TB diagnostics: global value chain and current pipeline

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McGill

Stop TB Partnership

Disclosure of conflicts

- No financial conflicts
- I consult for Foundation for Innovative New Diagnostics & Bill & Melinda Gates Foundation
- I co-chair the Stop TB Partnership's New Diagnostics Working Group (NDWG)

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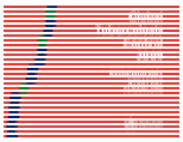
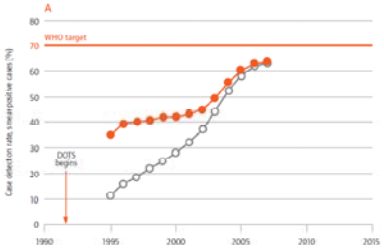
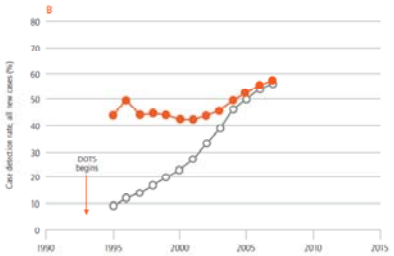
Global TB Case Detection



- 2.6 million new smear + cases notified in 2007
- 64% of the estimated 4.1 million cases



- 5.3 million new cases overall notified in 2007
- 57% of the estimated 9.3 million cases



WHO Report 2009 – Global Tuberculosis Control

Diagnostic challenges

- Smear-negative tuberculosis, particularly in HIV-infected persons
- Childhood tuberculosis
- MDR and XDR-TB in specific situations
- Extra-pulmonary tuberculosis
- Latent tuberculosis infection in high-risk populations (children, contacts, HIV)

Why is diagnosis the Achilles' heel of TB control?

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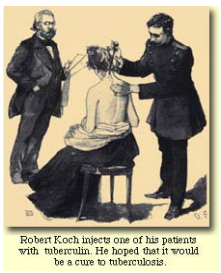
Diagnostic tools that Koch used…

Microscopy

Culture



Tuberculin test

6

are still in use today!

- Active TB
  - Sputum microscopy [1882]
  - Mycobacterial culture [1882]
  - Chest X-rays [1896]
- Latent TB (LTBI)
  - Tuberculin skin test [1890]

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Thanks to a resurgence of interest in new tools and massive funding

FIND FOUNDATION FOR INNOVATIVE NEW DIAGNOSTICS

TDR

Stop TB Partnership

gli global laboratory initiative advancing TB diagnosis

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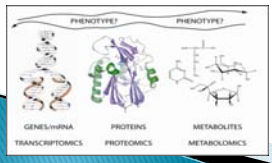
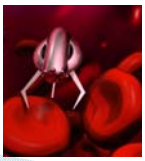
and advances in basic science

- Omics (genomics, proteomics, etc)
- Immunology
- Molecular biology
- Biotechnology
- Nanotechnology





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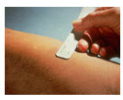
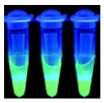
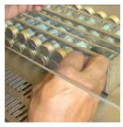
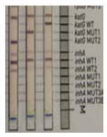
We now have a strong diagnostics pipeline









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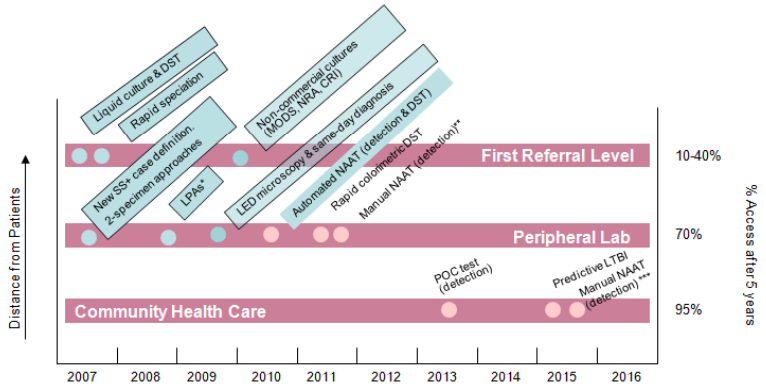
TB diagnostics pipeline in 2010



