

Better Diagnostics for Tuberculosis: A Bolder Vision for TB Control...

Peter M. Small, MD
Senior Program Officer
peter.small@gatesfoundation.org

June 21, 2010

BILL & MELINDA
GATES *foundation*

Disclosure

- **No financial/industry conflicts**
- **Patent signed over to Stanford University student organization**

TB in the 21st Century: DOTS and SPOTS

November 23, 1998

- **With in 10 years:**
 - **DNA microarrays -> salivary dipstick**
 - **Understand latency -> rational design of drugs**
 - **Scientific and political consensus -> eradication possible**

Int J Tuber Lung Dis 3(11) 949; 1999

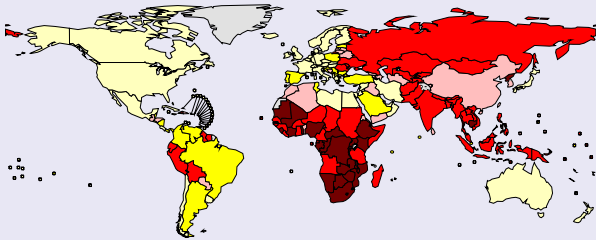
EVERY PERSON DESERVES
THE CHANCE TO LIVE A
HEALTHY, PRODUCTIVE LIFE.



Today's Talk

- Context
- Technology pipelines
- Impediments
- Some predictions

Global Burden of TB in 2008



**Estimated
number of
cases**

**Estimated
number of
deaths**

All forms of TB

**9.4 million
(range, 8.9–9.9 m)**

**1.8 million
1.6 – 2.3m**

HIV-associated TB

**1.4 million
(15%)
1.3 – 1.6 m**

**0.52 million
0.45 – 0.62m**

**Multidrug-resistant
TB (MDR-TB)**

**0.44 million
0.39 – 0.51m**

**150,000
0.05 – 0.27m**

Current TB Control Efforts

Broad scale-up of DOTS

- DOTS implemented in 184 countries that account for 99% of cases
- 70% case detection and 85% treatment success achieved in 36 countries

Global incidence, prevalence and mortality declining slowly

- But, total number of cases still growing (decline offset by population growth)

Significant new funding needed to support Stop TB Strategy

- Projected US\$30.8 billion funding gap through 2015

MDR-TB and TB/HIV threaten recent successes

- MDR-TB has emerged in nearly every country of the world
- Africa and Eastern Europe will not meet TB control targets largely due to drug resistance and TB/HIV co-infection

Key Challenge:

Keep the best of DOTS while upgrading the technology

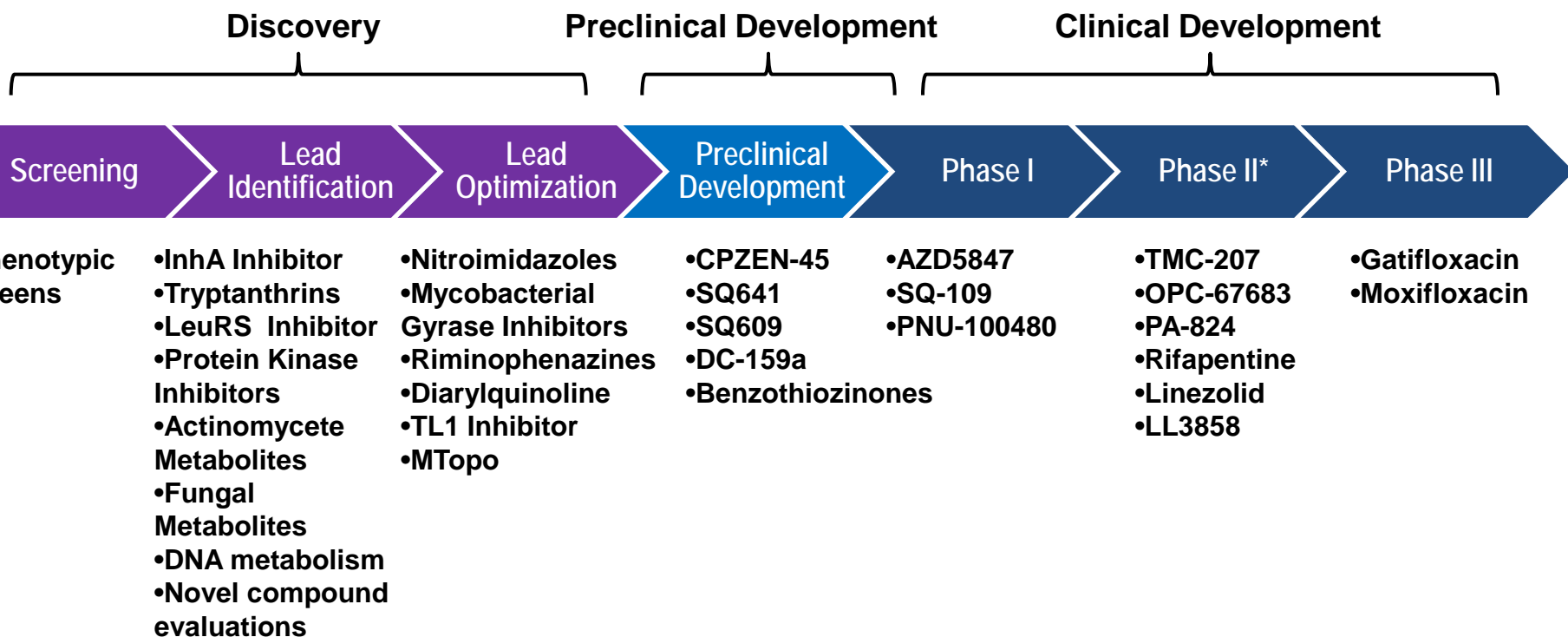
- Today's TB vaccine was invented 85 years ago
- The most commonly used diagnostic tool is 125 years old
- Standard drug regimens have not changed in over 40 years

