs over time.[3,4] Novel TB diagnostics can follow a similar route. is implementing progressive rollout of Xpert MTB/RIF, and India is contemplating progressive rollout. Low-income countries should commit to doing the same, with international assistance. Public health, ethics, and human rights obligations apply equally to high TB burden low-income countries too.

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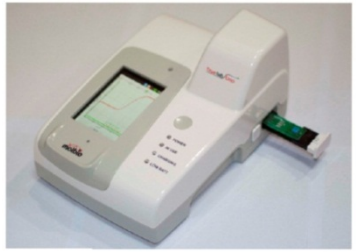
Disclosure: The authors work on the ESC[2] Program in Global Health, which is funded by the Bill & Melinda Gates Foundation. JAS was a member of the WHO Task Force on Addressing Ethical Issues in TB Care and Control Programmes.

References

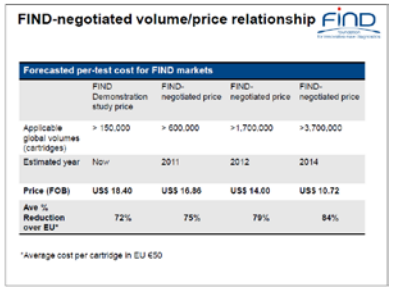
1 Trébucq A, Enarson D A, Chiang C Y, et al. Xpert® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how? Int J Tuberc Lung Dis 2011; 15: 1567–1571.
2 World Health Organization. Guidance on ethics of tuberculosis prevention, care and control. WHO/HTM/TB/2010.16. Geneva,

How can we lower costs of current best tools, to enable scale-up in resource-limited settings?

$$$



Reducing the price of Xpert

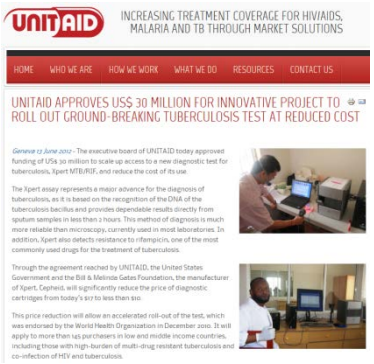


FIND-negotiated volume/price relationship FIND

Forecasted per-test cost for FIND markets

	FIND Demonstration study price	FIND-negotiated price	FIND-negotiated price	FIND-negotiated price
Applicable global volumes (cartridges)	> 150,000	> 600,000	>1,700,000	>3,700,000
Estimated year	Now	2011	2012	2014
Price (FOB)	US$ 18.40	US$ 16.86	US$ 14.60	US$ 10.72
Ave % Reduction over EU*	72%	75%	79%	84%

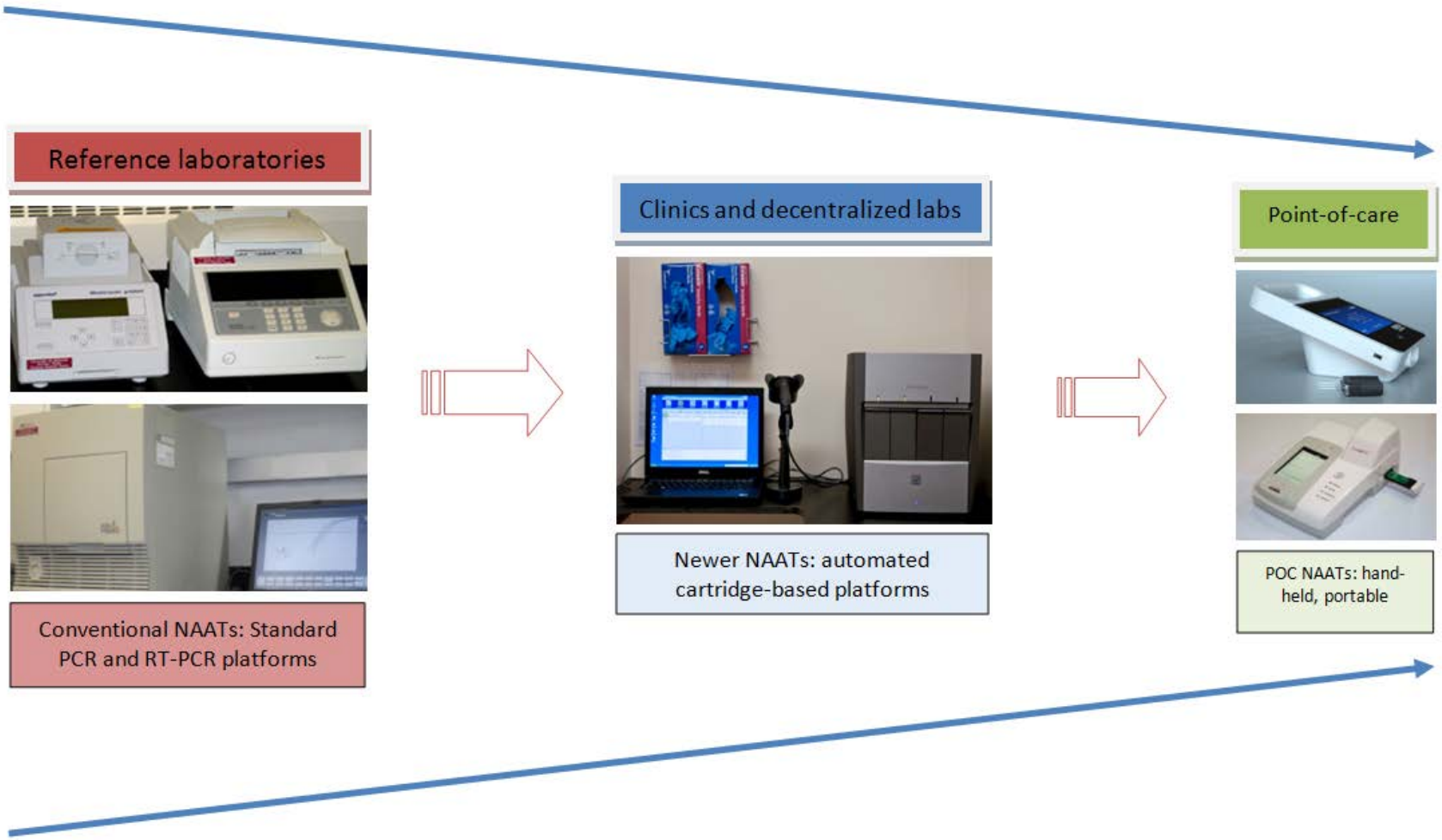
*Average cost per cartridge in EU €50



Fast-followers that are more affordable

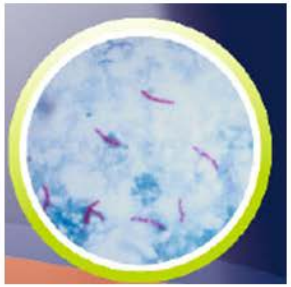
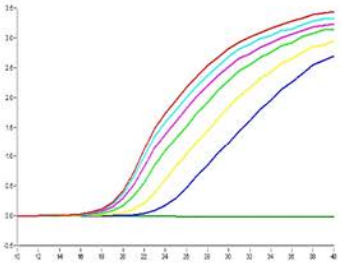
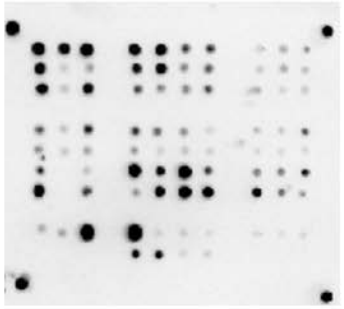
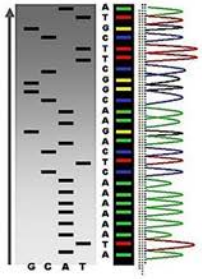
"frugal engineering and delivery innovation"

The evolution of TB NAATs: from reference labs to "point-of-care"



Pai NP, Pai M. Discovery Med 2012

The evolution of NAATs: from simpler to complex systems

Analog Approach	Real time PCR Approach	Microarray Approach	Sequencing Approach
			
			
Past	*Current*	*Next Wave*	*Futuristic*
MTB	MTB / *Rif*	MTB / MDR-TB / XDR-TB	Genotyping

Source: Akonni Biosystems

Can BRICS lead the next wave of innovations?