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

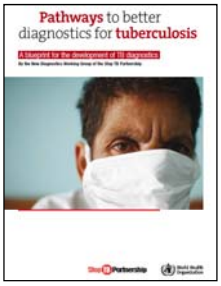
* Manual NAAT: technology for MTB Drug Susceptibility Testing
** Manual NAAT: technology for MTB detection at the Peripheral Lab
*** Manual NAAT: technology for MTB detection at the Community Health Care Level

Technologies in boxes: endorsed by WHO

Courtesy: STP NDWG

What is the blueprint (pathway) to new TB diagnostics?

Stop TB Partnership's New Diagnostics Working Group



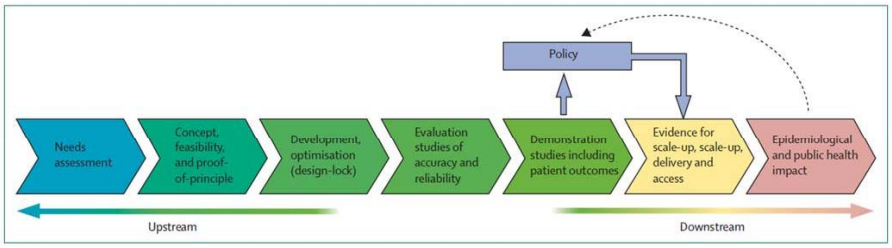
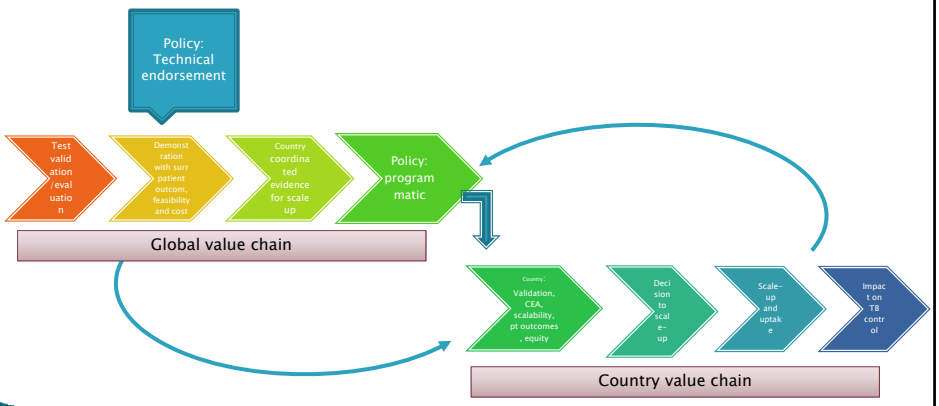


Figure 4: Schematic showing the pathway to tuberculosis diagnostics, from concept to delivery
Source: Stop TB Partnership's New Diagnostics Working Group. Pathways to better diagnostics for tuberculosis: a blueprint for the development of TB diagnostics (2009),[180] and reproduced with permission from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

STP NDWG 2009

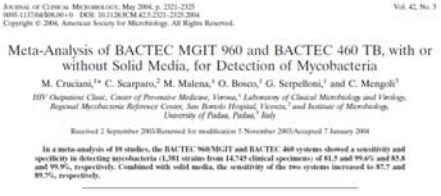
Global versus local value chains



Policy on culture

Liquid Culture

- Liquid culture systems reduce delays in obtaining results to days rather than weeks
  - For DST, delay may be as little as 10 days vs. 28-42 days with solid media
- Liquid systems are more sensitive - increase the case yield by ~10% over solid media
- Liquid systems are, however, more prone to contamination by other micro-organisms.
  - In experienced laboratories, ~5-10% of specimens cannot yield results because of contamination