TB Vaccine Pipeline

Vaccine Candidate	Pre-Clinical	Phase I	Phase II	Phase IIb	Phase III
AERAS402/Crucell Ad35 <i>Crucell N.V./Aeras</i>	[Progress bar]				
MVA85A/AERAS-485 <i>OETC/Aeras</i>	[Progress bar]				
GSK M72 <i>GSK Biologicals/Aeras</i>	[Progress bar]				
Hybrid 1 SSI IC-31 <i>SSI, TBVI, Intercell</i>	[Progress bar]				
HyVac4/AERAS-404 <i>sanofi pasteur/SSI/Intercell/Aeras</i>	[Progress bar]				
VPM 1002 <i>Max Planck/Vakzine Projekt Management GmbH/TBVI</i>	[Progress bar]				
AdAg85A <i>McMaster University</i>	[Progress bar]				
RUTI <i>Archivel Farma, S.I.</i>	[Progress bar]				
Hybrid 1 SSI CAF01 <i>SSI</i>	[Progress bar]				
AERAS-rBCG <i>Aeras</i>	[Progress bar]				
AERAS-Capsid <i>Aeras</i>	[Progress bar]				
Other rBCG rMtb <i>Albert Einstein S. of Med., Institute Pasteur, Univ. of Zaragoza, TBVI</i>	[Progress bar]				
AERAS-other virus <i>Aeras</i>	[Progress bar]				
Protein/Polysaccharides <i>Inst. Pasteur de Lille/Inserm, Albert Einstein S. of Med., Aeras, Karolinska Instit.</i>	[Progress bar]				

Additional research at the discovery/early pre-clinical level: Bhagawan Mahavir Medical Research Center; Cardiff University; EpiVax, Inc.; ImmunoBiology Ltd.; Infectious Disease Research Institute; Institute de Pharmacologie, Puso; Karolinska Institute; Malaysia-Finlay Institute, NIAID; NIH; Osaka University; Shanghai H&G Biotech; Sequella; UCLA; and, Vanderbilt University.