FT.com FINANCIAL TIMES **Reports**

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Guest column: Emerging global leaders should take a stand

By Jorge Sampaio
Published: March 23 2011 18:02 | Last updated: March 23 2011 18:02

This month, Forbes Magazine published its annual "rich list". The most striking feature of the 2011 list is the prominence of super-rich people in the Bric countries (Brazil, Russia, India, China). In the past year, 108 Bric-based billionaires have joined the ranks, bringing the total of billionaires to 301. This is a reasonable proxy for the strength of these countries' fast-growing economies.

World Tuberculosis Day is a good moment to reflect on another feature these rising giants share in common: a huge burden of tuberculosis (TB). India has the highest TB rate in the world and China the fourth. The Russian Federation and Brazil rank 11th and 16th respectively. In addition, two-thirds of all cases of multidrug-resistant TB (MDR-TB) are currently emerging in China, India and Russia.

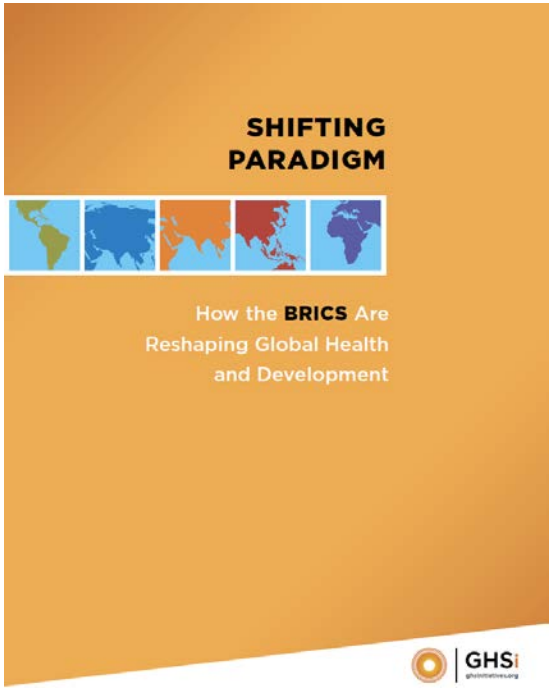
If all four countries aspire to continue their current pace of growth, it behoves them to make TB a top priority.

TB is having an enormous impact on working populations in the Bric countries. The disease generally strikes people during their most productive years, between the ages of 15 and 45. It keeps men and women out of work and children out of school, presenting a limit to the rate of further growth.

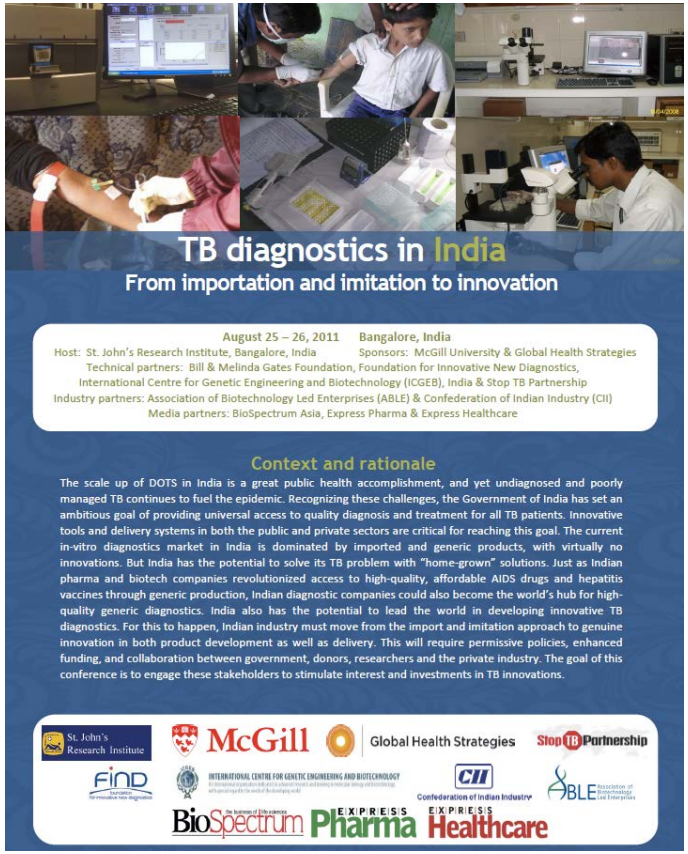
TB is robbing the Brics of a significant proportion of their workforce in an irretrievable manner, jeopardising those countries' growth and development. More than 500,000 die of TB in the Bric countries each year. This is a terrible waste, since a person can be cured of TB as an outpatient for as little as $100.

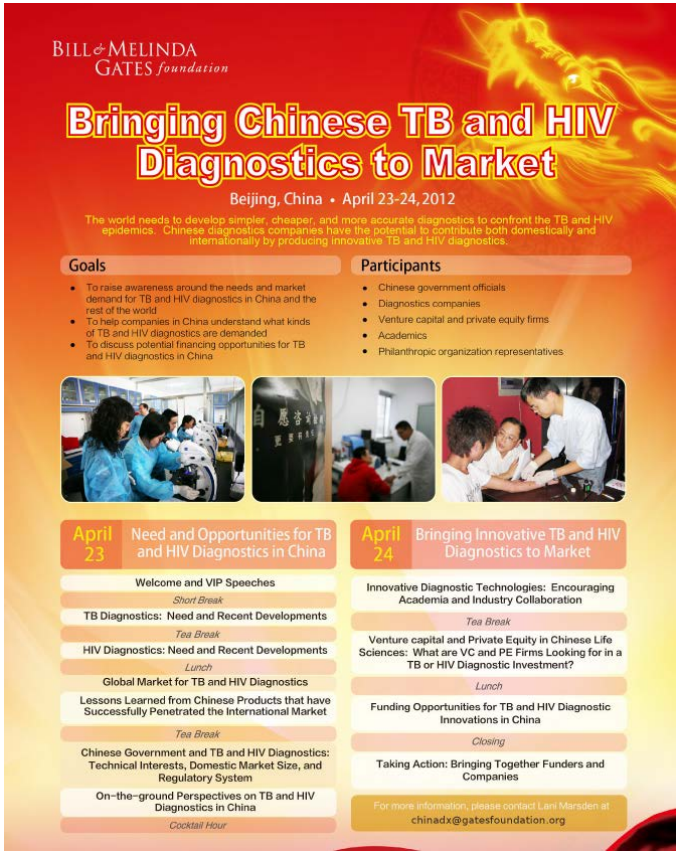
Brazil, Russia, India and China all have the capacity to make rapid progress on TB. With sufficient political commitment and reprioritisation of their national budgets, it is in their power to cut TB deaths to near zero in a matter of years.

Brazil, for example, has already proved its mettle in the realm of domestic health through its landmark HIV treatment and prevention programme, which provides free ARV drugs to every HIV-positive Brazilian citizen. Why not make a comparable push on TB, where progress is lagging?