Meta-Analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without Solid Media, for Detection of Mycobacteria

http://www.who.int/tb/dots/laboratory/policy/en/index3.html

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WHO policy in 2007

The use of liquid medium for culture and DST

WHO recommends, as a step-wise approach:

1. The use of liquid medium for culture and DST in middle- and low-income countries.

2. The rapid species identification to address the needs for culture and drug susceptibility testing (DST).

Taking into consideration that liquid systems will be implemented in a phased manner, integrated into a country specific comprehensive plan for laboratory capacity strengthening and addressing the following key issues:

1. **Appropriate biosafety level;**
2. **detailed customer plan describing guarantees and commitments of the manufacturer;**
3. **appropriate training of staff;**
4. **maintenance of infrastructure and equipment in laboratories;**
5. **quick transportation of samples from the peripheral to the culture laboratory;**
6. **rapid communication of results.**

More information

1. Background documentation
2. Definition of a new sputum smear-positive TB case
3. Reduction of number of smears for the diagnosis of pulmonary TB
4. The use of liquid medium for culture and DST
5. Moving research findings into new WHO policies

World Health Organization

Use of Liquid TB Culture and Drug Susceptibility Testing (DST) in Low and Medium Income Settings

Summary report of the

Expert Group Meeting on the use of liquid culture media,

Geneva, 26 March 2007

http://www.who.int/tb/dots/laboratory/policy/en

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Policies on smear microscopy

New policy on smear microscopy (2007)

Definition of a new sputum smear-positive TB case

The revised definition of a new sputum smear-positive pulmonary TB case is based on the presence of at least one acid fast bacilli (AFB+) in at least one sputum sample in countries with a well functioning external quality assurance (EQA) system.

Detailed background information [pdf 144kb]

Proposal for a revision of the case definition of "Sputum Smear-Positive Tuberculosis" [pdf 1.99Mb]
Background document prepared by Hans L. Rieder and Armand Van Deun

More information

1. Background documentation
2. Definition of a new sputum smear-positive TB case
3. Reduction of number of smears for the diagnosis of pulmonary TB
4. The use of liquid medium for culture and DST
5. Moving research findings into new WHO policies

Reduction of number of smears for the diagnosis of pulmonary TB

WHO recommends the number of specimens to be examined for screening of TB cases can be reduced from three to two, in places where a well-functioning external quality assurance (EQA) system exists, where the workload is very high and human resources are limited.

Detailed background information [pdf 144kb]

BACKGROUND

The WHO Stop TB Strategy and the Global Plan to Stop TB, 2006-2015 recognizes the weakness of the health system as one of the greatest challenges to TB control and indeed to the achievement of the Millenium Development Goals (MDGs) in general. The Global Plan also recognizes that patients, particularly poor patients, face economic barriers in accessing TB control services and that patients with TB in many resource-limited settings face long and sometimes costly pathways to diagnosis. In most of these countries, the laboratory services are often neglected and may be considered to be among the weakest components of the health system.

More information

1. Background documentation
2. Definition of a new sputum smear-positive TB case
3. Reduction of number of smears for the diagnosis of pulmonary TB
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5. Moving research findings into new WHO policies

http://www.who.int/tb/dots/laboratory/policy/en/ 19

LED Microscopy

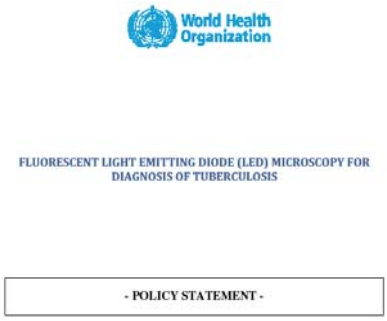
Table 1. Comparison of commercial light-emitting diode products currently available for TB diagnostics.

