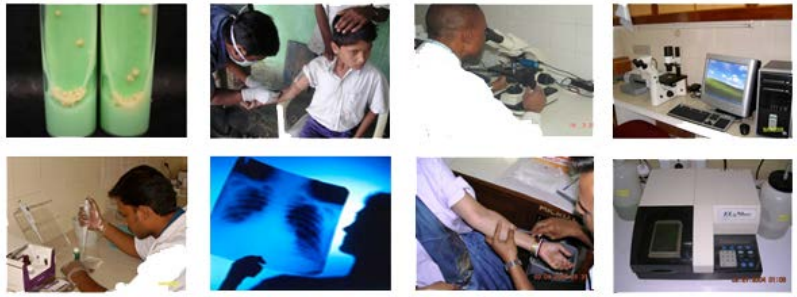
TB diagnostics: value chain, pipeline, and gaps



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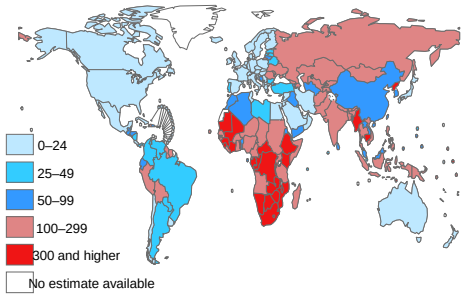
Disclosure

- No industry/financial conflicts
- I co-chair the Stop TB Partnership's New Diagnostics Working Group
- I consult for the Bill & Melinda Gates Foundation
- I have previously consulted for FIND, Geneva

The Global Burden of TB -2009



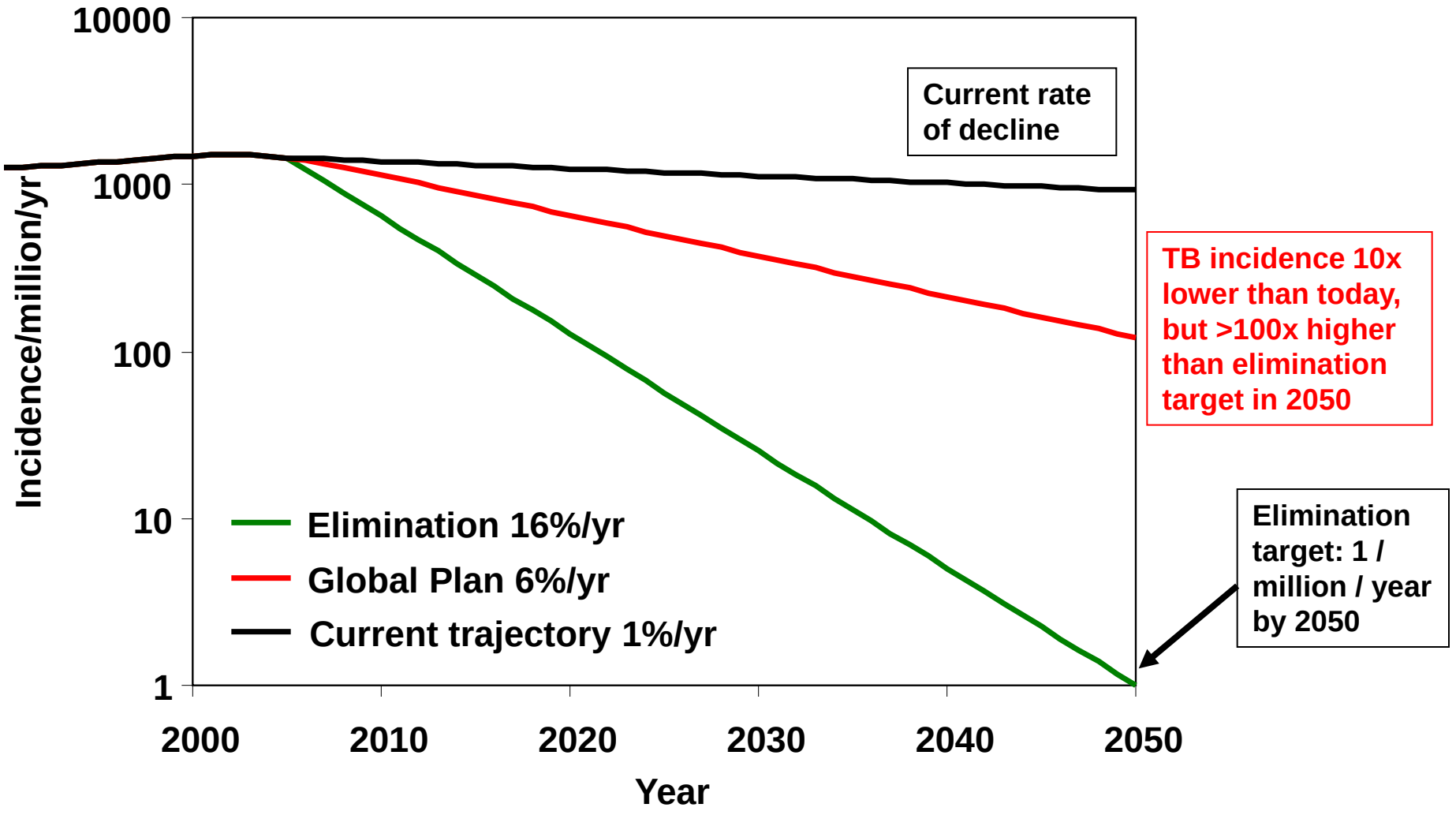
	Estimated number of cases	Estimated number of deaths
All forms of TB	9.4 million (range: 8.9–9.9 million)	1.7 million* (range: 1.5–2.0 million)
HIV-associated TB	1.1 million (12%) (range: 1.0–1.2 million)	380,000 (range: 320,000–450,000)
Multidrug-resistant TB (MDR-TB)	440,000 (range: 390,000–510,000)	about 150,000

**including deaths among PLHIV*

Courtesy: WHO Stop TB Department

World Health Organization

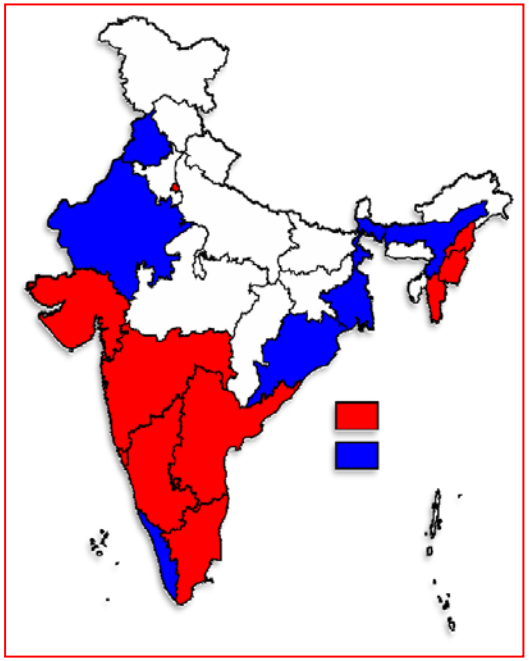
Full implementation of Global Plan: 2015 MDG target reached but TB not eliminated by 2050



Courtesy: WHO Stop TB Department

India as a case study: country with largest number of TB cases in the world

100% of the Indian population is covered by the DOTS program



TB Burden in India, despite 100% DOTS coverage and meeting 70/85 targets

THE TIMES OF INDIA | India

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2m new TB cases in India last year

Kounteya Sinha, TNN, Nov 15, 2010, 04.21am IST

Article | Comments | AA | MORE

Tags: Tuberculosis | TB Cases

SHARE AND DISCUSS

NEW DELHI: India is saddled with highest burden of tuberculosis — with nearly 2 million new cases recorded in 2009. Out of an estimated 1.3 million people who died of TB in 2008, the nation alone accounted for 2.8 lakh lives.

FACTBOX - India's state of health, how it compares with others

Ranbir, 26 months old, lies on a bed in the Nutritional Rehabilitation Centre in Shivpuri district in the central Indian state of Madhya Pradesh April 7, 2010.
Credit: Reuters/Reinhard Krause/Files

HONG KONG | Tue Jan 11, 2011 6:57pm IST

(Reuters) - Despite India's rapid economic growth its healthcare system has remained in the doldrums and is struggling with high rates of child and maternal deaths, malaria, tuberculosis (TB) and a growing problem with chronic diseases.

Related News

Sickly India needs universal healthcare by 2020
Jan 11, 2011

Britain is tuberculosis capital of Europe - report
Dec 17, 2010

Iraqi refugees match Californians in obesity rates
Dec 17, 2010

Major push could end malaria deaths by 2015: WHO

India had 2 million new cases of TB in 2009, and it killed 280,000 people that year

New goal this year: Universal access

TB eradication programme gets new look, may get new logo too

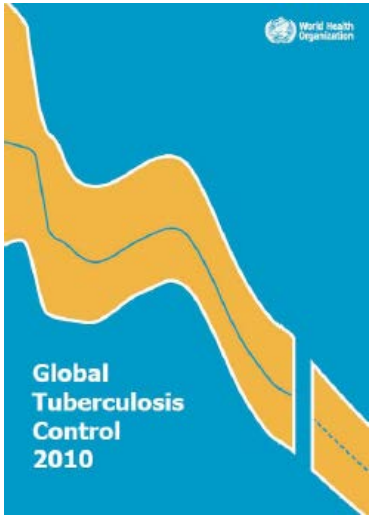
TNN, Mar 24, 2011, 04.43am IST

LUCKNOW: A new area of focus has been fixed for the revised national tuberculosis control programme. A government release said that having achieved global objectives of new case-detection of 70% and treatment success rate of 85% for the last three consecutive years, the National Tuberculosis Control Programme (NTCP) is being revised. Its new objective would be `universal access to quality TB care for all TB patients'. The new logo would be launched in the city on Thursday.

Under this, all TB patients in the community, including vulnerable and marginalised persons, will have access to early, good quality diagnosis and treatment services. The intermediate target is to detect 90% of all TB cases and successfully treat 90% of them by 2015. The new objective of Universal Access will be marked by the launch of a new DOTS logo that will be in use from World TB control awareness day 2011 being observed on Thursday.