Getting BRICS to invest in affordable diagnostics development





India, Aug 2011

China, Sept 2012

Global CEA is helpful but…

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Rapid Diagnosis of Tuberculosis with the Xpert MTB/RIF Assay in High Burden Countries: A Cost-Effectiveness Analysis

Anna Vassall[1,2], Sanne van Kampen[1], Hojoon Sohn[3], Joy S. Michael[4], K. R. John[5], Saskia den Boon[6], J. Lucian Davis[7], Andrew Whitelaw[8,9], Mark P. Nicol[8,9], Maria Tarcela Gler[10], Anar Khaliqov[11], Carlos Zamudio[12], Mark D. Perkins[13], Catharina C. Boehme[13], Frank Cobelens[1]*

1 Department of Global Health, and Amsterdam Institute of Global Health and Development, Academic Medical Center, Amsterdam, The Netherlands, **2** Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, United Kingdom, **3** Department of Epidemiology and Biostatistics, McGill University, Canada, **4** Christian Medical College, Vellore, India, **5** National TB Program, Vellore, India, **6** Makerere University - University of California, San Francisco (MU-UCSF) Research Collaboration, Kampala, Uganda, **7** Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco, United States of America, **8** National Health Laboratory Service, Groote Schuur Hospital, Cape Town, South Africa, **9** Division of Medical Microbiology and Institute for Infectious Diseases and Molecular Medicine, University of Cape Town, South Africa, **10** Tropical Disease Foundation, Manila, Philippines, **11** Special Treatment Institution, Baku, Azerbaijan, **12** Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru, **13** Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland

Abstract

Background: Xpert MTB/RIF (Xpert) is a promising new rapid diagnostic technology for tuberculosis (TB) that has characteristics that suggest large-scale roll-out. However, because the test is expensive, there are concerns among TB program managers and policy makers regarding its affordability for low- and middle-income settings.

Methods and Findings: We estimate the impact of the introduction of Xpert on the costs and cost-effectiveness of TB care using decision analytic modelling, comparing the introduction of Xpert to a base case of smear microscopy and clinical diagnosis in India, South Africa, and Uganda. The introduction of Xpert increases TB case finding in all three settings; from 72%–85% to 95%–99% of the cohort of individuals with suspected TB, compared to the base case. Diagnostic costs (including the costs of testing all individuals with suspected TB) also increase: from US$28–US$49 to US$133–US$146 and US$137–US$151 per TB case detected when Xpert is used "in addition to" and "as a replacement of" smear microscopy, respectively. The incremental cost effectiveness ratios (ICERs) for using Xpert "in addition to" smear microscopy, compared to the base case, range from US$41–$110 per disability adjusted life year (DALY) averted. Likewise the ICERS for using Xpert "as a replacement of" smear microscopy range from US$52–$138 per DALY averted. These ICERs are below the World Health Organization (WHO) willingness to pay threshold.

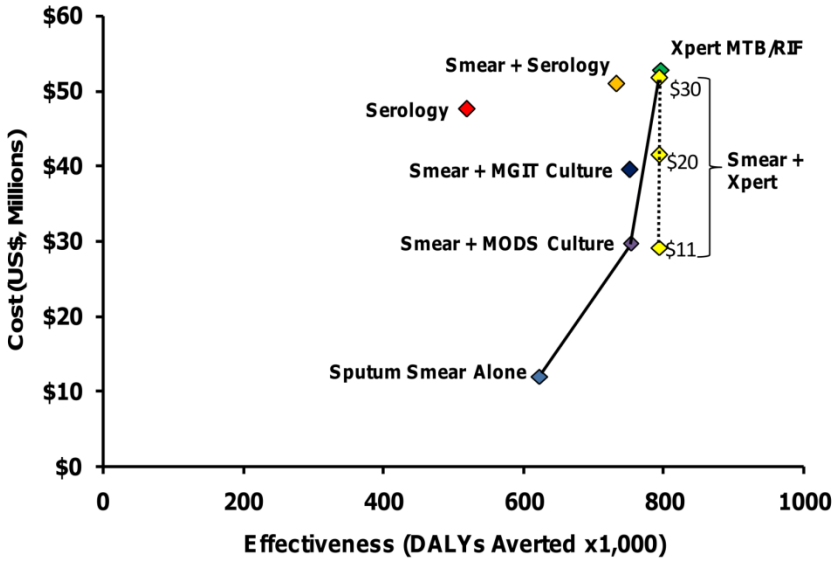
Conclusions: Our results suggest that Xpert is a cost-effective method of TB diagnosis, compared to a base case of smear microscopy and clinical diagnosis of smear-negative TB in low- and middle-income settings where, with its ability to substantially increase case finding, it has important potential for improving TB diagnosis and control. The extent of cost-effectiveness gain to TB programmes from deploying Xpert is primarily dependent on current TB diagnostic practices. Further work is required during scale-up to validate these findings.

Please see later in the article for the Editors' Summary.

Citation: Vassall A, van Kampen S, Sohn H, Michael JS, John KR, et al. (2011) Rapid Diagnosis of Tuberculosis with the Xpert MTB/RIF Assay in High Burden Countries: A Cost-Effectiveness Analysis. PLoS Med 8(11): e1001120. doi:10.1371/journal.pmed.1001120

Need country-level CEA: At what price point will Xpert become cost-effective at the country level?

INDIA



Dowdy D et al.

S AFRICA

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PLoS one

The Impact and Cost of Scaling up GeneXpert MTB/RIF in South Africa

Gesine Meyer-Rath[1,2]*, Kathryn Schnippel[1], Lawrence Long[1], William MacLeod[1,2], Ian Sanne[1,2], Wendy Stevens[3,4,5], Sagie Pillay[3,4], Yogan Pillay[6], Sydney Rosen[1,2]

1 Health Economics and Epidemiology Research Office (HE2RO), Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 2 Center for Global Health and Development, Boston University, Boston, Massachusetts, United States of America, 3 National Health Laboratory Service, Johannesburg, South Africa, 4 Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, 5 Department of Molecular Medicine and Haematology, University of the Witwatersrand, Johannesburg, South Africa, 6 National Department of Health, Pretoria, South Africa

Abstract

Objective: We estimated the incremental cost and impact on diagnosis and treatment uptake of national rollout of Xpert MTB/RIF technology (Xpert) for the diagnosis of pulmonary TB above the cost of current guidelines for the years 2011 to 2016 in South Africa.

Methods: We parameterised a population-level decision model with data from national-level TB databases (n = 199,511) and implementation studies. The model follows cohorts of TB suspects from diagnosis to treatment under current diagnostic guidelines or an algorithm that includes Xpert. Assumptions include the number of TB suspects, symptom prevalence of 5.5%, annual suspect growth rate of 10%, and 2010 public-sector salaries and drug and service delivery costs. Xpert test costs are based on data from an in-country pilot evaluation and assumptions about when global volumes allowing cartridge discounts will be reached.

Results: At full scale, Xpert will increase the number of TB cases diagnosed per year by 30%–37% and the number of MDR-TB cases diagnosed by 69%–71%. It will diagnose 81% of patients after the first visit, compared to 46% currently. The cost of TB diagnosis per suspect will increase by 55% to USD 60–61 and the cost of diagnosis and treatment per TB case treated by 8% to USD 797–873. The incremental capital cost of the Xpert scale-up will be USD 22 million and the incremental recurrent cost USD 287–316 million over six years.

Conclusion: Xpert will increase both the number of TB cases diagnosed and treated and the cost of TB diagnosis. These results do not include savings due to reduced transmission of TB as a result of earlier diagnosis and treatment initiation.

Citation: Meyer-Rath G, Schnippel K, Long L, MacLeod W, Sanne I, et al. (2012) The Impact and Cost of Scaling up GeneXpert MTB/RIF in South Africa. PLoS ONE 7(5): e36966. doi:10.1371/journal.pone.0036966

Thinking beyond technology

systems and business models

How can we combine new tools with delivery strategies to reduce diagnostic delays?