Device		Manufacturer	Standalone microscope	Attachment	Light transmission	Battery powered	Weight (kg)	Cost (US $)	Ref.
Primo Star iLED		Carl Zeiss, Oberkochen, Germany	Yes	NA	Epifluorescent	Yes	9.5	4825*	[101]
Lumin™		LW Scientific, Lawrenceville, GA, USA	No	Objective lens replacement (20, 40, 60 and 100× oil)	Epifluorescent	Yes	0.448	700–2000*	[102]
ParaLens		QBC™ Diagnostics, Philipsburg, PA, USA	No	Objective lens replacement (40, 60 and 100× oil)	Epifluorescent	Yes	1.27	995§	[103]
FluoLED		Fraen Corporation Srl, Settimo Milanese, Italy	No	Adaptor attached to base and filter installed on head of microscope	Transfluorescent	Yes	5	1977–3530¶	[104]
CyScope®		Partec, Gorlitz, Germany,	Yes	NA	Epifluorescent	Yes	2.7	2372–3699¶	[105]

Minion et al. *Exp Rev Med Dev* 2009

2010 WHO policy on LED microscopy

WHO recommends that conventional fluorescent microscopy be replaced by LED microscopy, and that LED microscopy be phased in as an alternative for conventional ZN light microscopy.

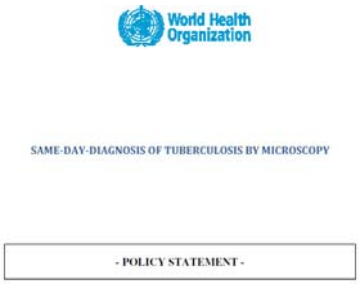


http://www.who.int/tb/laboratory/policy_statements/en/index.html

2010 WHO policy on same-day smear diagnosis

WHO recommends that countries that have successfully implemented current WHO policy for a two-specimen case-finding strategy consider a switch to the same-day-diagnosis approach, especially in settings where patients are likely to default from the diagnostic process.

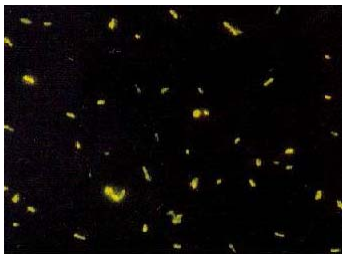
Countries that are still using the three specimen case-finding strategy should consider a gradual change to the same-daydiagnosis approach, once WHO-recommended EQA systems are in place and good quality microscopy results have been documented.



http://www.who.int/tb/laboratory/policy_statements/en/index.html

Putting it all together

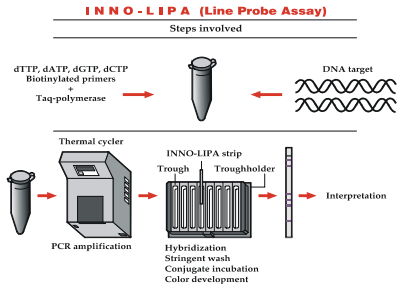
- 2 sputum smears
  - Can be on the same day
- Fluorescence microscopy
  - Preferably LED microscopy
  - Concentrated, if possible
- One of two is positive = TB



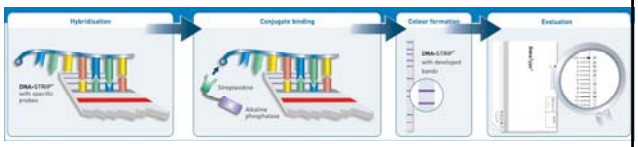
Policy on rapid tests for MDR-TB

Line Probe Assays

- Detection of MTB & RIF-resistance (*rpo*B)
- Requires extraction, amplification
- Colorimetric development using immobilized probes
- Innogenetics, INNO-LiPA Rif TB
- Hain, GenoType MTBDRplus