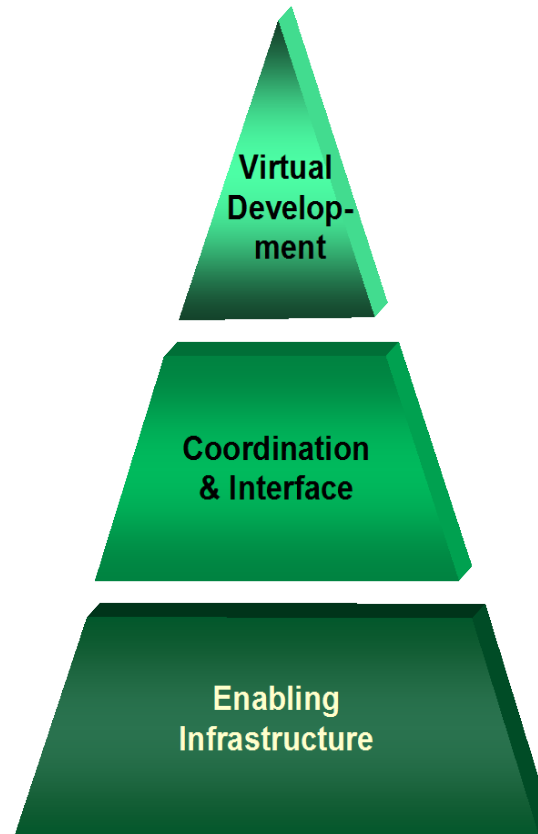
Global TB Drug Pipeline



Develop Better Diagnostics: ca 2003

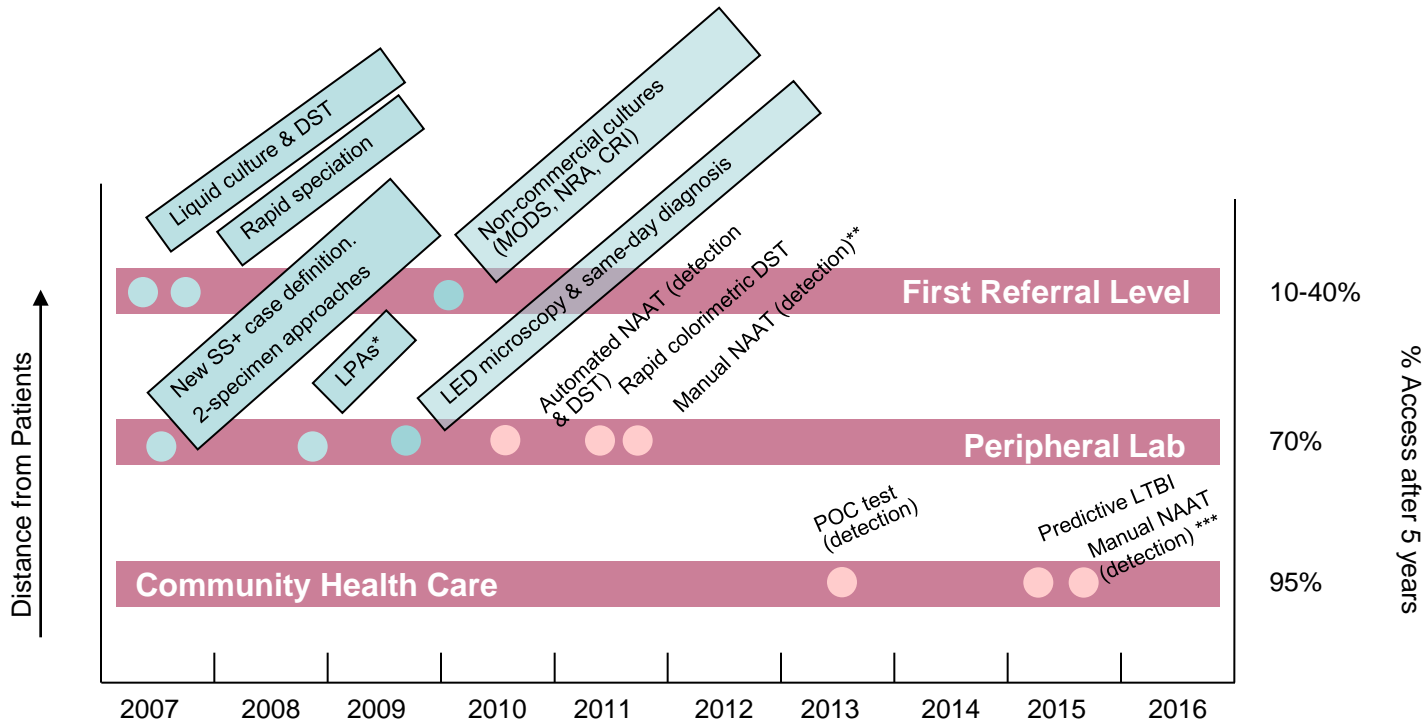
Obstacles

- Lack of financing
- Lack of coordination, need for information and interfacing
- Lack of basic to develop and test new diagnostics



FIND's Role

- Manage portfolio of investments for test development, evaluation, and demonstration
- Foster relationships and provide guidance & information to improve effective and efficient diagnostics development
- Establish/maintain basic infrastructure to enable development of appropriate diagnostics



Abbreviations

- DST: Drug Susceptibility Test
- NAAT: Nucleic Acid Amplification Test
- LTBI: Latent TB Infection
- POC: Point of Care
- MODS: Microscopic observation drug-susceptibility
- NRA: Nitrate reductase assay
- CRI: Colorimetric redox indicator assay
- LED: Light-emitting diode
- LPA: Line probe assay