The potential impact of new diagnostic tests on tuberculosis epidemics

Christopher Dye

***Results*: New diagnostic tests for active TB will have a bigger impact sooner where: disease incidence is high and most cases are due to recent infection; advances in test technology (test sensitivity, specificity, *etc.*) are combined with early diagnosis; new tests have not only better technical specifications than current tests, but also compensate for the misuse of existing tests; health system delays are long compared with patient delays, assuming the former are more amenable to change.**

***Interpretation & conclusions*: New diagnostic tests will certainly improve TB control, but the highest impact will be obtained by applying tests with higher sensitivity and specificity early in the infectious period. Refined behavioural and epidemiological models should be able to investigate the mechanisms by which early diagnosis could be achieved, in addition to the consequent epidemiological effects.**

Ind J Medical Research 2012

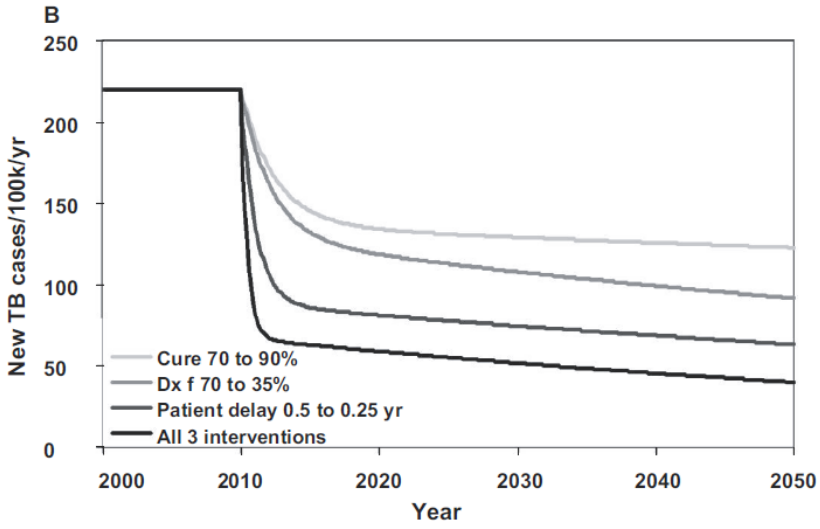
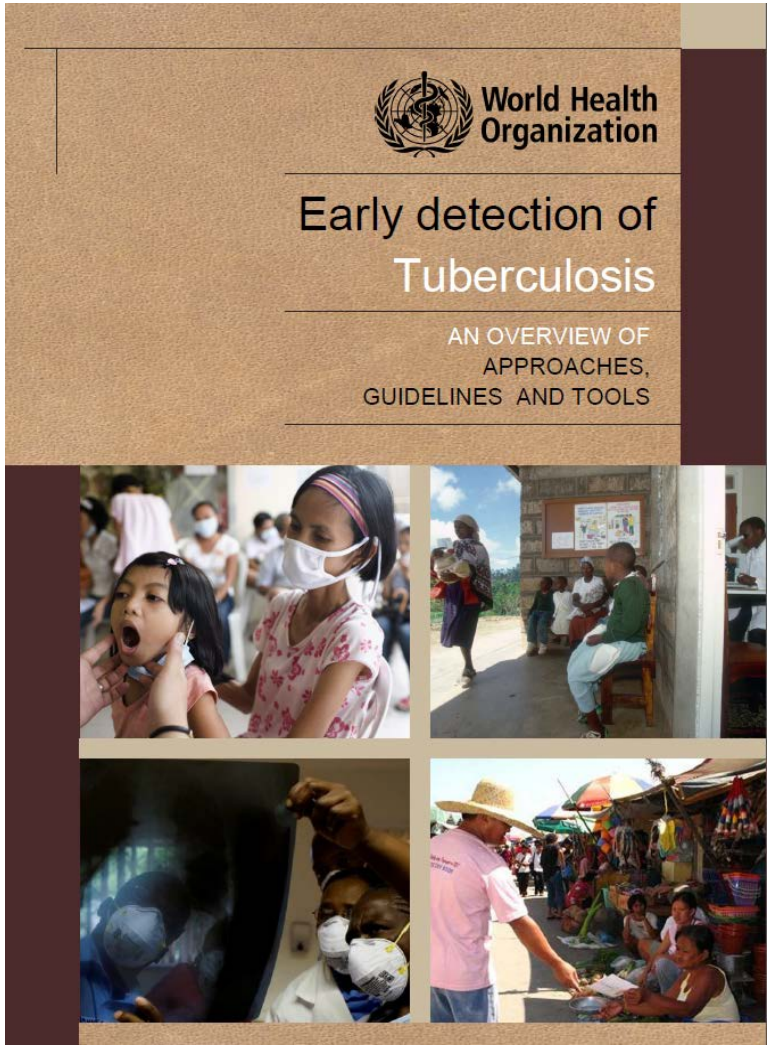


Fig. 4. Comparative impact of three interventions, singly and in combination, on **(A)** the average duration of infectiousness, and consequently **(B)** TB incidence through time. Interventions begin in 2010. Below the elimination threshold of 0.78 yr in A, $R_0 < 1$ and TB will eventually be eliminated.

Not diagnosis, but EARLY diagnosis!



http://whqlibdoc.who.int/hq/2011/WHO_HTM_STB_PSI_2011.21_eng.pdf

Will reference labs for culture & DST methods have an impact on reducing diagnostic delays?

What is the best near-patient setting to implement Xpert? DMCs? District level centres? HIV/ART clinics?

Decentralized versus centralized TB testing for TB diagnosis in India: modeling project

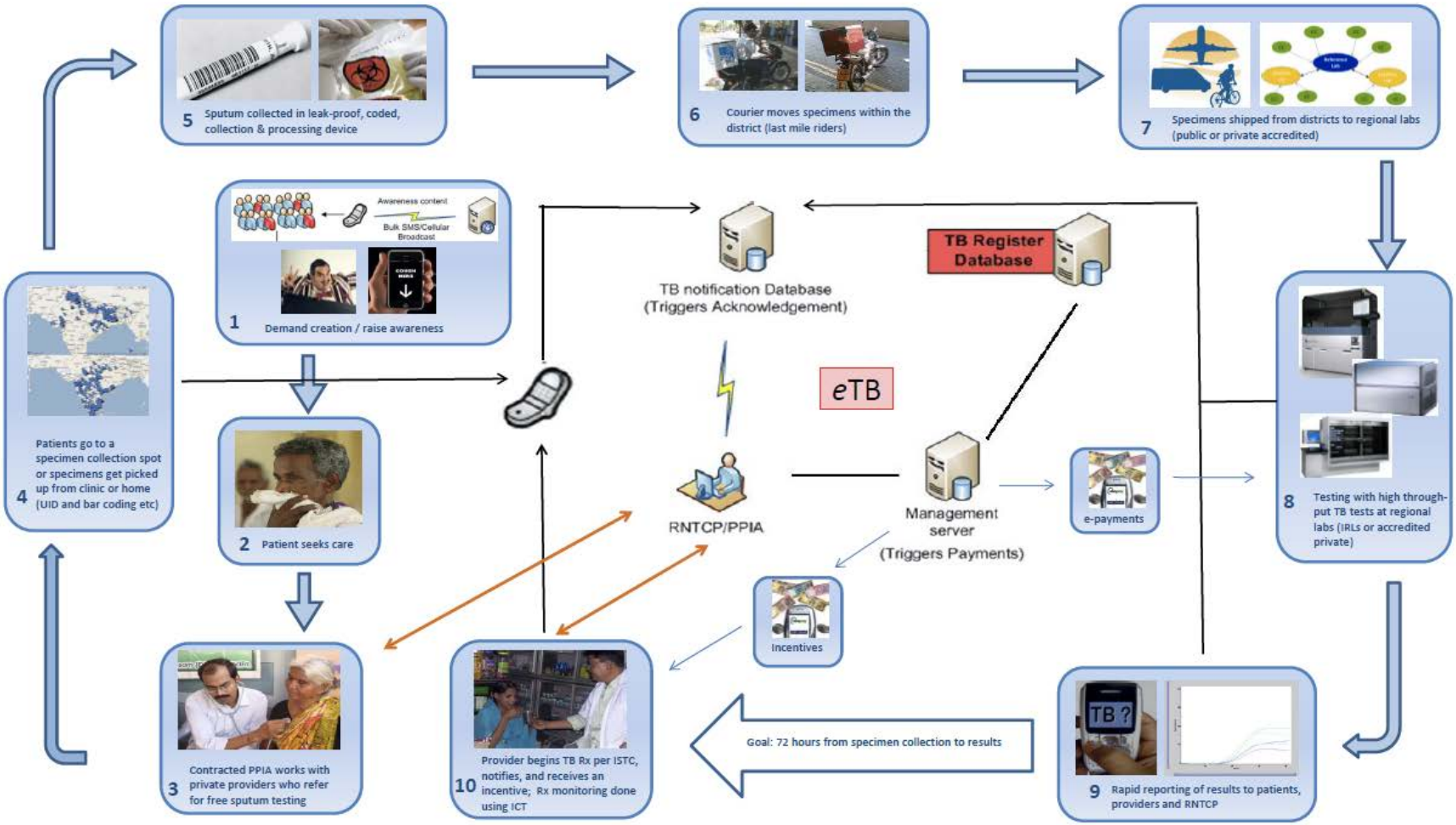
David Dowdy[1], Sarang Deo[2], Amanda Sun[1], Madhukar Pai[3]