Inno-LiPA Rif.TB assay
Innogenetics, Belgium

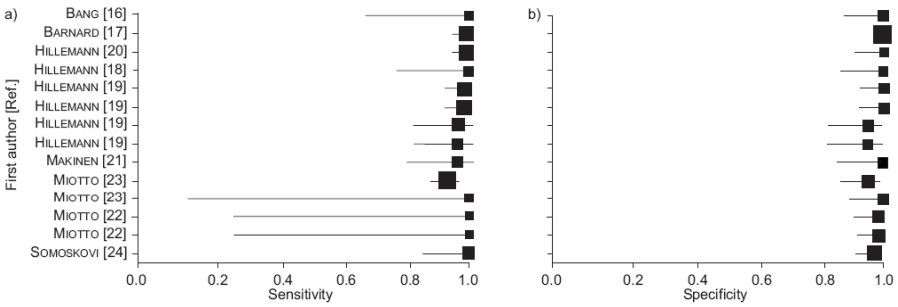


GenoType MTBDRplus assay
Hain Lifescience GmbH, Germany

Meta-analysis of GenoType MTBDR studies: rifampicin resistance

GenoType MTBDR assays for the diagnosis of multidrug-resistant tuberculosis: a meta-analysis

D.I. Ling*, A.A. Zwerling* and M. Pai*,#



98% Sensitivity

99% Specificity

Ling, Zwerling & Pai. ERJ 2008

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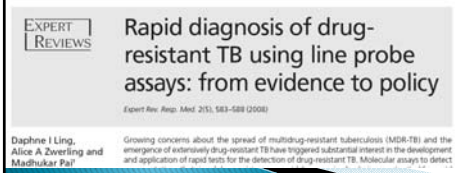
New WHO policy on line probe assays (2008)

http://www.who.int/tb/features_archive/mdrtb_rapid_tests/en/index.html



http://www.who.int/tb/laboratory/policy_statements/en/index.html

New initiatives by WHO, Stop TB Partnership, UNITAID and FIND

http://www.unitaid.eu

EXPAND-TB supplies MDR-TB diagnostics to high-burden countries. With a new grant of US$ 61 482 085, the project, led by the GLI in close collaboration with FIND and GDF, will be expanded to increase the countries covered from 16 to 27. The overall objective is to jump-start strengthening of laboratories in these countries, through collaboration between a variety of partners.

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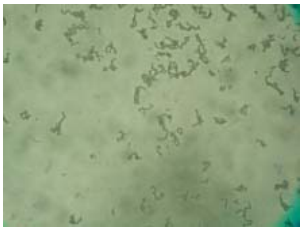
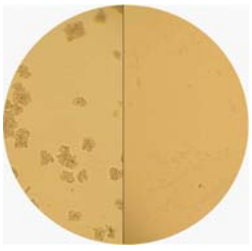
Non-commercial rapid culture methods

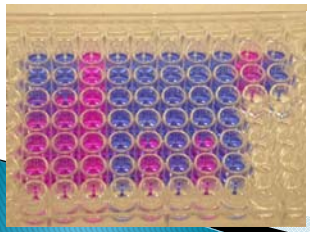
MODS



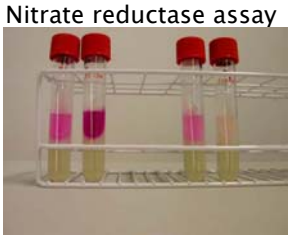
Thin layer agar



Colorimetric redox indicator assay



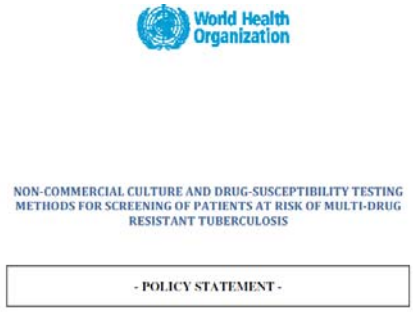
Nitrate reductase assay



2010 WHO policy on non-commercial rapid culture methods for DST

WHO recommends the selective use of one or more of the following non-commercial culture and DST methods, in reference laboratories, and under strict laboratory protocols:

- **CRI methods, as indirect tests on *M. tuberculosis isolates from patients suspected of*** having MDR-TB, and acknowledging that time to detection of MDR-TB would not be faster (but less expensive) than conventional DST methods using commercial liquid culture or molecular line probe assays;
- **MODS, as direct or indirect tests, for rapid screening of patients suspected of having** MDR-TB;
- **NRA, as direct or indirect tests, for screening of patients suspected of having MDRTB,** and acknowledging that time to detection of MDR-TB in indirect application would not be faster than conventional DST methods using solid culture.

