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TB Centre



## Evaluation of new TB diagnostics:

A capacity building workshop for public sector institutions in India

# Goals and key considerations

*Grant support from:*

Capital *for* Good 

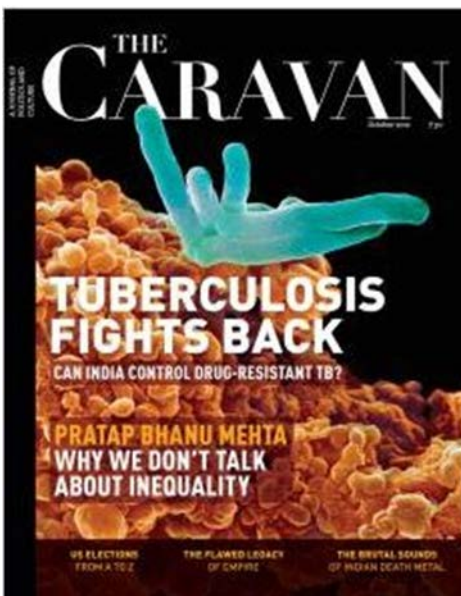
# Our previous course in Chennai in Dec 2010



# Goal

- To contribute to improved policy development in India, by strengthening TB diagnostics validation capacity and collaboration among the key Institutions involved in TB research (including ICMR institutes, medical colleges and National TB institutes under the Ministry of Health) and policy (RNTCP).

# TB in India remains a major public health challenge



## THE WALL STREET JOURNAL India in Race to Contain Untreatable Tuberculosis

By GEETA ANAND

MUMBAI—India's slow response to years of medical warnings now threatens to turn the country into an incubator for a mutant strain of tuberculosis that is proving resistant to all known treatments, raising alarms of a new global health hazard.

"We finally have ended up with a virtually untreatable strain" of tuberculosis in India, said Dr. Zarir Udwadia, one of the country's leading TB authorities.

In December, Dr. Udwadia reported in a medical journal that he had four tuberculosis patients resistant to all treatment. By January, he had a dozen cases, then 15.

A government backlash began immediately. Anonymous health-ministry officials denied the reports through media outlets. They accused Dr. Udwadia and his colleagues of starting a panic. A Mumbai city health official seized patient samples for verification in government labs.

In April, the government quietly confirmed the strain, according to internal Indian health-ministry

documents reviewed by The Wall Street Journal.

Spread of the strain could return tuberculosis to the fatal plague that killed two-thirds of people afflicted, before modern treatments were developed in the 1940s, said Mario Raviglione, director of the Stop TB Department of the World Health Organization. The WHO is now assisting India to combat the strain.

The number of known cases in India is small but geographically dispersed. Dr. Udwadia's patients are in Mumbai, at the P.D. Hinduja National Hospital & Medical Research Center. In the high-tech hub of Bangalore, St. John's National Academy of Health Sciences has seen six cases. And in New Delhi, the All India Institute of Medical Sciences has confirmed another two, said officials at the institutions.

"While this handful of cases is worrying, it's just the tip of the iceberg," said Dr. Soumya Swaminathan, of India's National Institute for Research in Tuberculosis. For treatments, Dr. Udwadia said, "We've got nothing."