[1] Johns Hopkins University School of Public Health, Baltimore, USA
[2] Indian School of Business, Hyderabad, India
[3] McGill University, Montreal, Canada

Setting	Number	Likely % of TB suspects seen	Likely turn-around-times for NAAT results	Likely % of suspects who drop-out and do not complete testing/f-up	Comment
Designated microscopy centres (DMCs)	13,000 (of which, only 500+ have temperature control)	75%	Same day or next day	10%	This is the most decentralized point of care within the RNTCP, but not all TB suspects access these sites
District TB Centers and district hospitals	650+	15%	2 – 3 days	20%	Located in district HQ, and can serve as referral centers within districts
State level intermediate reference labs (IRLs) and private accredited labs	30+	10%	2 – 7 days	30%	Mostly reserved for culture and DST

Example of a centralized testing model for India

A state-level system to improve TB diagnosis with engagement of private providers and laboratories, sputum collection and transport systems, centralized TB testing, linked with eTB/ICT



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*

Abstract

OBJECTIVE The World Health Organization recommends using Xpert MTB/RIF for diagnosis of pulmonary tuberculosis (PTB), but there is little evidence on the optimal placement of Xpert instruments in public health systems. We used recent South African data to compare the cost of placing Xpert at points of TB treatment (all primary clinics and hospitals) with the cost of placement at sub-district laboratories.
METHODS We estimated Xpert's cost/test in a primary clinic pilot and in the pilot phase of the national Xpert roll-out to smear microscopy laboratories; the expected future volumes for each of 223 laboratories or 3799 points of treatment; the number and cost of Xpert instruments required and the national cost of using Xpert for PTB diagnosis for each placement scenario in 2014.
RESULTS In 2014, South Africa will test 2.6 million TB suspects. Laboratory placement requires 274 Xpert instruments, while point-of-treatment placement requires 4020 instruments. With an Xpert cartridge price of $14.00, the cost/test is $26.54 for laboratory placement and $38.91 for point-of-treatment placement. Low test volumes and a high number of sites are the major contributors to higher point-of-treatment costs. National placement of Xpert at laboratories would cost $71 million/year; point-of-treatment placement would cost $107 million/year, 51% more.
CONCLUSION Placing Xpert technology at points of treatment is substantially more expensive than placing the instruments in smear microscopy laboratories. The incremental benefits of point-of-treatment placement, in terms of better patient outcomes, will have to be equally substantial to justify the additional cost to the national health budget.

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”

Lawn S et al.

Regardless of the test, what else is necessary for impact?

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

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.

Published Online
June 14, 2012
DOI:10.1016/S1473-3099(12)70116-0

See Online/Comment
DOI:10.1016/S1473-3099(12)70122-6

Interactive Research and Development, Shahrah-e-Faisal, Karachi, Pakistan (A J Khan PhD, F Qazi MPH, I Lotia MPH, A Habib MEng, U Khan MBBS, H Hussain MSc); **Indus Hospital Research Center, Korangi Crossing, Karachi, Pakistan** (A J Khan, S Khowaja MSW, F S Khan MSc, S Mohammed MPA/ID, F Amanullah FAAP); **Program in Infectious Disease and Social Change, Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA** (U Khan, F Amanullah, M C Becerra PhD, S Keshavjee MD); **and Stop TB Partnership, Geneva, Switzerland** (J Creswell MPH)

Business models are as important as technologies

Comment

Tuberculosis control: business models for the private sector

In many countries, the private health-care sector is a major provider of medical care. In India and Pakistan, for example, 70–80% of first contact care happens in the private sector. Private health care in these countries is a heterogeneous mix of qualified and unqualified providers, modern and alternative health systems, and facilities that range from corporate to charitable institutions. Quality of care, therefore, is highly variable.

The private health sector is part of the problem with tuberculosis control: diagnostic and treatment practices are suboptimum in Pakistan and India,[1–3] resulting in delays in case identification, irrational or unsupervised therapy, and unnecessary expenditure for patients.[4] These factors can lead to drug resistance and continued transmission of tuberculosis.[5] Also, private providers generally do not report or notify tuberculosis cases. However, the private health sector is also part of the solution. In view of their dominant role in tuberculosis care, engagement with private providers is crucial for achievement of tuberculosis control targets.[6]

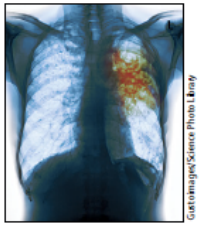
Attempts to engage private health-care providers in tuberculosis control on a large scale have yielded disappointing results. Although small-scale, public–private mix models have worked in many studies,[7] there are almost no examples of large-scale, successful, sustained engagement of the private health sector in tuberculosis control.

new technologies the answer? There is widespread excitement about the potential of new diagnostic technologies for improving case detection and reducing tuberculosis transmission. WHO has endorsed several tests and approaches, and efforts are underway to scale up rapid molecular technologies.[12]

Although we share the enthusiasm for new technology, a study by Khan and colleagues[13] from Karachi, Pakistan, in *The Lancet Infectious Diseases*, shows that technological innovations alone are not sufficient to engage the private sector. Process innovations with better business and service delivery models could be as important as product innovations.

Khan and colleagues implemented a new, multifaceted approach to tuberculosis screening and case detection in one intervention area of Karachi, and compared case-notification rates with those in an adjacent control area. Interventions included a communications campaign to increase demand for tuberculosis diagnosis and treatment services, involvement of laypeople as screeners in private clinics and hospitals, mobile-phone-based incentives for screeners, and referrals of patients with suspected tuberculosis to a private hospital that offered free tuberculosis care. The investigators reported a substantial increase in case notifications in the intervention area compared with the control area.[13]

This study raises several issues. With multiple



Published Online
June 14, 2012
DOI:10.1016/S1473-3099(12)70122-6

See Online/Articles
DOI:10.1016/S1473-3099(12)70116-0

Baloch NA & Pai M. Lancet Infect Dis 2012

We are still searching for the target product profile(s) that will have the biggest impact on the TB epidemic

- A large number of TPPs are possible
- Not just the technology, but also the business/delivery model
- Not just accuracy, but reduction in diagnostic delays
- Not just diagnosis, but rapid and correct treatment

- We may well need multiple TPPs and business models to achieve impact at the country level
  - E.g. public vs. private sectors in India

Some existing TPPs that need to be refined

Source: http://www.msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_ReportSummary_TowardsLabFreeTBDX_ENG_2011.pdf