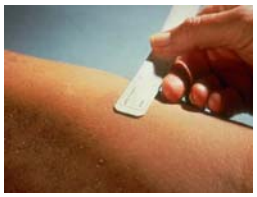


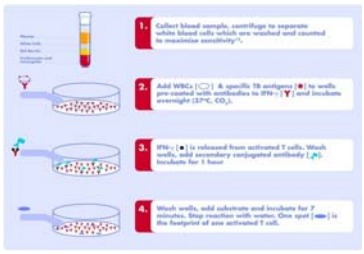
http://www.who.int/tb/laboratory/policy_statements/en/index.html

WHO policies in 2010

- IGRAs
- Serological, antibody-based tests for TB
- Automated molecular assay (Xpert MTB/Rif)

IGRAs





T-SPOT.*TB*® [Oxford Immunotec, UK]

QuantiFERON-TB Gold® In Tube [Cellestis Ltd, Australia]

2010: policy from WHO

- Active TB: The quality of evidence for use of IGRAS in diagnosis of active TB was low and it is recommended that these tests should not be used as a replacement for conventional microbiological diagnosis of pulmonary and extra-pulmonary TB in low- and middle-income countries (strong recommendation).
- LTBI: The quality of evidence for use of IGRAS for LTBI screening in various groups (HIV, contacts, children, HCWs) was very low and recommended that these tests should not be used as a replacement for TST for the assessment of LTBI (strong recommendation).

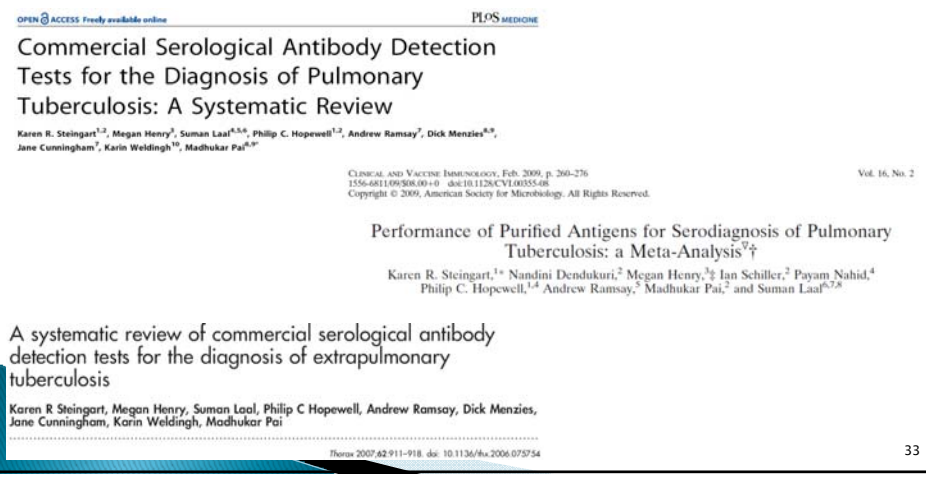
World Health Organization TDR For research on diseases of poverty

USE OF INTERFERON-γ RELEASE ASSAYS (IGRAs) IN TUBERCULOSIS CONTROL IN LOW- AND MIDDLE-INCOME SETTINGS

http://www.who.int/tb/advisory_bodies/stag_tb_report_2010.pdf

Serological tests for TB

- Attractive, especially if made into point of care (POC)
- Have been around for a long time
- Existing serological tests have failed
  - But still sold by many companies and used in developing countries



OPEN ACCESS Freely available online PLoS MEDICINE

Commercial Serological Antibody Detection Tests for the Diagnosis of Pulmonary Tuberculosis: A Systematic Review