Ashok Kumar, head of India's tuberculosis-con-

*Please turn to page A12*

### COVERSTORY

INDIA WILL SOON HAVE THE HIGHEST NUMBER OF PEOPLE SUFFERING FROM EXTREMELY DRUG-RESISTANT TUBERCULOSIS

# DOES ANYONE CARE?

BY GURJAN SHARMA



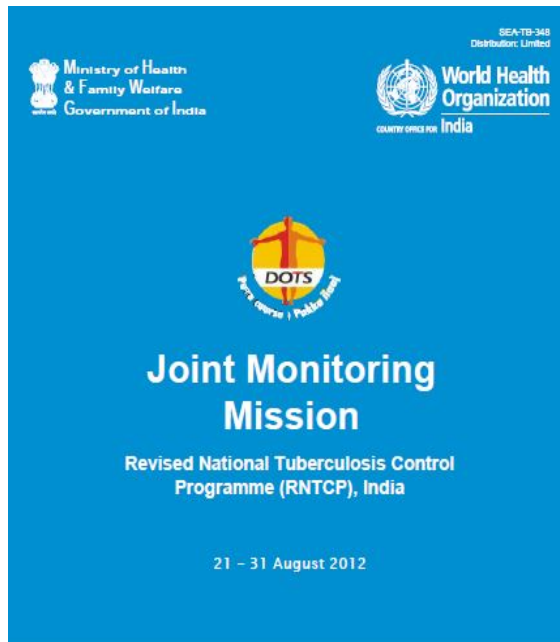
SEASON 3 ▾ SMJ ARCHIVE ▾ WE RECOMMEND MUMKIN HAI INSIGHTS DONATE ABOUT US 🔍



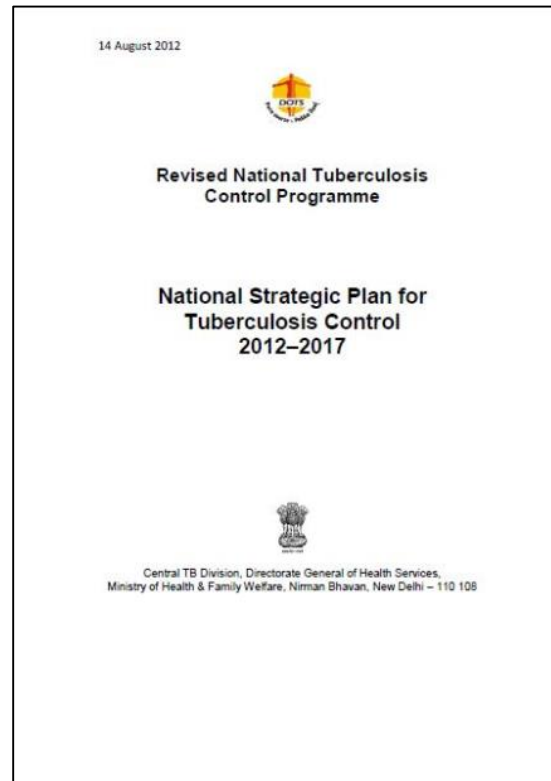
## Episode 04: TB - The Ticking Time Bomb

# The problem has been analyzed and reported

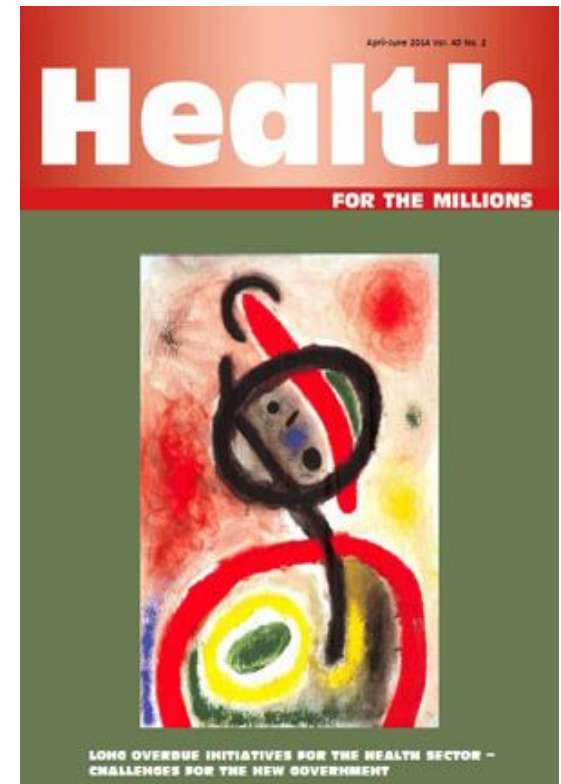
JMM Report , RNTCP,  
India, 2012



National Strategic Plan for  
TB Control (2012-2017)



VHAI Health For Millions



DFID Department for International Development

The Global Fund to Fight AIDS, Tuberculosis and Malaria

USAID U.S. Agency for International Development



# What can explain the high incidence, missing cases and MDR problem?

- Underlying social determinants are hardly addressed
- There is considerable diagnostic delay and thus ongoing transmission
- Even if diagnosis is made, treatment and monitoring are suboptimal
- We are still working with outdated tools and antiquated systems

# Average TB patient in India continues to struggle to find a diagnosis

## Public sector

?