APPENDICES

Table 3: Minimum specifications for a POC TB diagnostic test

Test specification	Minimum required value
Medical decision	Treatment initiation
Sensitivity - Adults [for pulmonary TB only; regardless of HIV status]	Pulmonary TB: - 95% for smear positive, culture positive - 60%-80% for smear negative, culture positive *[Detection of extrapulmonary TB being a preferred but not minimal requirement]*
Sensitivity - Children *[including extrapulmonary TB; regardless of HIV status]*	- 80% compared to culture of any specimen and - 60% of probable TB (noting problem of lack of a gold standard)
Specificity - adults	- 95% compared to culture
Specificity - children	- 90% for culture-negative probable TB (noting problem of lack of a gold standard) - 95% compared to culture
Time to results	3 hours max. (patient must receive results the same day) [Desirable would be <15min]
Throughput	20 tests/day minimum, by 1 laboratory technician
Specimen type	Adults: urine, oral, breath, venous blood, sputum *[Desired: NON sputum-based sample type and use of finger prick instead of venous blood]* Children: urine, oral, capillary blood (finger/heel prick)
Sample preparation	- 3 steps maximum - Safe: biosafety level 1 - Ability to use approximate volumes (i.e., no need for precise pipetting) - Preparation that is not highly time sensitive
Number of samples	One sample per test
Readout	- Easy-to-read, unambiguous, simple "yes", "no", or "invalid" answer - Readable for at least 1 hour
Waste disposal	- Simple burning or sharps disposal; no glass component - Environmentally acceptable disposal
Controls	- Positive control included in test kit - Quality control simpler and easier than with sputum smear microscopy
Reagents	- All reagents in self-contained kit - Kit contains sample collection device and water (if needed)
Storage/stability required	- Shelf life of 24 months, including reagents - Stable at 30°C, and at higher temperatures for shorter time periods - Stable in high humidity environments
Instrumentation	- If instrument needed, no maintenance required - Instrument works in tropical conditions - Acceptable replacement cost - Fits in backpack - Shock resistant
Power requirement	Can work on battery
Training	- 1 day maximum training time - Can be performed by any health worker
Cost	<US$10 per test after scale-up

Optimal and Minimal Product Characteristics for proposed simple and affordable molecular testing for active tuberculosis

Characteristic	Optimal	Minimal
Cost of consumables (all) FOB	<4 USD	<10 USD
Diagnostic sensitivity	> 98% smear-positive and 70% smear-negative patients	95% of smear-positive and 60% smear-negative patients
Diagnostic specificity	> 99%	>97%
Reagent Kit stability	24m at 40°C, 70% humidity, incl. transport stress (48h at 50°C)	12m at 30°C, 70% humidity, incl. transport stress (48h at 50°C)
Sample preparation and Assay processing (total steps)	Integrated	<5 steps
Thermal Tolerance of Platform/Assay	Operation at 40°C	Operation at 35°C
Time to Market	24 Months	36 Months
Time-to-result	< 1 hour	<3 hours
Additional equipment required	None	Heat block
Analytic sensitivity	$<10^2$ cfu/ml	$<10^3$ cfu/ml
Analytic specificity	No cross reactivity with other organisms including non-tuberculous mycobacteria(NTM)	No cross reactivity with other organisms including non-tuberculous mycobacteria(NTM)
Biosafety	No need for biosafety cabinet, and direct disposal of consumable	No need for biosafety cabinet, and autoclaved consumable
Controls	Internal full-process positive control and negative controls	External controls
Cost of instrumentation	<10,000 USD	<20,000 USD
Drug resistance screening	Detects rifampin resistance and fluoroquinolone resistance	No drug resistance testing
Electronics and software	Integrated	Separate computer required
Instrumentation	Single device	Sample prep + amp/detection
Power	Option for battery operation	110-220V AC current required
Quantitation	Semi-quantitative	Qualitative
Reagent integration	All reagents in consumable	<4 external reagents
Result capturing & documentation	Electronic and printed, wireless transmission capable	Electronic
Sample type	Sputum	Sputum

Product characteristics for high-throughput molecular TB testing

Characteristic	Optimal	Minimal
Sample type	Sputum; gastric lavage, CSF, pleural fluid, tissues	Sputum or digested decontaminated sputum
Sample Handling	Sputum – received 1-7 days of transport	Sputum - received <24 hours of transport
Throughput	>1000 Samples per 12 hour shift, asynchronously	>380 Samples per 12 hour shift, asynchronously or near equivalent
Multi-use platform	Yes	Yes
Analytic sensitivity	$\leq 10^2$ cfu/ml	$\leq 10^3$ cfu/ml
Analytic specificity	No cross reactivity with other organisms including NTMs	No cross reactivity with other organisms including NTMs
Diagnostic sensitivity	> 98% smear-positive and 70% smear-negative patients	95% of smear-positive and 60% smear-negative patients
Diagnostic specificity	> 99%	>97%
Total number of manual steps	≤2, fully automated	<10 steps
Time-to-result	≤1 shift	≤2 days
Cost of instrumentation	<100,000 USD	<500,000 USD
Cost of consumables (all) FOB	<5 USD	<15 USD
Reagent Kit stability	24m at 40°C, 70% humidity, incl. transport stress (48h at 50°C)	12m at 30°C, 70% humidity, incl. transport stress (48h at 50°C)
Operating temperature	≤45°C	≤35°C
Additional equipment required	None	Heat block, centrifuge, sample processing equipment
Biosafety	Equivalent to microscopy	BSL3 lab
Room separation	All activities in one room	Reagent prep, processing and amplification separate
Controls	Internal full-process positive control and negative controls	External controls
Drug resistance screening	Detects resistance to Rif, INH, FQ and PZA	Reflex to drug resistance on same platform with at least RIF
Electronics and software	Integrated	Separate computer required
Instrumentation	Single device	Sample prep + amp/detection
Walkaway operation and random access and STAT sampling	Yes	No
Quantitation	Semi-quantitative	Qualitative
Reagent integration	No need to pipet reagents	Pipetting sample and a buffer.
Result capturing & documentation	Printed and electronic wireless transmission capable	Electronic
Training & education needs	< 1 day, microscopy technician	<1 week, PCR technician

TPP for a POC test (MSF/TAG/STP)*

TPP for a simple and affordable molecular test

TPP for a high throughput molecular test for centralized laboratories

*Batz H-G, Cooke GS, Reid SD. Towards lab-free tuberculosis diagnosis. Treatment Action Group, Stop TB Partnership, Imperial College London; MÉDECINS SANS FRONTIÈRES, 1 – 36, 2011. http://www.msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_Report_TowardsLabFreeTBDX_2011_ENG.pdf

Proposed revised value chain for new TB diagnostics

Which New Diagnostics for Tuberculosis, and When?

Frank Cobelens,[1] Susan van den Hof,[1,2] Madhukar Pai,[3] S. Bertel Squire,[4] Andrew Ramsay,[5] and Michael E. Kimerling[6] on behalf of the Evidence for Scale-up Group