Karen R. Steingart[1,2], Megan Henry[3], Suman Laal[4,5,6], Philip C. Hopewell[1,2], Andrew Ramsay[7], Dick Menzies[8,9], Jane Cunningham[7], Karin Weldingh[10], Madhukar Pai[8,9]*

CLINICAL AND VACCINE IMMUNOLOGY, Feb. 2009, p. 260–276 Vol. 16, No. 2
1556-6811/09/$08.00+0 doi:10.1128/CVI.00355-08
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Performance of Purified Antigens for Serodiagnosis of Pulmonary Tuberculosis: a Meta-Analysis[▽†]

Karen R. Steingart,[1]* Nandini Dendukuri,[2] Megan Henry,[3‡] Ian Schiller,[2] Payam Nahid,[4] Philip C. Hopewell,[1,4] Andrew Ramsay,[5] Madhukar Pai,[2] and Suman Laal[6,7,8]

A systematic review of commercial serological antibody detection tests for the diagnosis of extrapulmonary tuberculosis

Karen R Steingart, Megan Henry, Suman Laal, Philip C Hopewell, Andrew Ramsay, Dick Menzies, Jane Cunningham, Karin Weldingh, Madhukar Pai

Thorax 2007;62:911–918. doi: 10.1136/thx.2006.075754

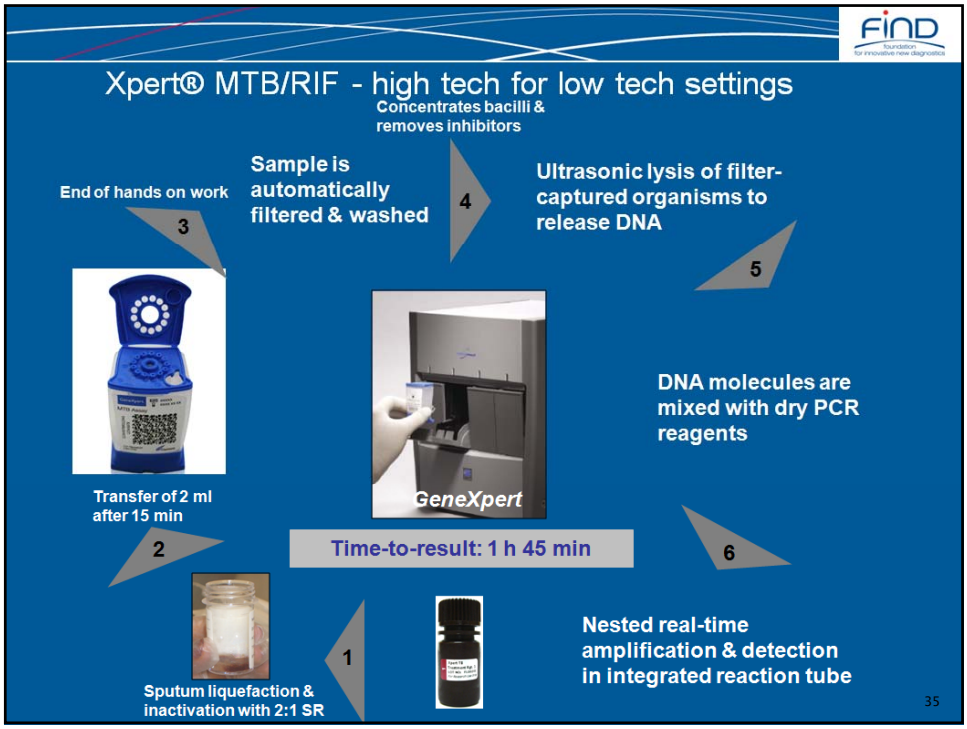
2010: negative policy from WHO

- Commercial serological tests provide inconsistent and imprecise estimates of sensitivity and specificity. There is no evidence that existing commercial serological assays improve patient-important outcomes.
- Overall data quality was graded as very low and the Expert Group strongly recommended that these tests not be used for the diagnosis of pulmonary and extra-pulmonary TB.