## Private sector



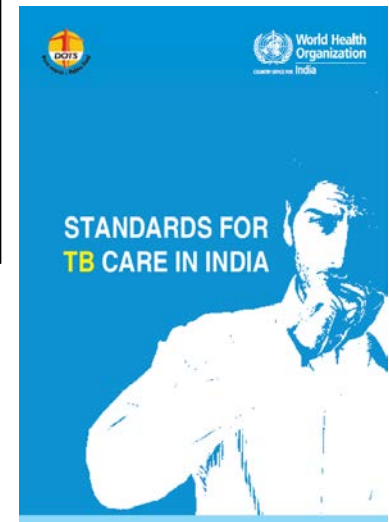
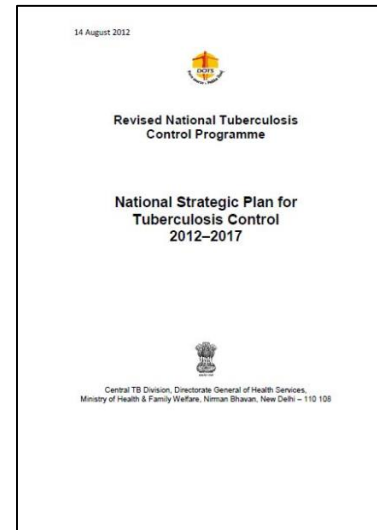
- Diagnosis by smear
- Free treatment, but not convenient
- Can now get MDR Dx/Rx, but poor access

- High OOP expenditure
- Mismanaged diagnosis
- Sub-standard treatment
- Unaffordable MDR Rx

# India has articulated high ambitions to transform TB control

## National Strategic Plan ('12-17) committed:

- **Universal Access:**  
90% of estimated incident TB cases diagnosed & treated as per nationally-accepted protocols
- **Reduction in TB deaths**  
≥30% TB mortality reduction compared to 2010
- **Real-time ICT surveillance:**  
100% of districts with RNTCP integrated into health blocks, with full ICT system implementation



THE

# END TB

STRATEGY



World Health  
Organization

*Global strategy and targets for  
tuberculosis prevention, care  
and control after 2015*



<b>VISION</b>	<b>A world free of tuberculosis</b> – zero deaths, disease and suffering due to tuberculosis
<b>GOAL</b>	<b>End the global tuberculosis epidemic</b>
<b>MILESTONES FOR 2025</b>	– 75% reduction in tuberculosis deaths (compared with 2015); – 50% reduction in tuberculosis incidence rate (compared with 2015) (less than 55 tuberculosis cases per 100 000 population) – No affected families facing catastrophic costs due to tuberculosis
<b>TARGETS FOR 2035</b>	– 95% reduction in tuberculosis deaths (compared with 2015) – 90% reduction in tuberculosis incidence rate (compared with 2015) (less than 10 tuberculosis cases per 100 000 population) – No affected families facing catastrophic costs due to tuberculosis

# We will not reach these targets without modernizing DOTS

Key elements	Current/Past	Future
<b>Political commitment with increased and sustained financing</b>	Poor funding for TB	Funding to match the goal of universal access and National Strategic Plan; universal health care
<b>Case detection through quality-assured bacteriology</b>	Mostly direct ZN microscopy	Rapid molecular testing with upfront DST
<b>Standardized treatment, with supervision and patient support</b>	HRZE, 6 months DOT	PaMZ or other shorter regimens (4 months); Multifaceted approach, including electronically observed therapy
<b>An effective drug supply and management system</b>	Erratic supply and stockouts	Improved supply chain management
<b>Recording and reporting system</b>	Paper-based	Fully digital/ICT

We have always wanted new tools, and  
they are here!

- New diagnostics
- New TB drugs and regimens
- ICT for adherence monitoring, notification, etc.