- * Manual NAAT: technology for MTB Drug Susceptibility Testing
- ** Manual NAAT: technology for MTB detection at the Peripheral Lab
- *** Manual NAAT: technology for MTB detection at the Community Health Care Level

Technologies in boxes: endorsed by WHO

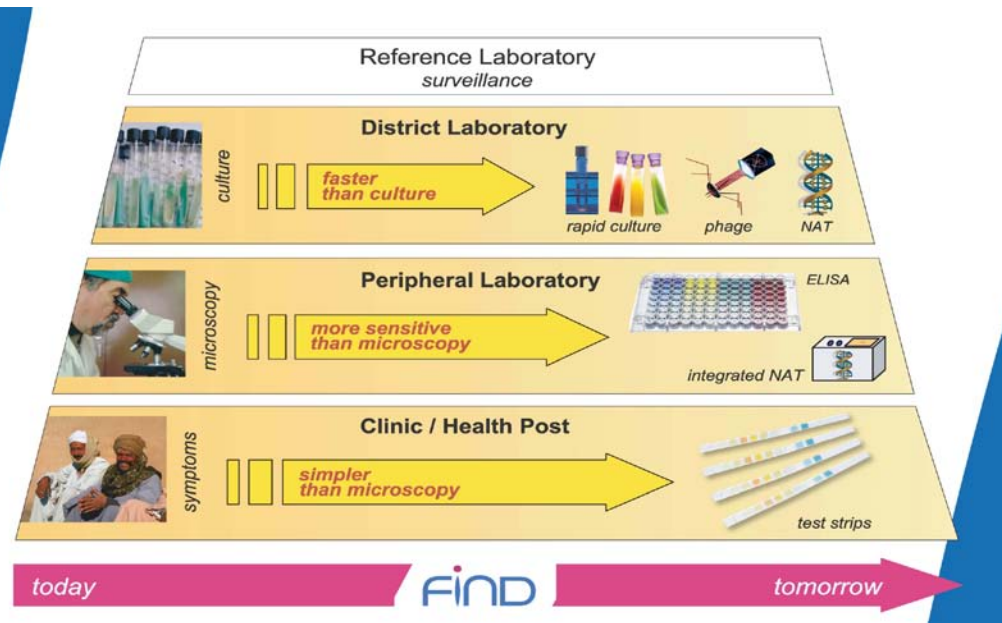
Progress in TB Diagnostics

- Pipeline
- Market segmentation
- Demand creation
- Policy clarification
- Global funding mechanisms
- Invigorated research community

What is missing...

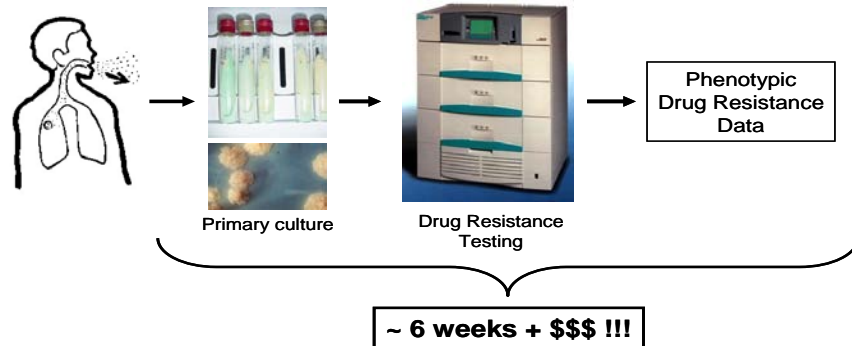
- **Biomarkers**
- **Platforms**
- **Validated list of DR mutations**
- **Delivery systems**
- **Coherent funding**
- **Vetted value propositions**
- **Self sustaining business models**

From the AFB to a Diagnostic Quiver



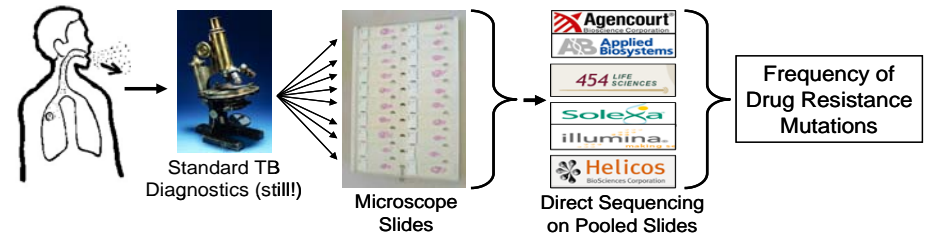
Episodic Surveillance to Real Time Monitoring

2007



Surveillance based on susceptibility test results from hundreds of patients

2011



Surveillance based on susceptibility test results from hundreds of thousands of patients

From Old Drugs to New Regimens

THE WALL STREET JOURNAL.