Although the program is now more ambitious, India cannot accomplish universal access without scaling up new diagnostics, and improving delivery

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]

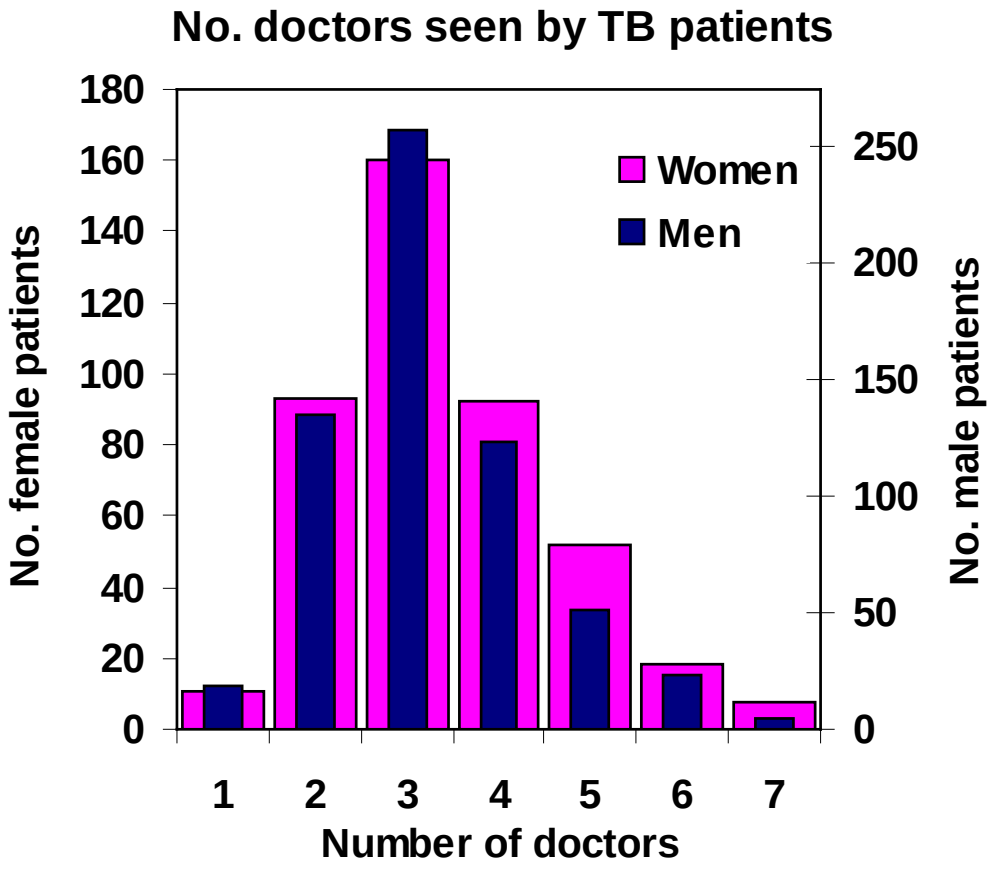
Address: [1]Department of International Health, Institute of General Practice and Community Medicine, University of Oslo, PO Box 1130 Blindern, N-0318 Oslo, Norway and [2]Competence Centre for Imported and Tropical Diseases, Ullevål University Hospital, Oslo, Norway

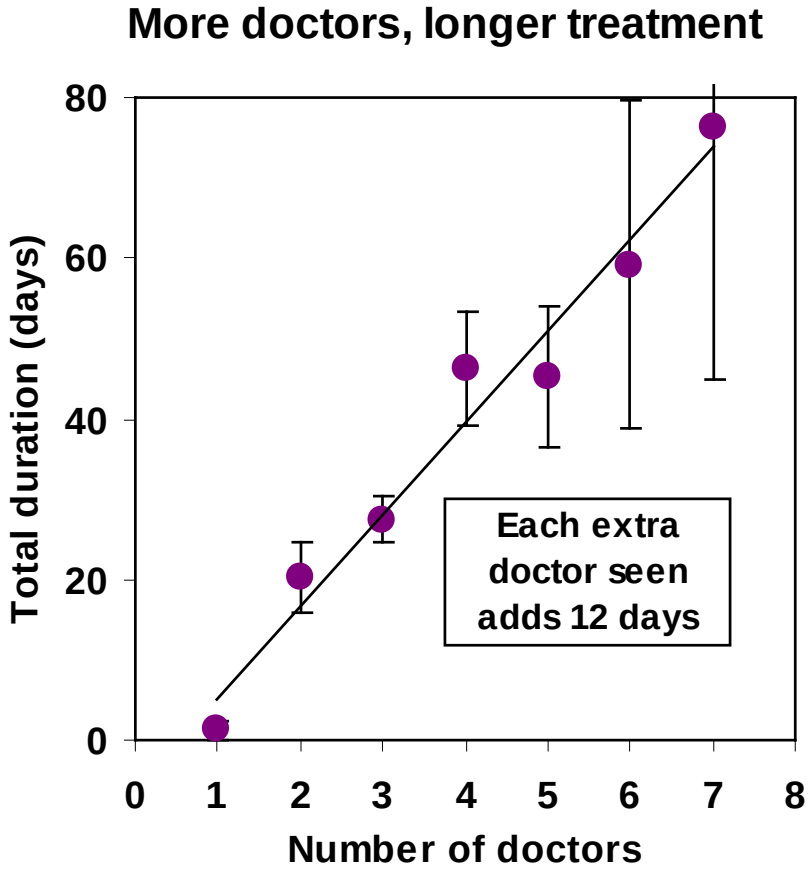
Only 63% of all forms of TB are notified

Average delays are as long as 2 – 3 months!

Doctors and delays, Bangalore

–Slide by Chris Dye





Pantoja 2009

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

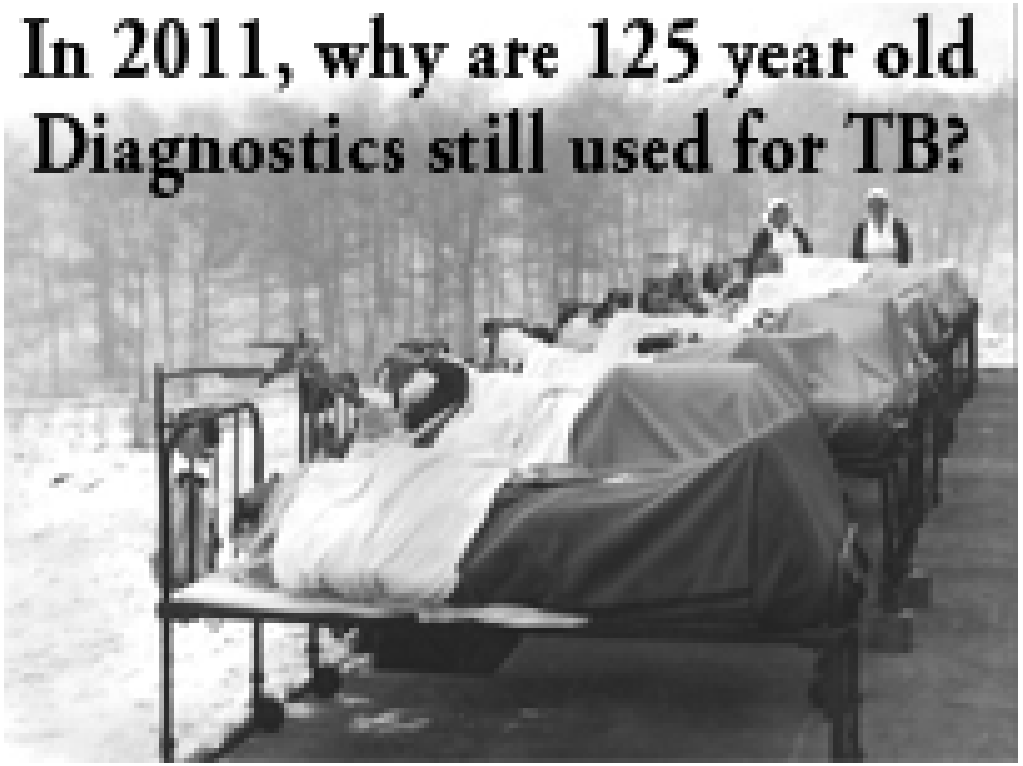
The Population Dynamics and Control of Tuberculosis

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 elimination is impossible with current tools