# New molecular diagnostics

**REFERENCE**

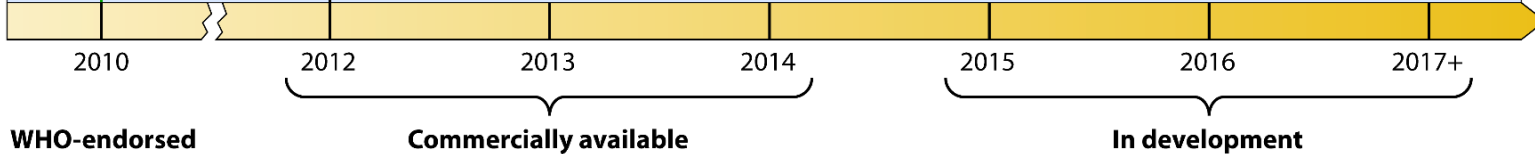
Autogenomics   CapitalBio   Seegene Anyplex® series   Roche Cobas®   Autogenomics OCTA   Abbott m2000   Zeesan MeltPro®

**INTERMEDIATE**

Xpert® MTB/RIF   iCubate   Tosoh TRC Rapid®   Hain Fluorotype®   Vereplex™   NanoBioSys   Hain Lights on/Lights off Fluorotype® RNA assay   EnigmaML® MDR TB   Xpert® MTB/RIF ULTRA   Xpert® Xtend-XDR   Stat-Diagnostica DiagCORE

**MICROSCOPY**

Eiken Loopamp™ MTBC   Epistem Genedrive®   MolBio Truelab™   Alere™ q   Insilixa HYDRA   Wave80 EOSCAPE   Ustar EasyNAT™   NWGHF   QuantuMDx Q-POC™   GenPOC   KGI TBDx System



# New TB drugs and regimens



**TB ALLIANCE**

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

2014 Q3

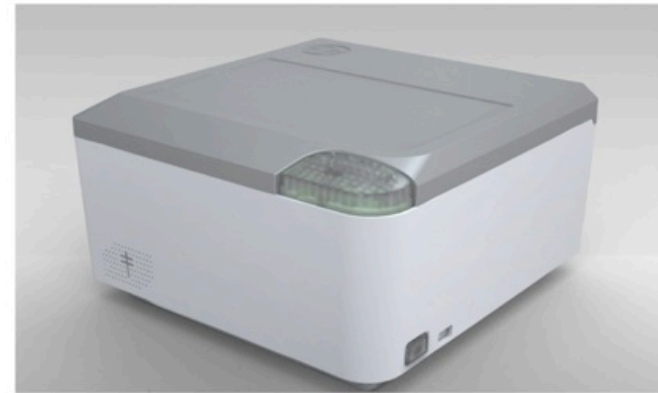
Discovery		Early Development			Late Development			
LEAD IDENTIFICATION	LEAD OPTIMIZATION	PRECLINICAL DEVELOPMENT	PHASE 1	PHASE 2A	PHASE 2B	PHASE 3	PHASE 4	
ATP Synthesis Inhibitors <i>Calibr</i>	Macrolides <i>Sanofi</i>	TBA-354	Pharmacokinetics of first-line drugs in children < 5kg <i>Stellenbsch University</i>	NC-003 Bedaquiline/ Clofazimine/ Pyrazinamide		STAND PA-824/ Moxifloxacin/ Pyrazinamide	Optimized Pediatric Formulations	
Whole-Cell Hit-to-Lead Program <i>Sanofi</i>	Ureas <i>Sanofi</i>	Preclinical TB Regimen Development <i>JHU</i>						PA-824/ Bedaquiline/ Clofazimine/ Pyrazinamide
Whole-Cell Hit-to-Lead Program <i>GSK</i>	Diarylquinolines <i>Janssen/University of Auckland/UIC</i>		PA-824/ Bedaquiline/ Clofazimine					Isoniazid/ Rifampicin for children > 5kg
RNA Polymerase Inhibitors <i>Rutgers University</i>	Indazoles <i>GSK</i>		PA-824/ Bedaquiline/ Clofazimine					Ethambutol for children > 5kg
Energy Metabolism Inhibitors <i>AZ/Upenn</i>	Thiophene Carboxamides <i>Calibr</i>		PA-824/ Bedaquiline/ Pyrazinamide					Isoniazid for children > 5kg
POA Prodrugs <i>Yonsei</i>	Azaindoles <i>AZ</i>							Pyrazinamide for children > 5kg
InhA Inhibitors	Cyclopeptides <i>Sanofi</i>							
Hit ID Program <i>Takeda</i>	Mmmpl3 Inhibitors							
Hit ID Program <i>Daiichi Sankyo</i>								
Hit ID Program <i>Shionogi</i>								