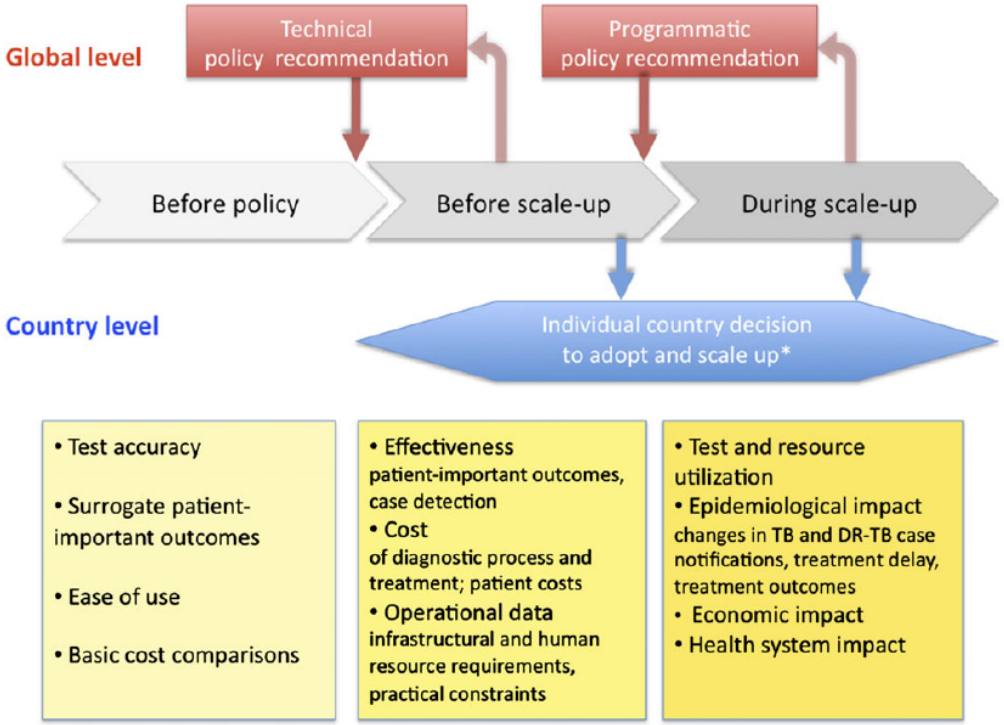


Figure 3. Proposal for a revised pathway focused on the postaccuracy phase of tuberculosis diagnostics, showing the proposed value chain for new diagnostic tests for tuberculosis. The grey arrows in the middle represent the stages in the evaluation pathway, and the colored boxes represent policy decisions at the global level (red) and the country level (blue). Countries would adopt implementation at different points and should provide feedback about their experiences (* in the blue box). In the stages before scale-up and during and after scale-up, evaluation data would be collected on diagnostic algorithms incorporating the new test.

Journal of Infect Dis 2012

Table 2. Description of the Main Research Questions, Designs, and Outcomes, per Stage, in the Proposed Revised Pathway Focused on the Postaccuracy Phase of Tuberculosis Diagnostics

Stage	Global or Local	Main Questions (Type of Evidence)	Type of Study Designs	Outcomes Evaluated
Before policy	Global	Does the test have the technical requirements and operational potential to improve the diagnosis of tuberculosis?	Controlled field validation and demonstration studies in a limited number of well-controlled settings.	Test accuracy (sensitivity and specificity), surrogate patient-important outcomes (turnaround times, time to diagnosis and treatment, and improvement of case detection in the study population), ease of use, and basic cost comparisons.
Before scale-up	Global and local	What are the test's effectiveness, cost-effectiveness, and operational requirements when used in routine practice?	Designs involve pilot implementations under routine programmatic conditions at the level in the healthcare system at which the tool is intended to be used, focusing on diagnostic algorithms or scenarios in which the tool is incorporated, in a number of countries/settings selected for their representativeness for major epidemiological settings and resource levels. Designs include pragmatic, randomized, or cluster-randomized trials, such as those involving a phased-implementation design.	Effectiveness data to be collected would include improvement in case detection, time until treatment initiation, pretreatment morbidity and mortality, and treatment outcomes. Cost and effectiveness data would cover the entire process and include diagnostic and treatment costs, both for the health system and for the patient. Operational data would include infrastructural and human resource requirements and practical constraints to implementation.
During and after scale-up	Local	Is the new diagnostic tool implemented to its optimum effect? What are constraints in scale-up, cost, and resource projections to reach and sustain full scale-up? What is epidemiological impact?	Designs primarily involve monitoring and evaluation of data sets from routine recording and reporting systems. Targeted operational studies may be needed, as well as larger studies to estimate the epidemiological impact of the new diagnostic scenario, such as population surveys of the prevalence of tuberculosis or tuberculous mycobacterial infection or representative surveys of drug resistance.	Indicators involve use of the test and associated resources; changes in case notifications of tuberculosis and drug-resistant tuberculosis, in tuberculosis incidence and prevalence, in proportions of patients who test positive, in treatment delay, and in treatment outcomes; changes in patient expenditures for tuberculosis diagnosis; and broader effects on the health system, such as integration of diagnostic services for various disorders. These indicators would be monitored over time and between relevant segments of the population.

Cobelens F, van den Hof S, Pai M et al. *Journal of Infect Dis* 2012

If we do end up scaling-up new tools, how will we know they have an impact?

INT J TUBERC LUNG DIS 14(12):1506–1507

EDITORIAL

Assessing the impact of new diagnostics on tuberculosis control

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Use modeling to estimate public health or epidemiological impact

If a test is scaled up and implemented widely, will it save lives or decrease disease burden at the population level?

Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics

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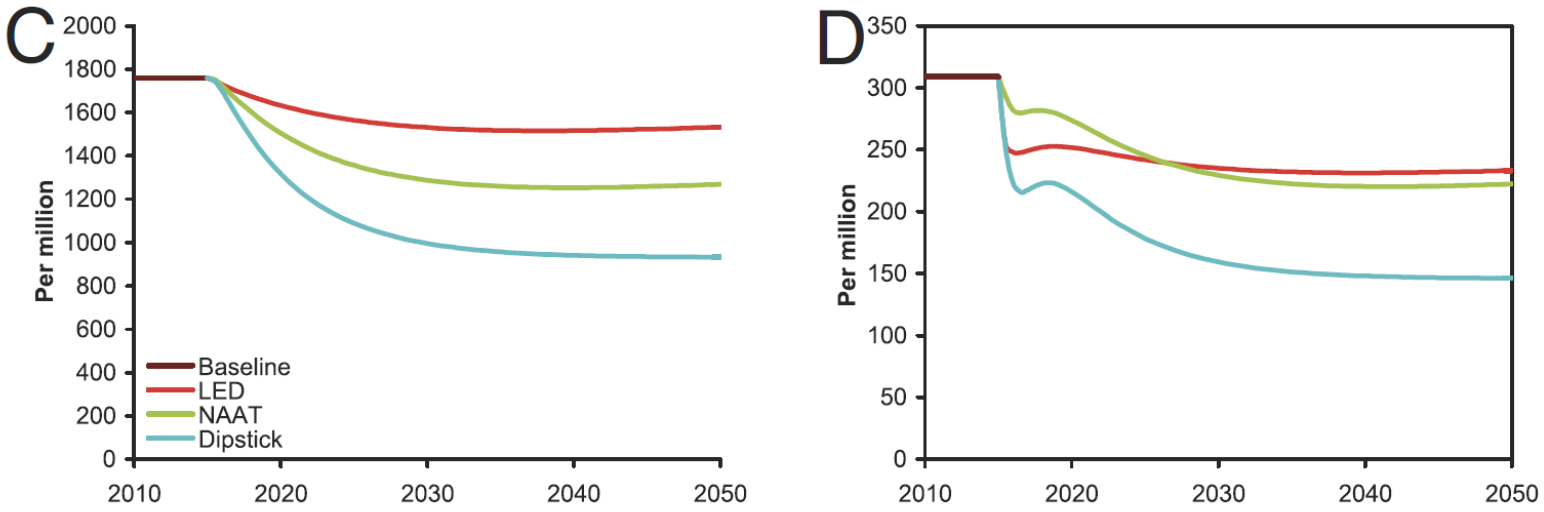

Effect by year up to 2050 of interventions and strategies begun in 2015 on TB (all-types) incidence per million (*left*) and TB related mortality (right) per million

Use routine monitoring data to make inferences on likely impact

Major Reduction in Anti-Malarial Drug Consumption in Senegal after Nation-Wide Introduction of Malaria Rapid Diagnostic Tests

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Abstract

Background: While WHO recently recommended universal parasitological confirmation of suspected malaria prior to treatment, debate has continued as to whether wide-scale use of rapid diagnostic tests (RDTs) can achieve this goal. Adherence of health service personnel to RDT results has been poor in some settings, with little impact on anti-malarial drug consumption. The Senegal national malaria control programme introduced universal parasite-based diagnosis using malaria RDTs from late 2007 in all public health facilities. This paper assesses the impact of this programme on anti-malarial drug consumption and disease reporting.

Methods and Findings: Nationally-collated programme data from 2007 to 2009 including malaria diagnostic outcomes, prescription of artemisinin-based combination therapy (ACT) and consumption of RDTs in public health facilities, were reviewed and compared. Against a marked seasonal variation in all-cause out-patient visits, non-malarial fever and confirmed malaria, parasite-based diagnosis increased nationally from 3.9% of reported malaria-like febrile illness to 86.0% over a 3 year period. The prescription of ACT dropped throughout this period from 72.9% of malaria-like febrile illness to 31.5%, reaching close equivalence to confirmed malaria (29.9% of 584873 suspect fever cases). An estimated 516576 courses of inappropriate ACT prescription were averted.