http://www.worldcarecouncil.org

TB diagnostics pipeline in 2011

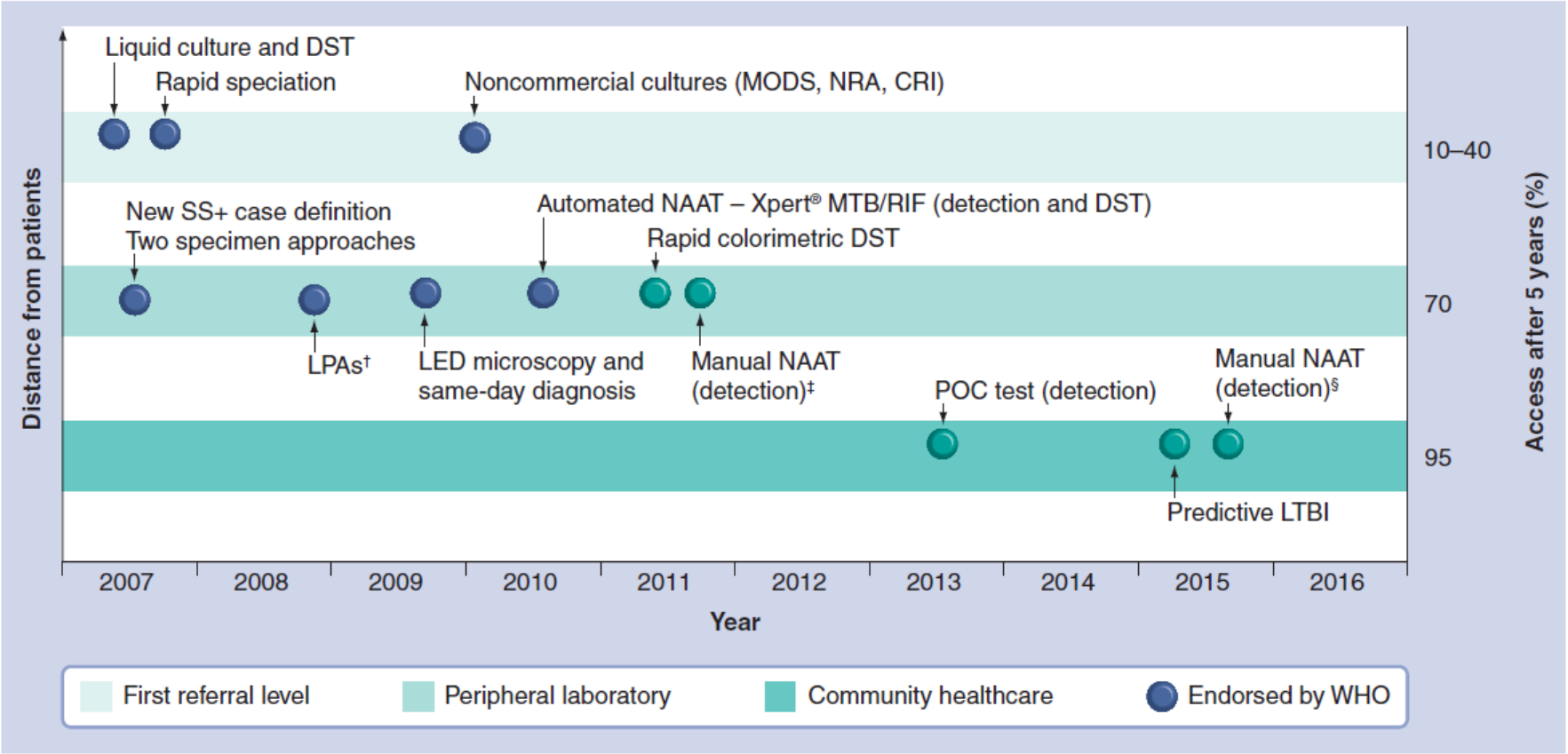


Figure 1. TB diagnostics pipeline in 2011.
†Manual NAAT: technology for MTB drug-susceptibility testing.
‡Manual NAAT: technology for MTB detection at the peripheral laboratory.
§Manual NAAT: technology for MTB detection at the community healthcare level.
CRI: Colorimetric redox indicator assay; DST: Drug-susceptibility test; LED: Light-emitting diode; LPA: Line probe assay; LTBI: Latent TB infection; MODS: Microscopic observation drug susceptibility; MTB: Mycobacterium tuberculosis; NAAT: Nucleic acid amplification test; NRA: Nitrate reductase assay; POC: Point of care; RIF: Resistance to rifampicin; SS+: Sputum smear-positive.
Adapted with permission from [6].

Courtesy: STP NDWG

Gaps in the pipeline and unmet needs

Key messages:

- The highest priorities questions are:
  (i) the identification of bacterial and/or host molecules that differentiate between persons in different stages of the disease spectrum,
  and
  (ii) the simplification and validation of novel tools for diagnosis at point of care level.

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

- Particular reference was made to the *need to identify combinations of methods to gather useful specimens in children.*

- Of high importance also is the definition and evaluation of performance of new *diagnostic tests* in terms of feasibility, cost-effectiveness, reduction in diagnostic delay, and impact on clinical decision-making and patient benefit.

- Another high priority is the development of a systemic marker of *bacterial load* in TB through various samples and methods;

- The automated NAAT technology is a "game-changer" for TB control, but needs to be decentralized to the point-of-treatment and implementation scaled up rapidly to achieve a population level impact, particularly in resource-limited settings.

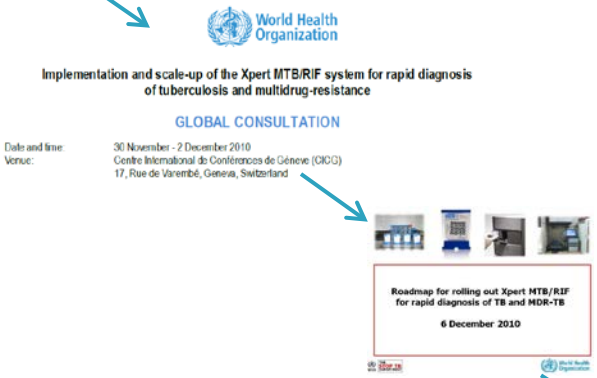
Biomarker and basic research

"Post-efficacy, post-policy pathway"

Value chain

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



Scale-up at the country level & impact

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 there are too many options, how do decisions get made?
  - If a tool is scaled up, how do we measure “impact”?
    - If there is no impact, how do we go back and revise policies?

Variations in diagnostics value chain/pathways

1. Phased evaluation of medical tests
2. WHO pathway
3. NDWG blueprint
4. FIND pathway
5. IAF

Phased evaluation of medical tests

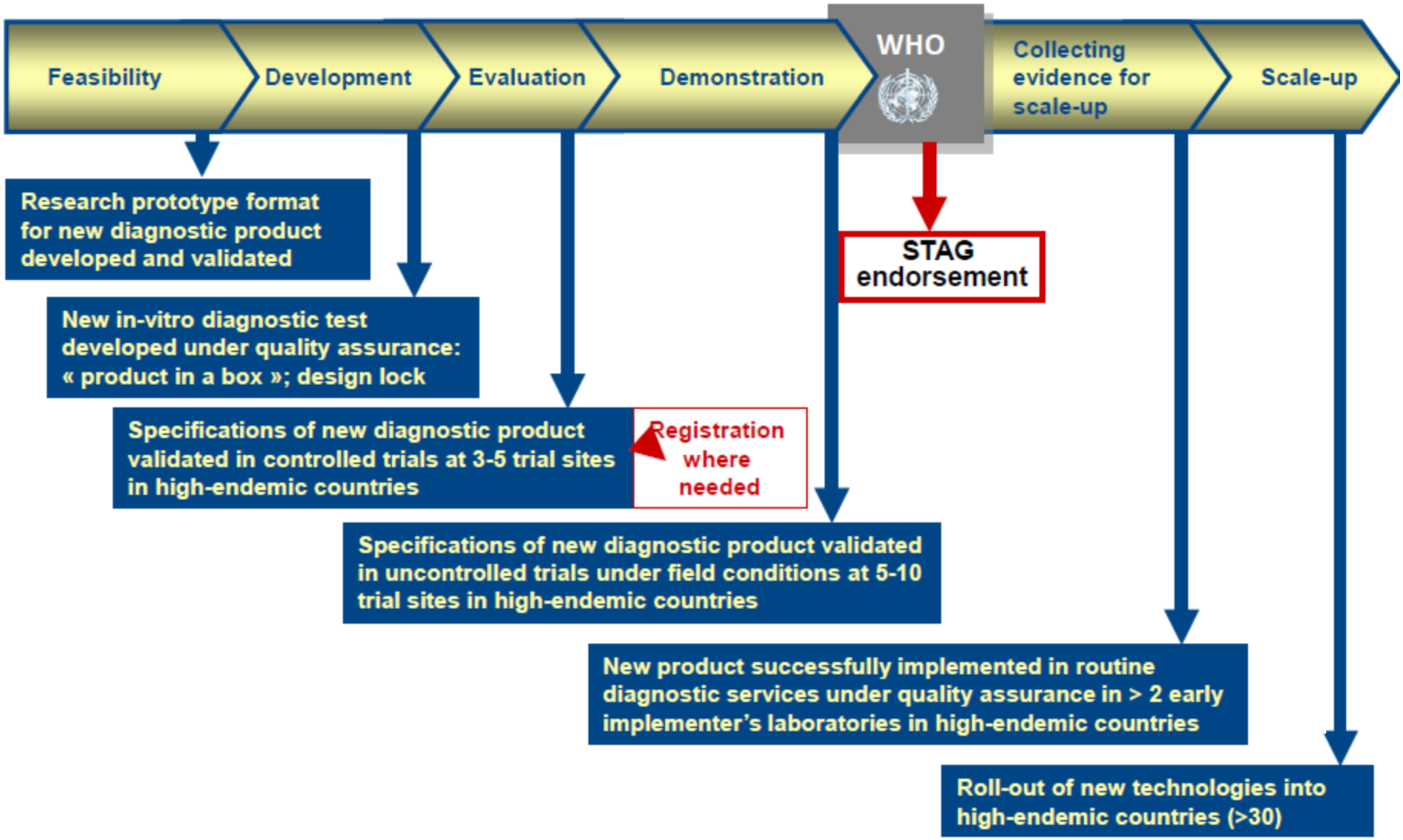
Levels/Phases
Technical efficacy
Intended use
Diagnostic accuracy
Usual range
Subgroups
Clinical population
Diagnostic thinking efficacy
Therapeutic efficacy
Patient outcome efficacy
Societal efficacy

Proposals for a Phased Evaluation of Medical Tests

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

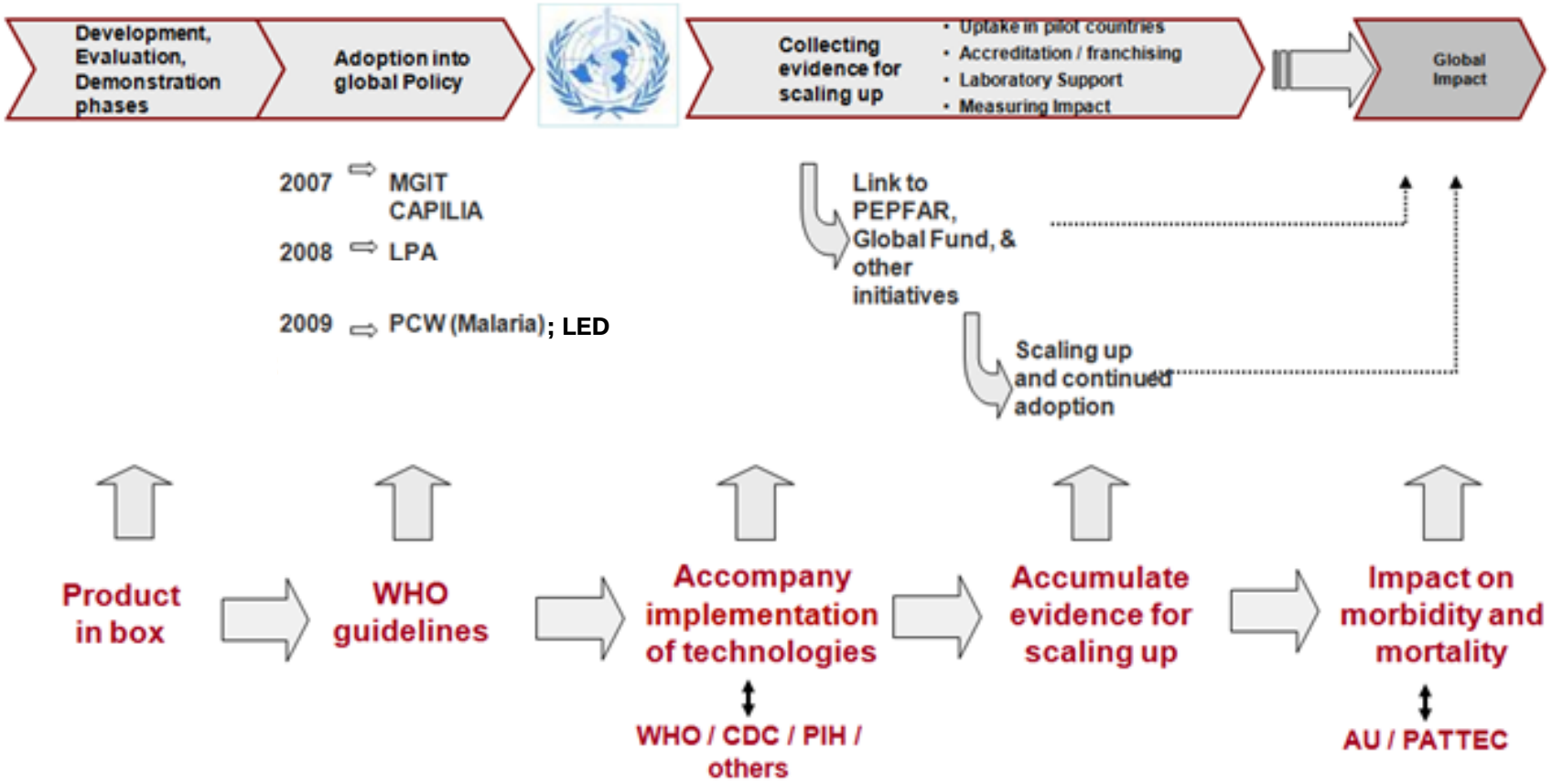
Med Desic Making 2009

WHO process (newly revised)