### TB Alliance R&D Partners:

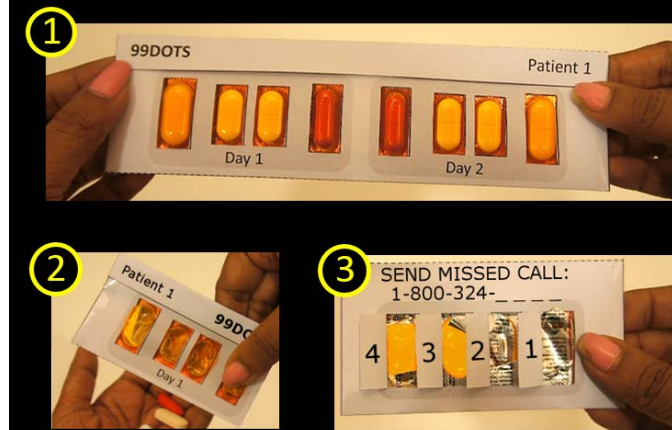
AstraZeneca (AZ)  
 Bayer Healthcare AG (Bayer)  
 Beijing Tuberculosis and Thoracic Tumor Research Institute  
 Calibr  
 Daiichi Sankyo  
 GlaxoSmithKline (GSK)  
 Institute of Materia Medica (IMM)  
 IMPAACT  
 Janssen [Johnson & Johnson]  
 Johns Hopkins University (JHU)  
 Medical Research Council (MRC)

New York Medical College  
 Rutgers University  
 Sanofi  
 Shionogi  
 Stellenbosch University  
 Takeda Pharmaceuticals  
 University College London (UCL)  
 University of Auckland  
 University of Illinois at Chicago (UIC)  
 University of Pennsylvania School of Medicine  
 Yonsei University

# New adherence monitoring tools



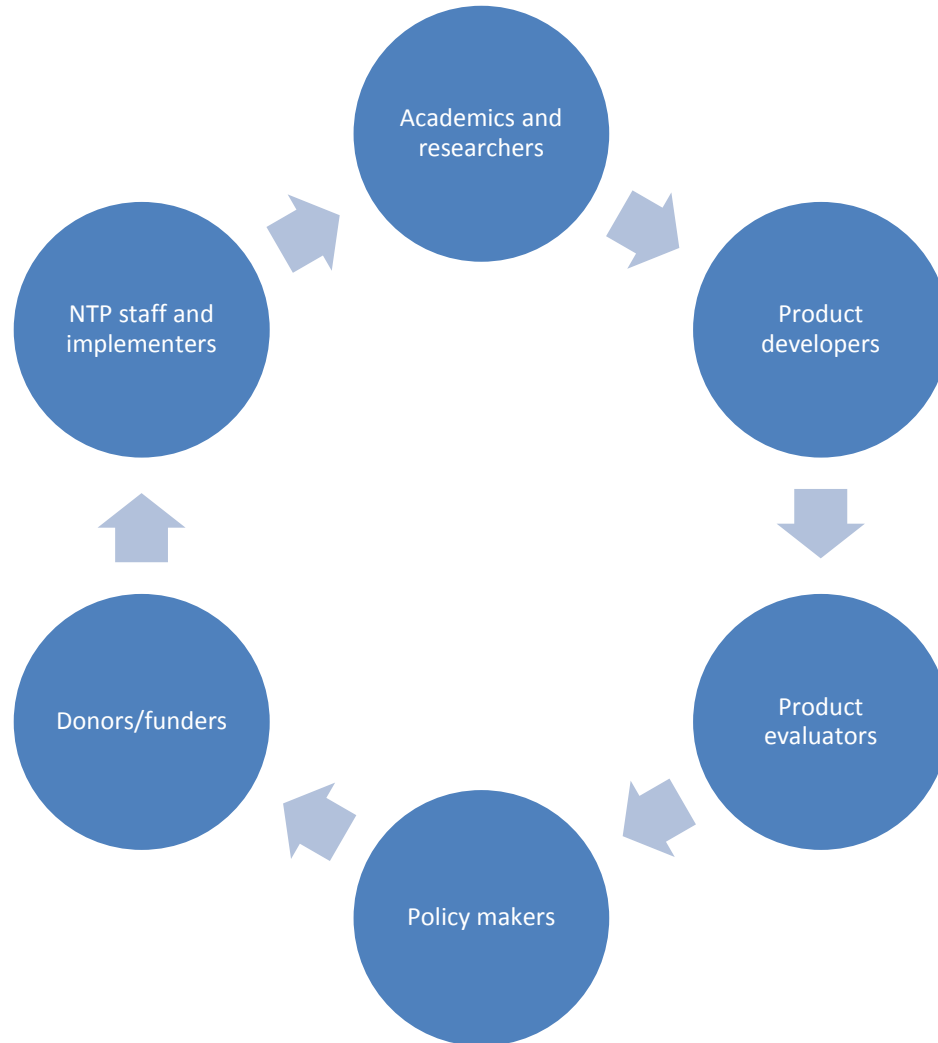
## 99DOTS: Real-Time Adherence Tracking at Very Low Cost