Conclusions: The data indicate high adherence of anti-malarial prescribing practice to RDT results after an initial run-in period. The large reduction in ACT consumption enabled by the move from symptom-based to parasite-based diagnosis demonstrates that effective roll-out and use of malaria RDTs is achievable on a national scale through well planned and structured implementation. While more detailed information on management of parasite-negative cases is required at point of care level to assess overall cost-benefits to the health sector, considerable cost-savings were achieved in ACT procurement. Programmes need to be allowed flexibility in management of these funds to address increases in other programmatic costs that may accrue from improved diagnosis of febrile disease.

Citation: Thiam S, Thior M, Faye B, Ndiop M, Diouf ML, et al. (2011) Major Reduction in Anti-Malarial Drug Consumption in Senegal after Nation-Wide Introduction of Malaria Rapid Diagnostic Tests. PLoS ONE 6(4): e18419. doi:10.1371/journal.pone.0018419

Conduct implementation studies to assess impact (e.g. stepped-wedge trials)

A

Cluster	Pre-innovation study period →	Post-innovation study period →
1	Control	Innovation
2	Control	Innovation

B

Cluster	Study period →
1	Innovation
2	Innovation
3	Control
4	Control

C

Cluster	Study period →	Study period →
1	Innovation	Control
2	Innovation	Control
3	Control	Innovation
4	Control	Innovation

D

Cluster	Study period →				
	1	2	3	4	5
1	Control	Innovation	Innovation	Innovation	Innovation
2	Control	Control	Innovation	Innovation	Innovation
3	Control	Control	Control	Innovation	Innovation
4	Control	Control	Control	Control	Innovation

Figure Illustration of different cluster-randomised trial designs with concurrent innovation and comparator arms: **A**) before and after; **B**) parallel groups; **C**) cross-over; **D**) stepped-wedge.

Squire B et al. IJTLD 2011

Before and after comparisons

Bastiaens *et al. Malaria Journal* 2011, **10**:76
http://www.malariajournal.com/content/10/1/76

RESEARCH Open Access

Malaria diagnostic testing and treatment practices in three different *Plasmodium falciparum* transmission settings in Tanzania: before and after a government policy change

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Abstract

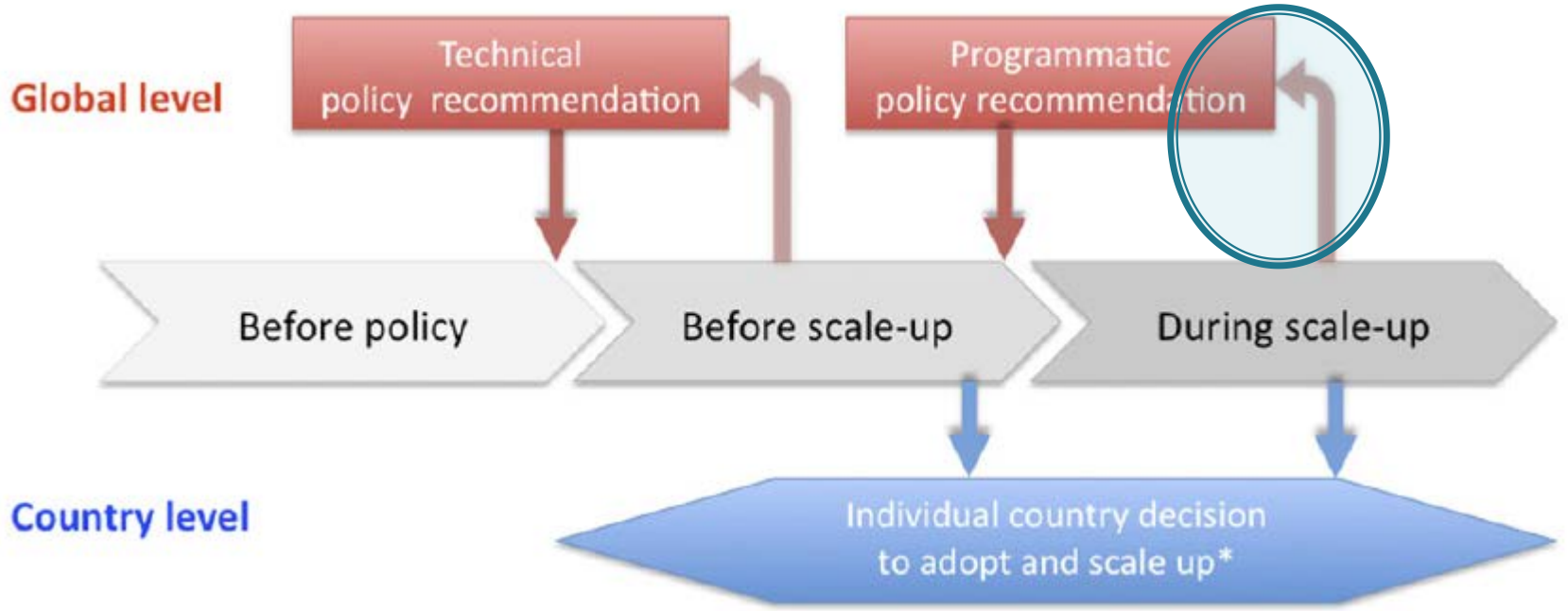
Background: Patterns of decreasing malaria transmission intensity make presumptive treatment of malaria an unjustifiable approach in many African settings. The controlled use of anti-malarials after laboratory confirmed diagnosis is preferable in low endemic areas. Diagnosis may be facilitated by malaria rapid diagnostic tests (RDTs). In this study, the impact of a government policy change, comprising the provision of RDTs and advice to restrict anti-malarial treatment to RDT-positive individuals, was assessed by describing diagnostic behaviour and treatment decision-making in febrile outpatients <10 years of age in three hospitals in the Kagera and Mwanza Region in northern Tanzania.

Methods: Prospective data from Biharamulo and Rubya Designated District Hospital (DDH) were collected before and after policy change, in Sumve DDH no new policy was implemented. Diagnosis of malaria was confirmed by RDT; transmission intensity was evaluated by a serological marker of malaria exposure in hospital attendees.

Results: Prior to policy change, there was no evident association between the actual level of transmission intensity and drug-prescribing behaviour. After policy change, there was a substantial decrease in anti-malarial prescription and an increase in prescription of antibiotics. The proportion of parasite-negative individuals who received anti-malarials decreased from 89.1% (244/274) to 38.7% (46/119) in Biharamulo and from 76.9% (190/247) to 10.0% (48/479) in Rubya after policy change.

Conclusion: This study shows that an official policy change, where RDTs were provided and healthcare providers were advised to adhere to RDT results in prescribing drugs can be followed by more rational drug-prescribing behaviour. The current findings are promising for improving treatment policy in Tanzanian hospitals.

Impact (or lack thereof) should then help revise policies



Cobelens F, van den Hof S, Pai M et al. *Journal of Infect Dis* 2012

Key messages

- TB dx pipeline is the best it has ever been
  - There are a few key gaps in the pipeline that should be addressed, hopefully, in the coming 5 years
    - POC and predictive LTBI tests will require the biomarker field to rapidly produce tangible results!
    - TPPs still need to be worked out
    - TPPs without business models are unlikely to have impact
- But without scale up, we cannot achieve impact
  - New tools are necessary but not sufficient
  - Policies are necessary but not sufficient
  - Policies must be implemented to achieve scale-up
- Good guideline and policy making requires data that goes beyond test accuracy
- Once policies are made, we need to overcome major challenges to ensure scale up of technologies
  - Scale-up is a country level issue and that is where the biggest challenges are
  - Scale-down (e.g. serology) is also a country level issue and not all countries scale-down bad tests
- After scale-up, we need to measure epidemiological and public health impact of new technologies