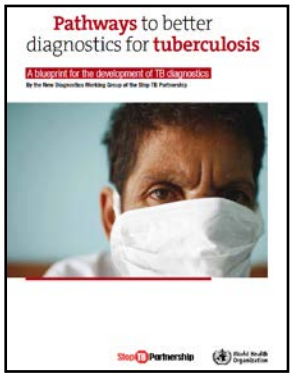
Source: Dr Karin Weyer, WHO

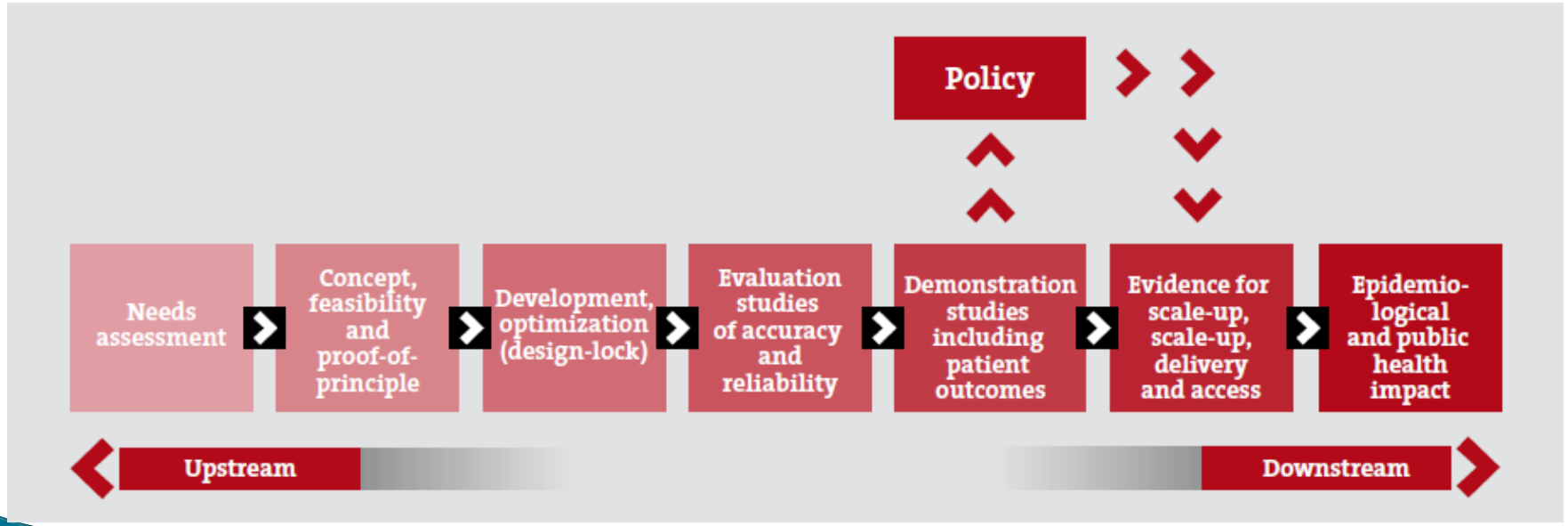
FIND



Courtesy: Foundation for Innovative New Diagnostics, Geneva

NDWG blueprint (original)





NDWG blueprint (revised)

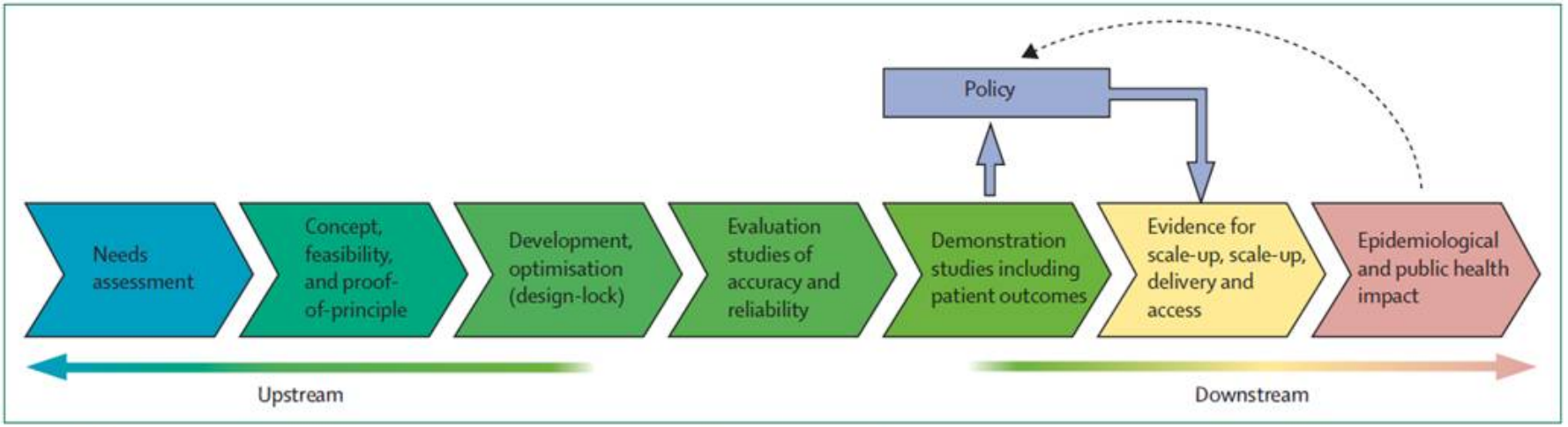


Figure 4: **Schematic showing the pathway to tuberculosis diagnostics, from concept to delivery**
Source: Stop TB Partnership's New Diagnostics Working Group. Pathways to better diagnostics for tuberculosis: a blueprint for the development of TB diagnostics (2009),[180] and reproduced with permission from author and publisher.

Wallis RS, Pai M, et al. Lancet 2010

Layer of assessment	Kinds of question(s) being addressed	References to studies addressing these questions
Layer 1 Effectiveness analysis	How well does the new tool work in terms of accuracy?	16
	How many additional cases will be identified who would otherwise not have been identified?	20
	How many additional cases will actually start (and complete) treatment as a result of using the new tool?	21
Layer 2 Equity analysis	Who benefits from the new tool (ambulant vs. hospitalised, poor/less poor, men/women, adults/children)?	27
	Why do these benefits accrue (level health system in which new diagnostic is deployed, change in time to issue of results, change in patient costs)?	22
Layer 3 Health system analysis	What are the human resource implications of introducing the new tool (training, number and cadre of staff)?	19
	What are the infrastructure implications (equipment, laboratory layout, safety installations)?	23
	What are the procurement implications (reagents, consumables, documentation)?	28
	What are the implications for quality assurance (internal and external)?	17
Layer 4 Scale-up analysis	What are the projected impacts of going to scale with the new tool? 1 Cost savings to patients in relation to income 2 Cost savings to health providers/ the health system 3 Effects on transmission of improved infection control as a result of the new tool	18
Layer 5 Policy analysis	What other similar technologies are available or likely to become available?	29
	How do similar existing or emerging technologies compare in their projected performance within each of the layers above?	25

Impact Assessment Framework

1 Layer 1: Effectiveness analysis
2 Layer 2: Equity analysis
3 Layer 3: Health systems analysis
4 Layer 4: Scale-up analysis
5 Layer 5: Policy analysis