# Urgent need

A clear, coordinated strategy to evaluate new tools and technologies, and to decide on their policy and scale-up

# To scale up new tools, we need key stakeholders to work together



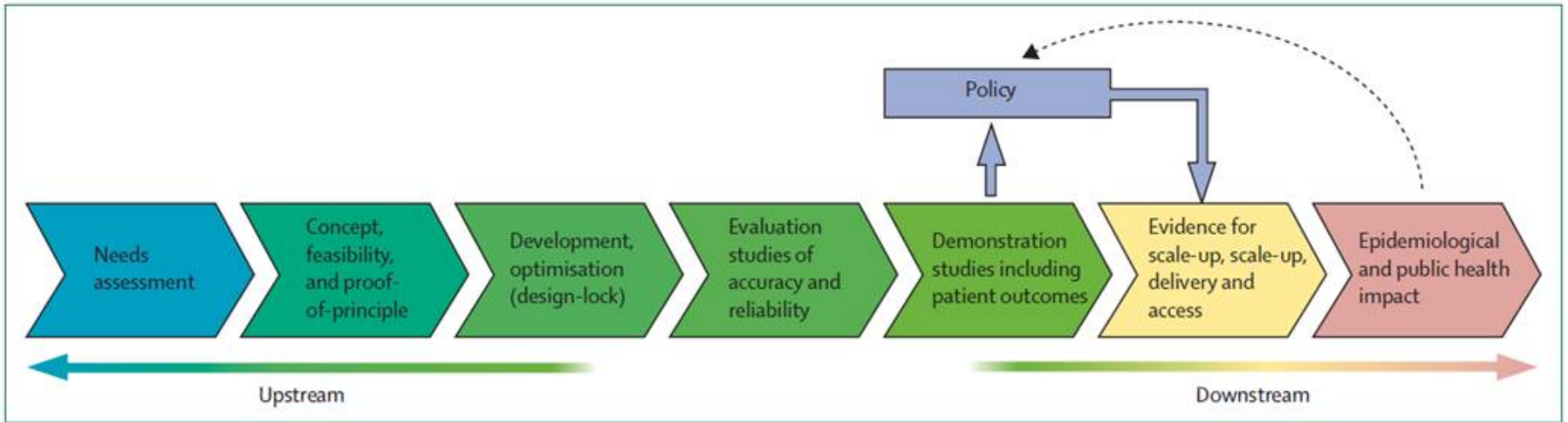
# Evaluation of new diagnostics

- **Public sector**
  - Revised National TB Control Program
  - National TB Institutes: NIRT, NTI, NITRD, JALMA
  - Other public sector research institutes and medical colleges
  - Supported by FIND, WHO, BMGF, USAID, and other partners
- **Private sector**
  - Private medical colleges and hospitals (e.g. Hinduja, CMC, St John's)
  - IPAQT (83 private labs engaged), coordinated by Clinton Health Access Initiative

# What we really care about

- New tools get developed
- They undergo adequate evaluation
- Evidence-based policies get formulated
- Products and policies get implemented in countries
- Impact is seen on disease burden

*This could be a single long value chain...*



**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),<sup>180</sup> and reproduced with permission from author and publisher.