AR Thursday, March 18, 2010 THE WALL STREET JOURNAL.

U.S. NEWS

FDA Is Easing Way for Drug Cocktails

Agency Draws Up Guidelines for Approving Two or More New Drugs Together to Fight Deadly Diseases Such as TB, AIDS

By MARK SCHRODS

The Food and Drug Administration is devising guidelines that could accelerate testing and approval of multiring regimens for some of the world's most deadly diseases.

At least two pharmaceutical companies are poised to take advantage of the forthcoming policy: a group of 10 drug companies and several nonprofit organizations convened by the Bill and Melinda Gates Foundation to develop medicines to fight tuberculosis; and pharmaceutical giant Merck & Co. and AstraZeneca PLC, which are jointly testing two anticancer agents.

Many diseases, such as AIDS, tuberculosis and cancer, require multiring combinations. Such drug cocktails can prevent the development of drug resistance, because the microbes or cancer cells need to undergo more mutations to escape several drugs than to escape just one. By attacking the disease in different ways, drug combinations

In the Pipeline | Tuberculosis compounds currently in development

Developer	Experimental drug	Class	How it kills the TB bacteria
Tibotec Johnson & Johnson subsidiary; Global Alliance for TB Drug Development	TMC-207	Diarylsamoline	Disrupts cellular energy production
Otsuka Pharmaceutical Global Alliance for TB Drug Development	OPC-67683 PA-824	Nitroimidazole Nitroimidazole	Disrupts synthesis of lipids and proteins
Lupin	LL 3858	Pyrimole derivative	Not well understood
Sequella	SQ 109	Ethyleneamines	Affects cell wall, may have other mechanisms

Development of TB drugs and cocktails

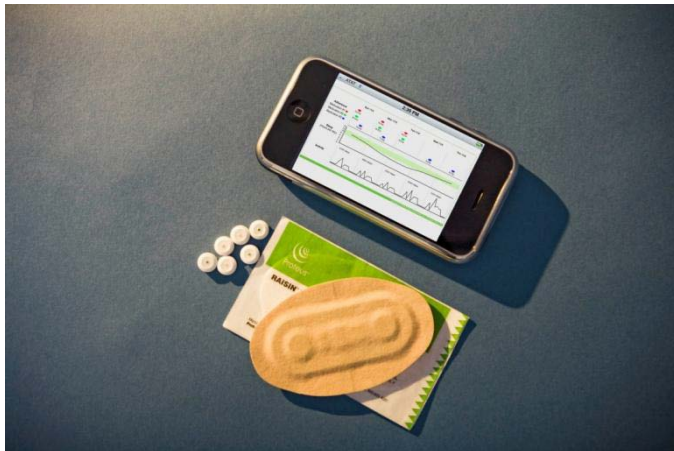
- 1952: First combination therapy using three drugs
- 1960s: One drug in cocktail replaced
- 1970s: Fourth drug added to cocktail
- 1980s: One drug in combination replaced

Source: Global Alliance for TB Drug Development; Stop TB Partnership's Working Group on New TB Drugs; WHO reporting; Jonathan Liu and Christian Lienhardt, article in *Clinical Chest Medicine*

...with the use of products in what research would be required in the test tube, animals and humans to determine side effects, proper dosage and each drug's contribution to any case certain side effects. "Society wouldn't tolerate this degree of uncertainty" except for drugs to treat Multiple-drug-resistant cases—exceeding half a million annually—take two years to treat with drugs that often cause severe side effects but only



From Paper Reports to Distributed Data



Proteus System



Stock Outs to Supply Chain Management



From Political Commitment to Patient Empowerment



“If every government has a sense of urgency, and innovation comes from every country, we can get the upper hand against TB”

Bill Gates

*Ministerial Meeting on MDR-TB
April 1, 2009, Beijing*



The Future

YESTERDAY

Episodic Surveillance

AFB

Old drugs

DOT

Paper records

Stock outs

Political proclamations

TOMORROW

Real time monitoring

Diagnostic quiver

New regimens

Electronically Observed Tx

Distributed data network

Supply chain management

Empowerment