Mann G et al. IJTLD 2010

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

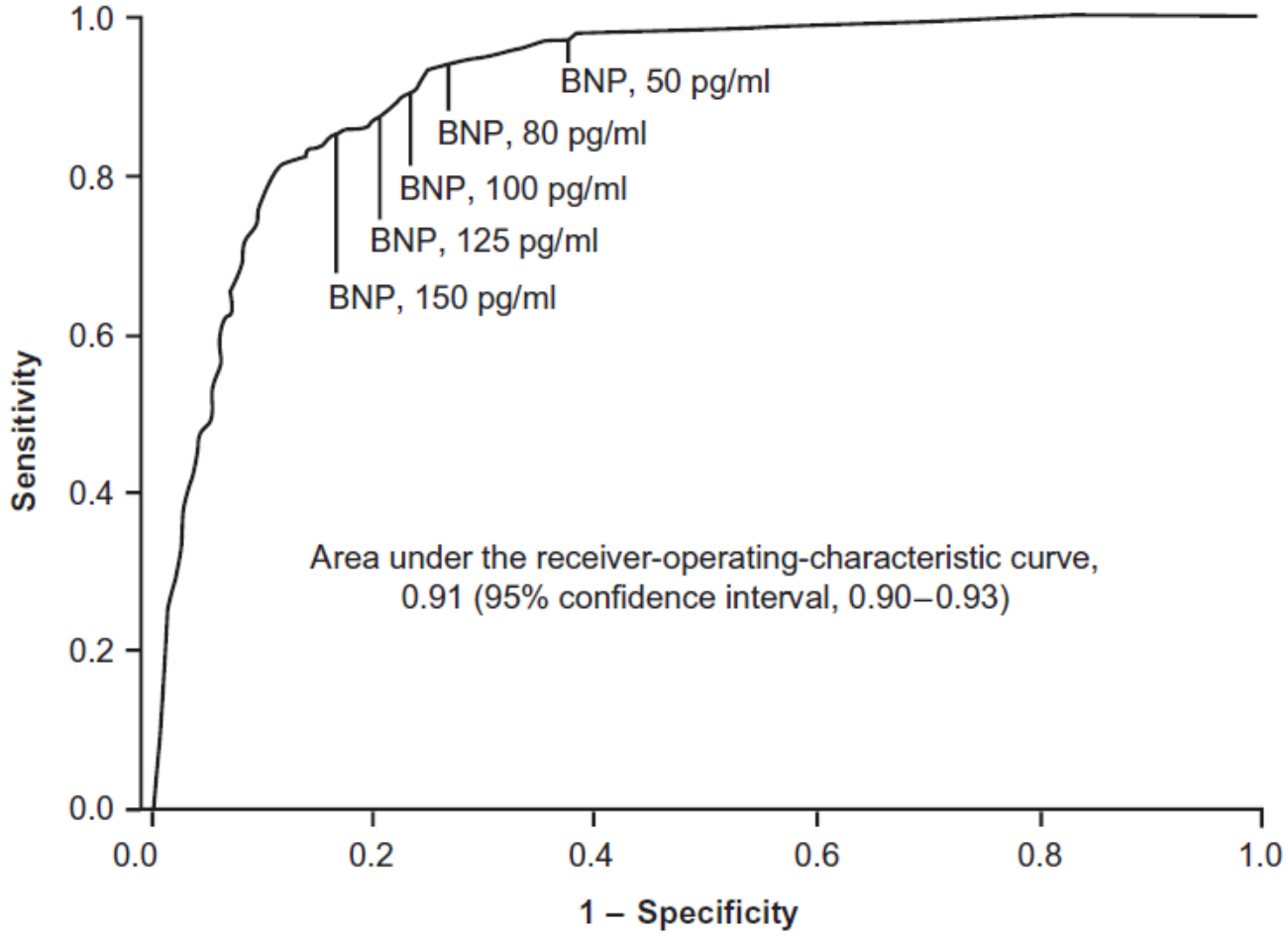
Test, # Studies (participants)	Design	Limitations	Directness	Inconsistency	Imprecise or sparse data	Publication Bias	Evidence Quality
MODS, 9 (1474)	CS & CC	Low	No evidence **-1**	Low	Low	Possible	Moderate
NRA, 19 (2304)	CS & CC	Low	No evidence **-1**	Low	Low	Possible	Moderate
CRI, 31 (2498)	CS & CC	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

Test accuracy may or may not result in clinical impact (on patient outcomes)

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.

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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

Kyabayinze *et al. Malaria Journal* 2010, **9**:200
http://www.malariajournal.com/content/9/1/200

MALARIA JOURNAL

RESEARCH **Open Access**

Use of RDTs to improve malaria diagnosis and fever case management at primary health care facilities in Uganda

Daniel J Kyabayinze*[1], Caroline Asiimwe[1], Damalie Nakanjako[2], Jane Nabakooza[3], Helen Counihan[4] and James K Tibenderana[1,5]

Abstract

Background: Early and accurate diagnosis of malaria followed by prompt treatment reduces the risk of severe disease in malaria endemic regions. Presumptive treatment of malaria is widely practised where microscopy or rapid diagnostic tests (RDTs) are not readily available. With the introduction of artemisinin-based combination therapy (ACT) for treatment of malaria in many low-resource settings, there is need to target treatment to patients with parasitologically confirmed malaria in order to improve quality of care, reduce over consumption of anti-malarials, reduce drug pressure and in turn delay development and spread of drug resistance. This study evaluated the effect of malaria RDTs on health workers' anti-malarial drug (AMD) prescriptions among outpatients at low level health care facilities (LLHCF) within different malaria epidemiological settings in Uganda.

Methods: All health workers (HWs) in 21 selected intervention (where RDTs were deployed) LLHF were invited for training on the use RDTs. All HWs were trained to use RDTs for parasitological diagnosis of all suspected malaria cases irrespective of age. Five LLHCFs with clinical diagnosis (CD only) were included for comparison. Subsequently AMD prescriptions were compared using both a 'pre - post' and 'intervention - control' analysis designs. In-depth interviews of the HWs were conducted to explore any factors that influence AMD prescription practices.

Results: A total of 166,131 out-patient attendances (OPD) were evaluated at 21 intervention LLHCFs. Overall use of RDTs resulted in a 38% point reduction in AMD prescriptions. There was a two-fold reduction (RR 0.62, 95% CI 0.55-0.70) in AMD prescription with the greatest reduction in the hypo-endemic setting (RR 0.46 95% CI 0.51-0.53) but no significant change in the urban setting (RR1.01, p-value = 0.820). Over 90% of all eligible OPD patients were offered a test. An average of 30% (range 25%-35%) of the RDT-negative fever patients received AMD prescriptions. When the test result was negative, children under five years of age were two to three times more likely (OR 2.6 p-value <0.001) to receive anti-malarial prescriptions relative to older age group. Of the 63 HWs interviewed 92% believed that a positive RDT result confirmed malaria, while only 49% believed that a negative RDT result excluded malaria infection.

Conclusion: Use of RDTs resulted in a 2-fold reduction in anti-malarial drug prescription at LLHCFs. The study demonstrated that RDT use is feasible at LLHCFs, and can lead to better targetting of malaria treatment. Nationwide deployment of RDTs in a systematic manner should be prioritised in order to improve fever case management. The process should include plans to educate HWs about the utility of RDTs in order to maximize acceptance and uptake of the diagnostic tools and thereby leading to the benefits of parasitological diagnosis of malaria.

Example: rapid HIV tests

Accuracy

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PLoS one

Evaluation of Diagnostic Accuracy, Feasibility and Client Preference for Rapid Oral Fluid-Based Diagnosis of HIV Infection in Rural India

Nitika Pant Pai[1]*, Rajnish Joshi[2], Sandeep Dogra[3], Bharati Taksande[2], S. P. Kalantri[2], Madhukar Pai[4], Pratibha Narang[2], Jacqueline P. Tulsky[5], Arthur L. Reingold[6]

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Background. Oral fluid-based rapid tests are promising for improving HIV diagnosis and screening. However, recent reports from the United States of false-positive results with the oral OraQuick® ADVANCE HIV1/2 test have raised concerns about their performance in routine practice. We report a field evaluation of the diagnostic accuracy, client preference, and feasibility for the oral fluid-based OraQuick® Rapid HIV1/2 test in a rural hospital in India. ***Methodology/Principal Findings***.. A cross-sectional, hospital-based study was conducted in 450 consenting participants with suspected HIV infection in rural India. The objectives were to evaluate performance, client preference and feasibility of the OraQuick® Rapid HIV-1/2 tests. Two Oraquick® Rapid HIV1/2 tests (oral fluid and finger stick) were administered in parallel with confirmatory ELISA/Western Blot (reference standard). Pre- and post-test counseling and face to face interviews were conducted to determine client preference. Of the 450 participants, 146 were deemed to be HIV sero-positive using the reference standard (seropositivity rate of 32% (95% confidence interval [CI] 28%, 37%)). The OraQuick test on oral fluid specimens had better performance with a sensitivity of 100% (95% CI 98, 100) and a specificity of 100% (95% CI 99, 100), as compared to the OraQuick test on finger stick specimens with a sensitivity of 100% (95% CI 98, 100), and a specificity of 99.7% (95% CI 98.4, 99.9). The OraQuick oral fluid-based test was preferred by 87% of the participants for first time testing and 60% of the participants for repeat testing. ***Conclusion/Significance***. In a rural Indian hospital setting, the OraQuick® Rapid- HIV1/2 test was found to be highly accurate. The oral fluid-based test performed marginally better than the finger stick test. The oral OraQuick test was highly preferred by participants. In the context of global efforts to scale-up HIV testing, our data suggest that oral fluid-based rapid HIV testing may work well in rural, resource-limited settings.

Citation: Pant Pai N, Joshi R, Dogra S, Taksande B, Kalantri SP, et al (2007) Evaluation of Diagnostic Accuracy, Feasibility and Client Preference for Rapid Oral Fluid-Based Diagnosis of HIV Infection in Rural India. PLoS ONE 2(4): e367. doi:10.1371/journal.pone.0000367

Example: rapid HIV tests

Clinical impact

OPEN ACCESS Freely available online PLOS MEDICINE

Impact of Round-the-Clock, Rapid Oral Fluid HIV Testing of Women in Labor in Rural India

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Methods and Findings

After they provided written informed consent, women admitted to the labor ward of a rural teaching hospital in India were offered two rapid tests on oral fluid and finger-stick specimens (OraQuick Rapid HIV-1/HIV-2 tests, OraSure Technologies). Simultaneously, venous blood was drawn for conventional HIV ELISA testing. Western blot tests were performed for confirmatory testing if women were positive by both rapid tests and dual ELISA, or where test results were discordant. Round-the-clock (24 h, 7 d/wk) abbreviated prepartum and extended postpartum counseling sessions were offered as part of the testing strategy. HIV-positive women were administered PMTCT interventions. Of 1,252 eligible women (age range 18 y to 38 y) approached for consent over a 9 mo period in 2006, 1,222 (98%) accepted HIV testing in the labor ward. Of these, 1,003 (82%) women presented with either no reports or incomplete reports of prior HIV testing results at the time of admission to the labor ward. Of 1,222 women, 15 were diagnosed as HIV-positive (on the basis of two rapid tests, dual ELISA and Western blot), yielding a seroprevalence of 1.23% (95% confidence interval [CI] 0.61%–1.8%). Of the 15 HIV test–positive women, four (27%) had presented with reported HIV status, and 11 (73%) new cases of HIV infection were detected due to rapid testing in the labor room. Thus, 11 HIV-positive women received PMTCT interventions on account of round-the-clock rapid HIV testing and counseling in the labor room. While both OraQuick tests (oral and finger-stick) were 100% specific, one false-negative result was documented (with both oral fluid and finger-stick specimens). Of the 15 HIV-infected women who delivered, 13 infants were HIV seronegative at birth and at 1 and 4 mo after delivery; two HIV-positive infants died within a month of delivery.

Conclusions

In a busy rural labor ward setting in India, we demonstrated that it is feasible to introduce a program of round-the-clock rapid HIV testing, including prepartum and extended postpartum counseling sessions. Our data suggest that the availability of round-the-clock rapid HIV testing resulted in successful documentation of HIV serostatus in a large proportion (82%) of rural women who were unaware of their HIV status when admitted to the labor room. In addition, 11 (73%) of a total of 15 HIV-positive women received PMTCT interventions because of round-the-clock rapid testing in the labor ward. These findings are relevant for PMTCT programs in developing countries.