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

Catharine C. Boehme, Mark P. Nicol, Pamela Ntshhe, Joy S. Michael, Edoardo Grillazzo, Rosim Tahiri, Mia Taratola-Gier, Robert Blakemore, William Henshke, Christian Gray, Lauren Hoenig, Juliana Garcia, Rajal Madhaya, Lawrence Raymond, Andrew Whittaker, Kabiluhen Segalosen, Heather Alexander, Heidi Albert, Frank Gebrey, Helen Cox, David Alland, Mark D Perkins

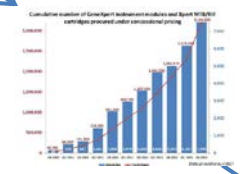
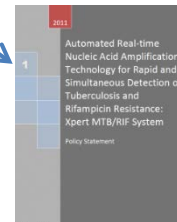
WHO Expert Group meeting on Xpert Sept 1 & 2, 2010



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 Varenbâ, Geneva, Switzerland



Scale-up at the country level & impact (future)

# Value chain for Xpert MTB/RIF

Looks linear, but is not

## In reality, several intersecting\* value chains...

- Product development value chain
- Product evaluation value chain (diagnostic research and evidence)
- Policy value chain (global and country-specific)
- Implementation value chain (scale up)
- Impact assessment value chain

\*often, these value chains do not intersect and that is a problem!

# Weak links in this value chain

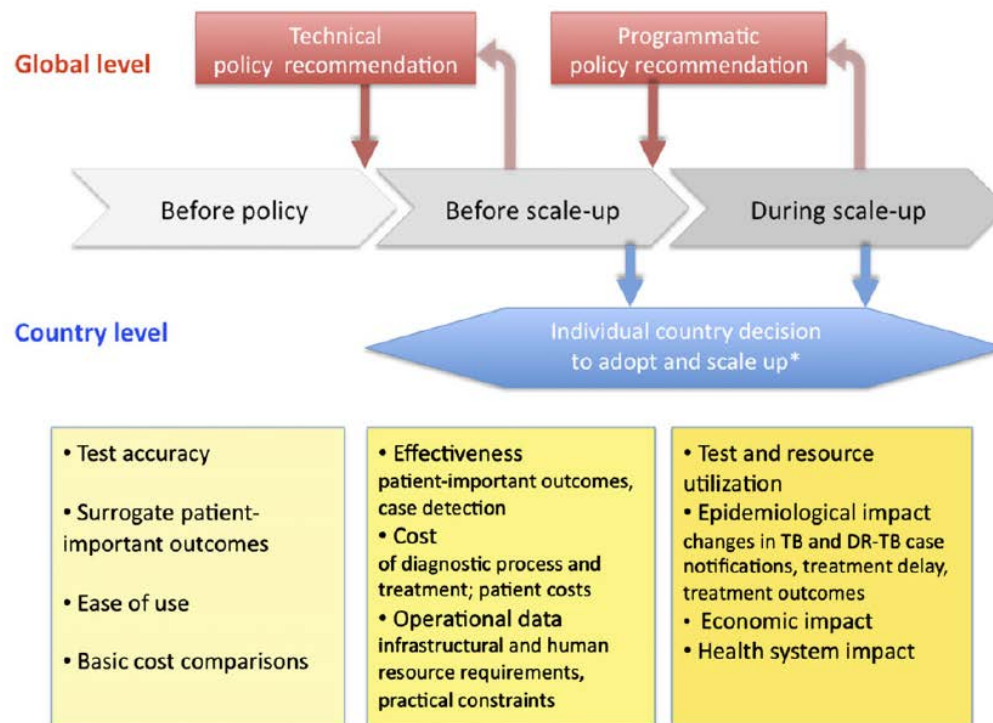


- Global value chain is envisioned in a linear way
- The global and local value chains are not well aligned
- WHO approval not mandatory, but might help for country adoption
- Even if WHO approved, local studies are often needed
  - On feasibility, cost-effectiveness, fit with algorithms, HR and lab implications, delivery models, willingness to pay, price point analysis, etc.
  - There is a need for a coordinated mechanism to collect in-country evidence quickly to support local scale-up decisions

# Proposed revised value chain for new TB diagnostics

## Which New Diagnostics for Tuberculosis, and When?

Frank Cobelens,<sup>1</sup> Susan van den Hof,<sup>1,2</sup> Madhukar Pai,<sup>3</sup> S. Bertel Squire,<sup>4</sup> Andrew Ramsay,<sup>5</sup> and Michael E. Kimerling<sup>6</sup> 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.