Example: RIDTs

Accuracy

OPEN ACCESS Freely available online

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

Separating clinical from 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 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. If Xpert is scaled-up in a country, 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

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?
    - WHO policy, for example, is useful, but not sufficient
    - Confusion on which test to scale up and when
    - Feasibility, cost-effectiveness, fit with algorithms, HR and lab implications, delivery models, willingness to pay, price point analysis, etc.
- 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
      - 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 and cost-effectiveness
    - 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

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PLoS one

Retooling National TB Control Programmes (NTPs) with New Diagnostics: The NTP Perspective

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Abstract

Background: A delay is evident between the development of new policies on TB diagnostics and their implementation at country level. The Stop TB Partnership would benefit from information from national TB program (NTP) managers on progress towards implementation of new recommendations as well as the opportunities and challenges encountered in the process.

Methods and Findings: To solicit information on the introduction of new TB diagnostics at country level, questionnaires were sent out to NTP managers of high-burden TB countries and a subset of managers was interviewed. The results indicate that about 50% of high-burden TB countries are using the TB diagnostic tools newly recommended by the World Health Organization (WHO). Most NTP managers reported that new diagnostics would only be implemented when officially endorsed by the WHO. All countries have plans to adopt newly endorsed diagnostics at reference laboratory level, while approaches to optimize smear microscopy at lower levels of the health service are given less attention. NTP managers reported diverse challenges to the implementation of new diagnostics.

Conclusions: More information on the obstacles and advantages of introducing new diagnostic tools should be provided to NTP managers to ensure the rational adoption of new diagnostics. A single recommendation covering the introduction of a package of diagnostic tools might be preferable to NTP managers and facilitate implementation in high-burden TB countries.

Citation: van Kampen SC, Ramsay AR, Anthony RM, Klatser PR (2010) Retooling National TB Control Programmes (NTPs) with New Diagnostics: The NTP Perspective. PLoS ONE 5(7): e11649. doi:10.1371/journal.pone.0011649

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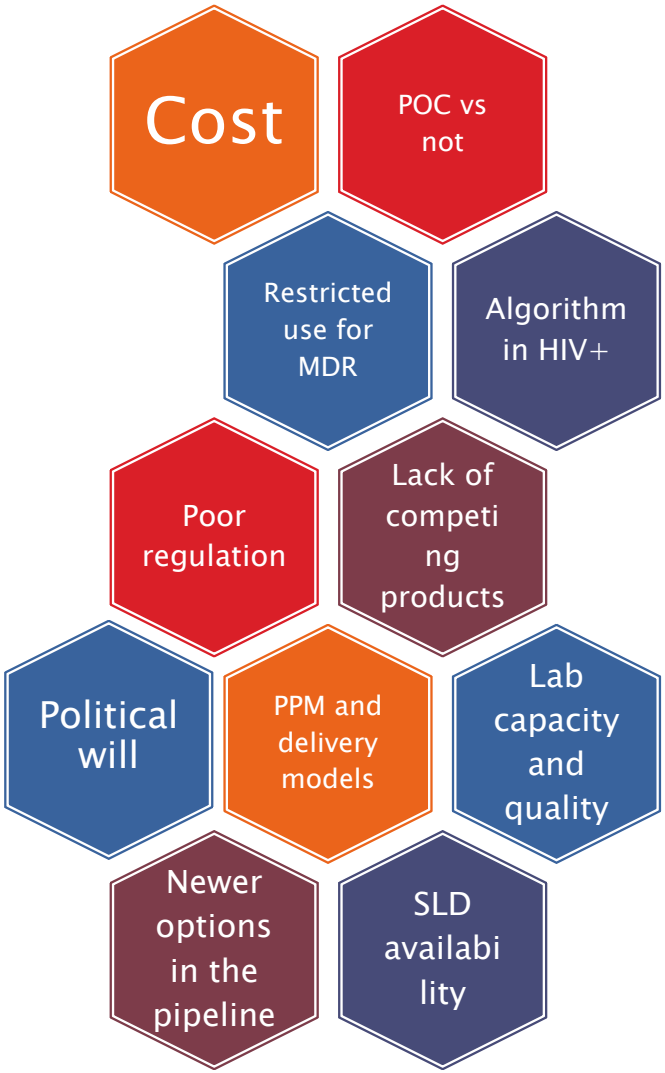
Adoption and scale-up issues in India (for example)

- LED:
  - Not enthusiastic –they had recently purchased a large number of light microscopes
  - LED will replace light microscopes in a phase manner
  - FM EQA under development
- LPA and MGIT:
  - Plan to have 43 culture/DST labs by 2013 [as of now, 27 labs are operational]
  - Building labs is very time consuming, tedious and expensive
    - A few private/NGO labs are accredited, but many more can be engaged
    - Accreditation is time consuming and often delayed
    - Tension between building vs buying services
      - Lack of systems for timely reimbursement is a big problem for buying services from private/NGO sector

Scale-up issues in India (for example)

- 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 planned
    - 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
- Universal access:
  - Most of RNTCP's current lab activities (e.g. culture/DST labs) will help with MDR-TB management, but the effort on thinking, planning, funding for activities that will contribute to universal access is currently insufficient.
  - The focus is not really on improving diagnosis of drug-sensitive TB and reducing transmission/incidence
  - No clarity on how to address the big problem of diagnostic delays

Challenges for scale-up of Xpert



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

$$$

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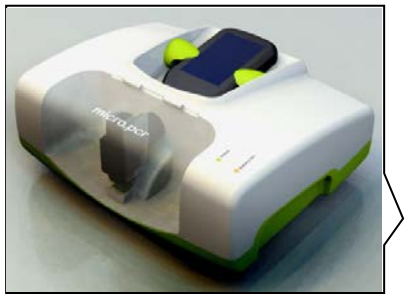

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FIND-negotiated volume/price relationship

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$ 14.00**	**US$ 10.72**
Ave % Reduction over EU*	**72%**	**75%**	**79%**	**84%**

*Average cost per cartridge in EU €60

Volume-based price negotiations

Low-cost generics and innovative tools from BRICS

"frugal engineering and delivery innovation"

Can BRICS lead the next wave of innovations?

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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?

Gates favours cheaper treatment for TB

PTI | 05:03 PM,Mar 24,2011

New Delhi, Mar 24 (PTI) Favouring a cheaper treatment for Tuberculosis, software czar and philanthropist Bill Gates today said the need of the hour was to develop a vaccine for the disease towards which Indian scientists should work."Innovation is the key word. India will be a key for a lot of innovations," Gates said at a press conference here.Lamenting that the tests to check for TB were very slow, he said most of the people who are afflicted with the disease find out only much later and thus their treatment gets delayed.He said that after using the microscope to detect the TB bacteria, a new tool called the GeneXpert is being used.He wished that the Indian scientists would take the "basic idea" and make it more viable and cheap."The most magic thing would be to have a vaccine," he added.India accounts for one-fifth of global TB cases and the government has announced that it is all set to revise its National Tuberculosis Control Programme with a new objective of universal access to quality TB care.Under universal access, all TB patients in the community, including vulnerable and marginalised persons, will have access to early, good quality diagnosis and treatment services.The intermediate target is to detect 90 per cent of all TB cases and successfully treat 90 per cent of them by 2015.India's DOTS programme is the largest in the world in terms of patients initiated on treatment, placing on an average of more than 1,25,000 patients on treatment every month.

India: Success story with generic ARVs and Hep B vaccines

Waning et al. Journal of the International AIDS Society 2010, 13:35
http://www.jiasociety.org/content/13/1/35

JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

SHORT REPORT Open Access

A lifeline to treatment: the role of Indian generic manufacturers in supplying antiretroviral medicines to developing countries

Brenda Waning[1,2*], Ellen Diedrichsen[1], Suerie Moon[3]

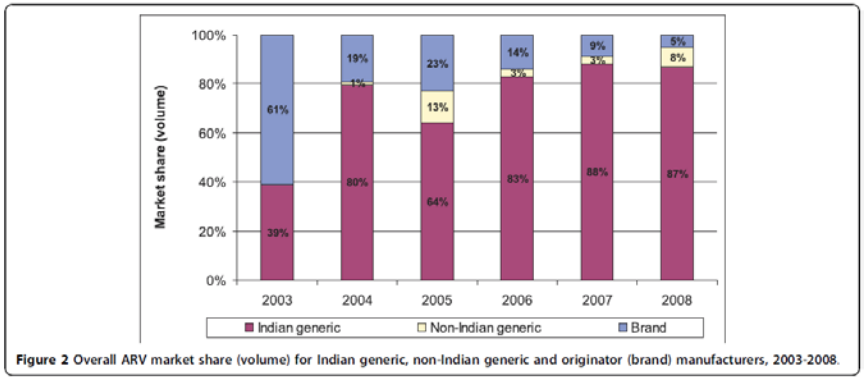


Figure 2 Overall ARV market share (volume) for Indian generic, non-Indian generic and originator (brand) manufacturers, 2003-2008.

CASE STUDY COMMENTARY

India's billion dollar biotech

Justin Chakma, Hassan Masum, Kumar Perampaladas, Jennifer Heys & Peter A Singer

By focusing on an unmet medical need, providing a cost-efficient solution and reinvesting the resulting revenues into R&D and state-of-the-art manufacturing, Shantha Biotechnics was able to build one of India's first biotech successes.

$23 per dose of GSK Hep B vaccine to $0.25 per dose for Shanvac-B

TB diagnostics in India

From importation and imitation to innovation

August 25-26, 2011, Bangalore, India

Host: St. John's Research Institute, Bangalore, India

Sponsors: McGill University & Global Health Strategies

Technical partners: Bill & Melinda Gates Foundation, Foundation for Innovative New Diagnostics, International Centre for Genetic Engineering and Biotechnology (ICGEB), India & Stop TB Partnership

Industry partners: Association of Biotechnology Led Enterprises (ABLE) & Confederation of Indian Industry (CII)

Media partners: BioSpectrum Asia, Express Pharma & Express Healthcare

Context and rationale

The scale up of DOTS in India is a great public health accomplishment, and yet undiagnosed and poorly managed TB continues to fuel the epidemic. Recognizing these challenges, the Government of India has set an ambitious goal of providing universal access to quality diagnosis and treatment for all TB patients. Innovative tools and delivery systems in both the public and private sectors are critical for reaching this goal. The current in-vitro diagnostics market in India is dominated by imported and generic products, with virtually no innovations. But India has the potential to solve its TB problem with "home-grown" solutions. Just as Indian pharma and biotech companies revolutionized access to high-quality, affordable AIDS drugs and hepatitis vaccines through generic production, Indian diagnostic companies could also become the world's hub for high-quality generic diagnostics. India also has the potential to lead the world in developing innovative TB diagnostics. For this to happen, Indian industry must move from the import and imitation approach to genuine innovation in both product development as well as delivery. This will require permissive policies, enhanced funding, and greater collaboration between government, donors, researchers and the private industry.

St. John's Research Institute | McGill | Global Health Strategies | Stop TB Partnership

FIND | International Centre for Genetic Engineering and Biotechnology | CII Confederation of Indian Industry | ABLE

BioSpectrum | Express Pharma | Express Healthcare

Content and themes

This conference will convene industry leaders, innovative thinkers, researchers, funders, and policy makers, to stimulate increased industry engagement in diagnostic innovations that can help TB control in India and elsewhere. Sessions will focus on topics such as market size for TB diagnostics, IVD market analysis and value chain, target product profiles and market needs, frugal innovation and affordable diagnostics, intellectual property, regulation of diagnostics, sources of funding, prize models, business models for engaging private sector, scientific obstacles for R&D, barriers to innovation in India, academia-industry relations, and role of emerging economies and BRICS in the next wave of TB innovations.

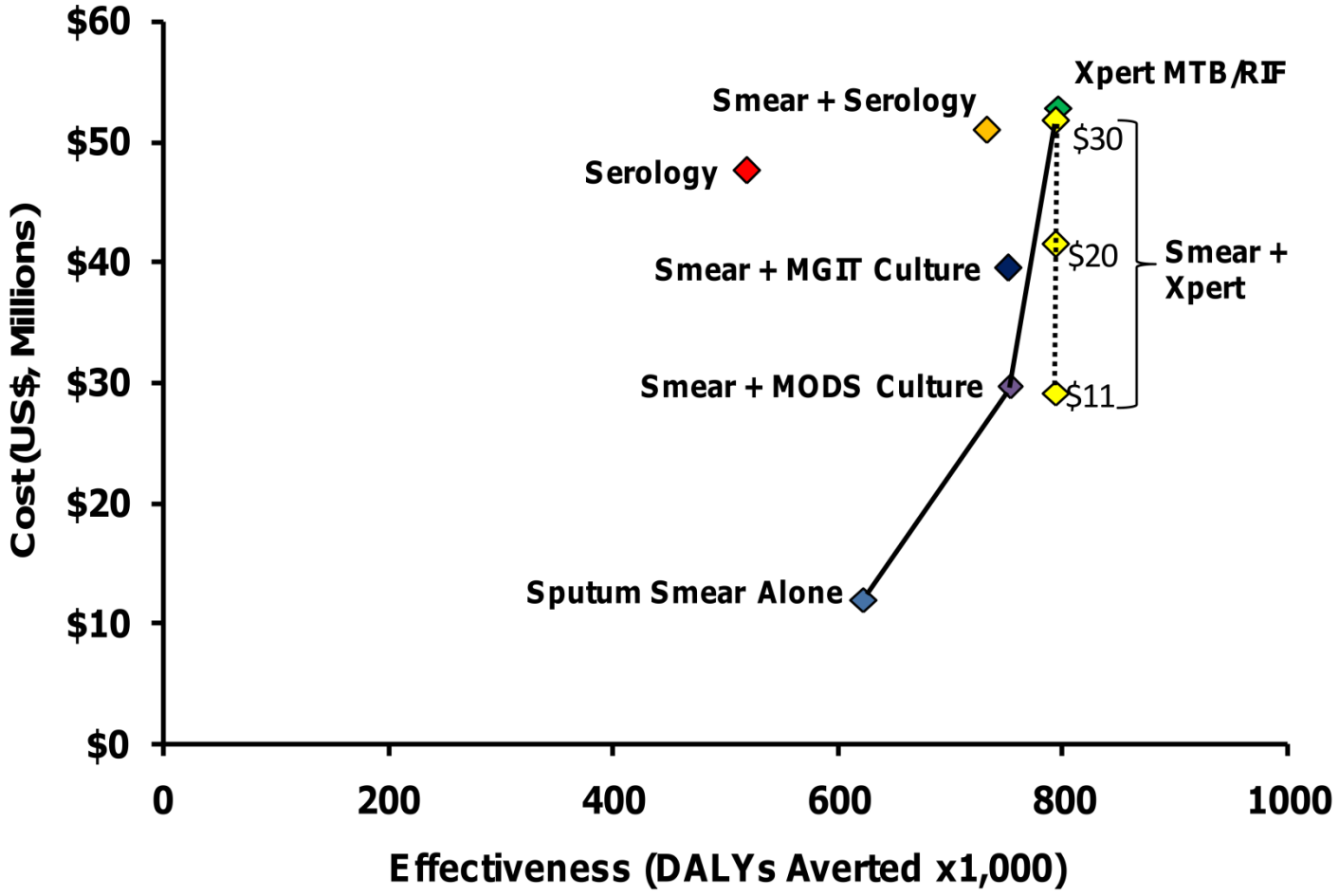
Confirmed speakers & panelists

Anu Acharya, Ocimum Biosolutions, Hyderabad, India
Ramnik Ahuja, Confederation of Indian Industry, India
Tanjore Balganesh, AstraZeneca, Bangalore, India
Steven Buchsbaum, Bill & Melinda Gates Foundation, USA
Sanjeev Chaudhry, SRL, India
Vir S. Chauhan, ICGEB, New Delhi, India
Anand Daniel, Accel Partners, Bangalore, India
Satya Dash, Association of Biotechnology Led Enterprises, India
Dhananjaya Dendukuri, Achira Labs, Bangalore, India
Pradip Desai, Span Diagnostics, Surat, India
Bindu Dey, Department of Biotechnology, New Delhi, India
Puneet Dewan, WHO, SEARO, New Delhi, India
Gopi Gopalakrishnan, World Health Partners, New Delhi, India
Sami Guzder, Avesthagen, Bangalore, India
Rekha Hemrajani, Exelixis Inc. & Omidyar Network, USA
Szymon Jaroslawski, IBAB, Bangalore, India
Nalini Krishnan, REACH, Chennai, India
Rishikesha Krishnan, IIM, Bangalore, India
Ashok Kumar, Central TB Division, DGHS, New Delhi, India
Blessi Kumar, TB/HIV activist and consultant, Delhi, India
BV Ravi Kumar, XCyton Diagnostics, Bangalore, India
Bala S Manian, ReaMetrix, Bangalore, India
Jaykumar Menon, X Prize Foundation, USA
Shirshendu Mukherjee, Wellcome Trust, India
Chandrasekhar Nair, BigTec Labs, Bangalore, India
Anjali Nayyar, Global Health Strategies, India
Mark Perkins, Foundation for Innovative New Diagnostics, Geneva
Dinesh Puri, Medived Innovations, Bangalore, India
V Raja, GE Healthcare, Bangalore, India
Viveka Roychowdhury, Express Pharma & Express Healthcare, India
Camilla Rodrigues, Hinduja Hospital, Mumbai, India
Gayatri Saberwal, IBAB, Bangalore, India
Sandeep Sen, Sen Labs, Patna, India
Anand Sivaraman, Remidio, Bangalore, India
Narayanan Suresh, BioSpectrum Asia & Technology Review, India
Peter Small, Bill & Melinda Gates Foundation, USA
Natarajan Sriram, Tulip Group, Goa, India
Soumya Swaminathan, TRC, Chennai
Javid Syed, Treatment Action Group, New York, USA
Jaya Tyagi, AIIMS, New Delhi, India
Brad Tytel, Global Health Strategies, India & New York
Suresh Vazirani, Transasia Biomedicals, Mumbai, India
Suri Venkatachalam, Connexios, Bangalore, India
Gene Walther, Bill & Melinda Gates Foundation, USA

Space is limited. Industry participants from India will get preference.
Registration form available at: www.sjrires.in

Meeting coordinators
Dr John Kenneth, MD, SJR, Bangalore [johnkennet@gmail.com]
Dr Madhukar Pai, MD, PhD, McGill University, Montreal [madhukar.pai@mcgill.ca]

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

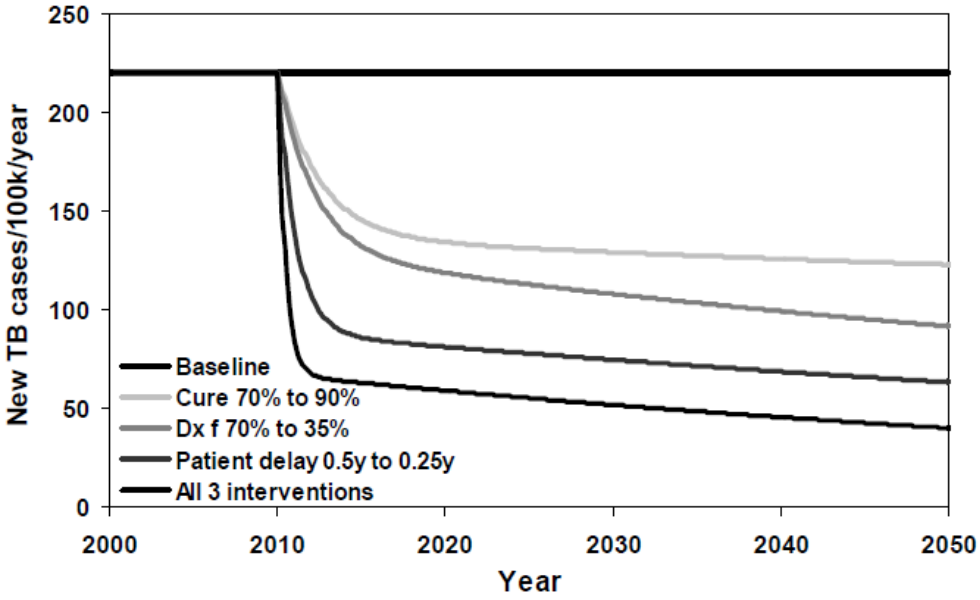


Dowdy D et al.

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

"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."

– Dye C. Ind J Med Res (in press)



Will the 43 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?