# Product evaluation is the focus of this workshop, and protocol development is a key outcome

- We will hear about new diagnostics and innovations
- We will learn how to design high-quality evaluation studies
- We will work in 5 small groups to develop protocols for their evaluation
  - Team **Koch** (Mayank Ghedia and Ranjani R)
  - Team **Mullis** (Neeraj Raizada)
  - Team **Pasteur** (Samuel Schumacher)
  - Team **Buchner** (Hojoon Sohn)
  - Team **Rontgen** (Srinath S)

# Our hope

- You will go home excited about the potential of new tools
- You will consider taking on evaluation studies of new diagnostics
- You will join multi-centric evaluation studies
- Once policies are made, you will help implement new tools

# Resources

- USB drive with lots of very good materials, including sample protocols
- PPT of all talks will be uploaded on [www.teachepi.org](http://www.teachepi.org)
- Some important resources:
  - [www.teachepi.org](http://www.teachepi.org)
  - [www.tbevidence.org](http://www.tbevidence.org)
  - [www.tbfaqs.org](http://www.tbfaqs.org)
  - UNITAID landscape reports

Home

Courses

Fundamentals of Epidemiology

Systematic Reviews and Meta-analysis

Diagnostic Research, Stellenbosch University

Meta-analysis of Diagnostic Test Accuracy

GRADE Workshop

Montreal Tuberculosis Course

Advanced TB Diagnostic Research, 2011

TB Diagnostic Research, India

Systematic Reviews and Meta-analysis in Tuberculosis

Advanced TB Diagnostic Research, 2012 [SA]

Advanced TB Diagnostic Research, 2012 [Mtl]

Advanced TB Diagnostic Research, 2013 [Mtl]

Introduction to Tuberculosis Modeling

Teaching Resources

The B-Files (Bias Case Studies)

**Madhukar Pai, MD, PhD**  
**Associate Professor**  
**McGill University, Montreal, Canada**



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# Evidence-Based Tuberculosis Diagnosis

A Comprehensive Resource For Evidence Syntheses, Policies, Guidelines And Research Agendas On TB Diagnostics

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- Foundation for Innovative New Diagnostics (FIND)**
- Special Programme for Research and Training in Tropical Diseases (TDR)**
- Global Laboratory Initiative (GLI)**
- Public Health Agency of Canada (PHAC)**
- Curry International Tuberculosis Center, UCSF**
- McGill TB Research Group**



# TB Diagnostics: Top 10 FAQs By Test Developers

## RESOURCES POSTED

Useful resources for each question are now available on our website.

## Latest News

Publications Related to This Site

2014 Diagnostics by Design, Panel Discussion

### **Tuberculosis diagnostics: test developers' FAQs**

**Diagnostics for tuberculosis: what test developers want to know**

**A new resource for TB diagnostics developers**





**2012**

**TUBERCULOSIS**  
**Diagnostic Technology Landscape**



**2013**

**TUBERCULOSIS**  
**Diagnostics Technology**  
**and Market Landscape**

2nd edition



**2014**

**TUBERCULOSIS**  
**Diagnostics Technology**  
**and Market Landscape**

3<sup>RD</sup> EDITION

# Thank you

- Everyone, for your interest & participation
- Soumya Swaminathan, NIRT
- NIRT Team: Dina Nair, S Balaji, Banu Rekha, Senthil Murugan
- Speakers, panelists, and small group facilitators
- FIND: Catharina Boehme, Neeraj Raizada, Claudia Denkinger
- Kate Volpicelli, Geneva Global and Capital for Good
- McGill team: Samuel Schumacher, Hojoon Sohn, Srinath S, Caroline Vadnais
- Industry colleagues