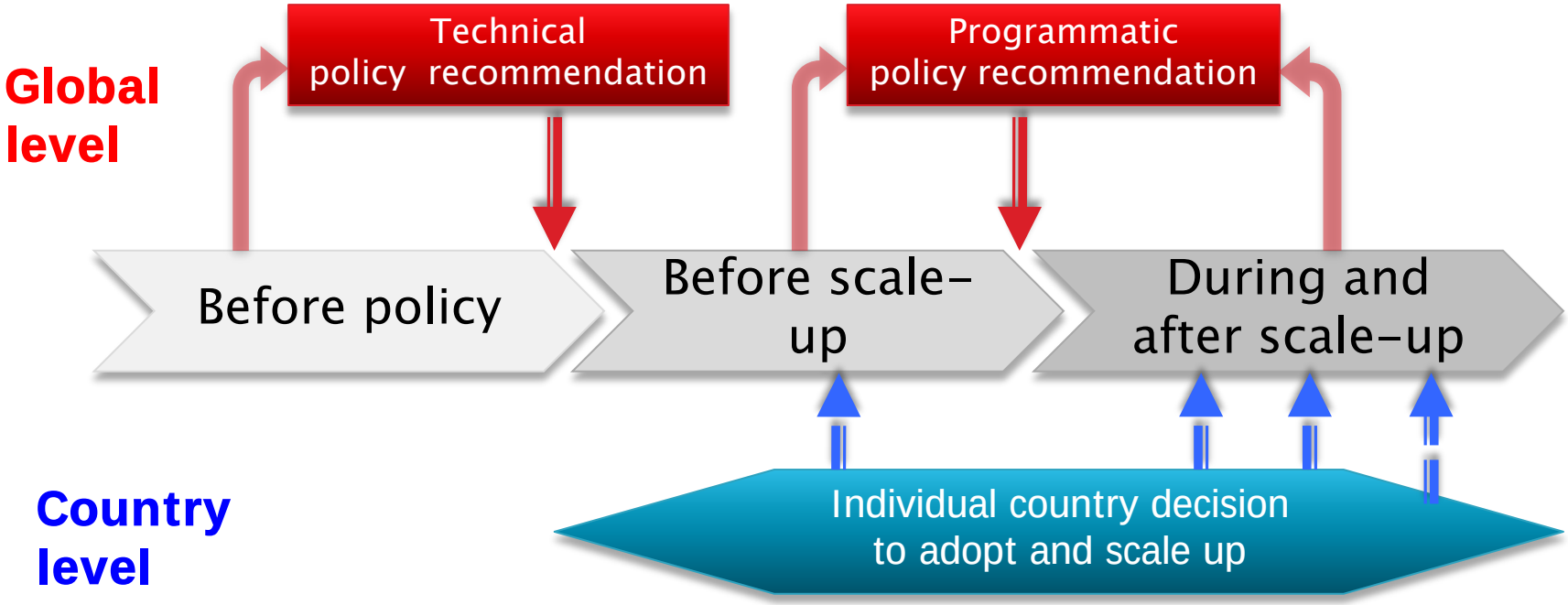
WORKSHOP REPORT

EVIDENCE FOR SCALE-UP OF NEW DIAGNOSTICS FOR TUBERCULOSIS

December 1-2, 2010

Bill and Melinda Gates Foundation

Seattle



- Test accuracy
- Surrogate patient-important outcomes
  e.g. turnaround times
- Ease of use
- Basic cost comparisons

- Effectiveness
  patient-important outcomes, case detection
- Cost
  of diagnostic process and treatment; patient costs
- Operational data
  infrastructural and human resource requirements, practical constraints

- Epidemiological impact
  changes in TB and DR-TB case detection, treatment delay, treatment outcomes, incidence and prevalence
- Health system impact
  Test and resource utilization
- Economic impact

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

Andrew Ramsay, PhD*
Karen R. Steingart, MD, MPH†
Madhukar Pai, MD, PhD‡
*UNICEF/UNDP/World Bank/WHO
Special Programme for
Research and Training in Tropical Diseases
World Health Organization
Geneva, Switzerland
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Biostatistics & Occupational Health
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Montreal, Quebec, Canada
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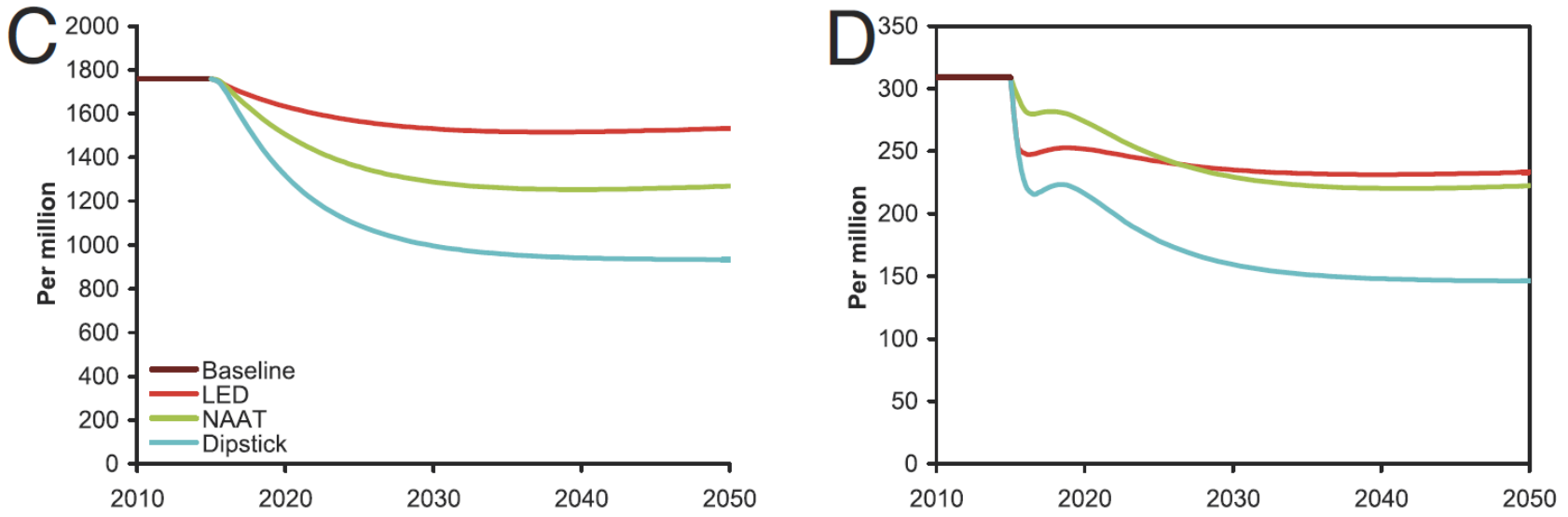
Use modeling to estimate societal or epidemiological impact

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

Laith J. Abu-Raddad[a,1], Lorenzo Sabatelli[a], Jerusha T. Achterberg[a,b,c], Jonathan D. Sugimoto[a,b], Ira M. Longini, Jr.[a,d], Christopher Dye[e], and M. Elizabeth Halloran[a,d,2]



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

Sylla Thiam[1], Moussa Thior[1], Babacar Faye[2], Médoune Ndiop[1], Mamadou Lamine Diouf[1], Mame Birame Diouf[1], Ibrahima Diallo[1], Fatou Ba Fall[1], Jean Louis Ndiaye[2], Audrey Albertini[3], Evan Lee[3], Pernille Jorgensen[3], Oumar Gaye[2], David Bell[4]*

1 Programme National de lutte contre le Paludisme, Ministère de la Santé, Dakar Fann, Senegal, **2** Faculté de Médecine, Université Cheikh Anta Diop de Dakar, Fann Dakar, Sénégal, **3** Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland, **4** Global Malaria Programme, World Health Organization, Geneva, Switzerland

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

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

MALARIA JOURNAL

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

Guido JH Bastiaens[1†], Erik Schaftenaar[1†], Arnold Ndaro[2], Monique Keuter[1], Teun Bousema[3] and Seif A Shekalaghe[2,4,5*]

Abstract

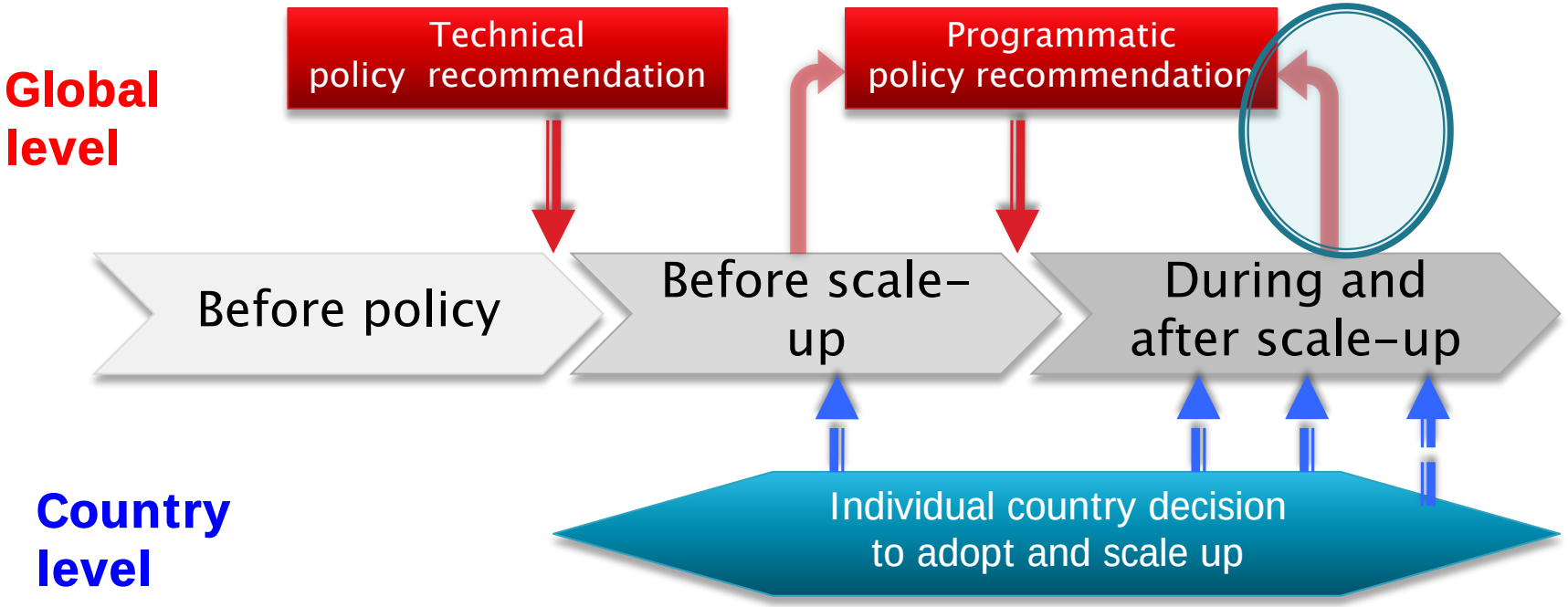
Background: Patterns of decreasing malaria transmission intensity make presumptive treatment of malaria an unjustifiable approach in many African settings. The controlled use of anti-malarials after laboratory confirmed diagnosis is preferable in low endemic areas. Diagnosis may be facilitated by malaria 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: currently there is no clear feedback loop



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!
- 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
- After scale-up, we need to measure epidemiological and public health impact of new technologies