World Health Organization TDR For research on diseases of poverty

COMMERCIAL SERODIAGNOSTIC TESTS
FOR DIAGNOSIS OF TUBERCULOSIS

http://www.who.int/tb/advisory_bodies/stag_tb_report_2010.pdf



Automated molecular assay: Xpert™ MTB/RIF [Cepheid, USA]

>98% sensitivity in S+/C+

~70% sensitivity in S−/C+

>99% specificity in C−

2 hours to result

Rifampin resistance Y/N

Courtesy: FIND

Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB

6 December 2010

WHO THE STOP TB DEPARTMENT

World Health Organization

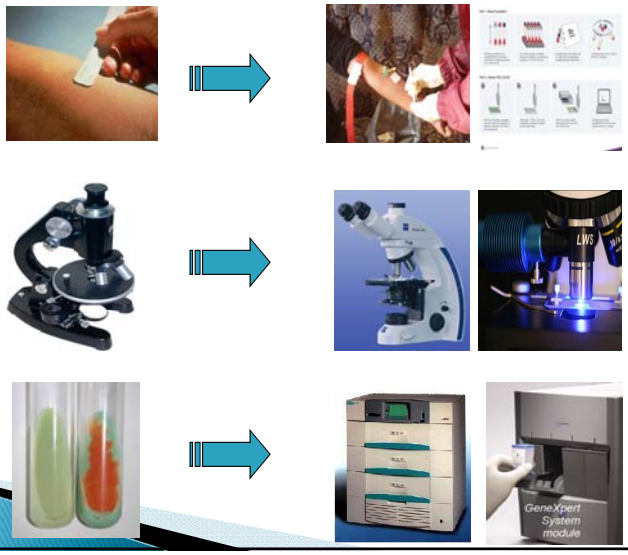
http://www.who.int/tb/features_archive/new_rapid_test/en/index.html

About WHO Expert Group and STAG-TB recommendations

- The WHO evidence synthesis process confirmed a solid evidence base to support widespread use of Xpert MTB-RIF for detection of TB and rifampicin resistance. The **Expert Group** that met on 1 September 2010 therefore recommended that:
  - Xpert MTB/RIF should be used *as the initial diagnostic test* in individuals suspected of MDR-TB or HIV-associated TB (strong recommendation);
  - Xpert MTB/RIF may be used as a follow-on test to microscopy in settings where MDR and/or HIV is of lesser concern, especially in smear-negative specimens (conditional recommendation, recognising major resource implications).
- Xpert MTB/RIF is suitable for use at district and sub-district level, outside of conventional laboratory settings, compared to conventional culture and DST which are suitable only at national or regional level in reference laboratory settings.
- Xpert MTB/RIF technology does not eliminate the need for conventional microscopy culture and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.
- Several operational conditions need to be met for successful implementation of Xpert MTB/RIF - stable electrical supply, security against theft, trained personnel, adequate storage space, annual calibration of the instrument by a commercial supplier, and biosafety precautions similar to those for direct sputum microscopy should all be in place.

http://www.who.int/tb/features_archive/new_rapid_test/en/index.html

In conclusion, much progress has been made in improving TB diagnosis, but…



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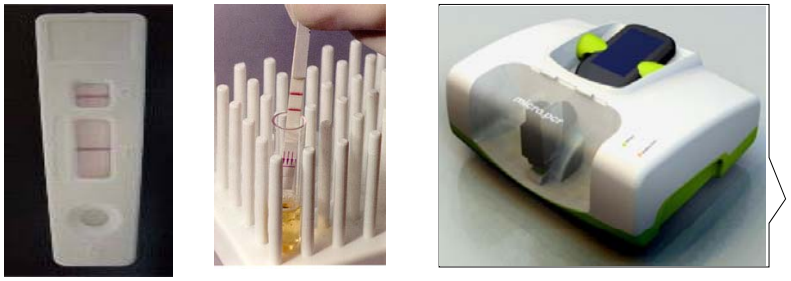
We still do not have a good point of care test



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We do not have a good biomarker(s) that will predict risk of progression to disease

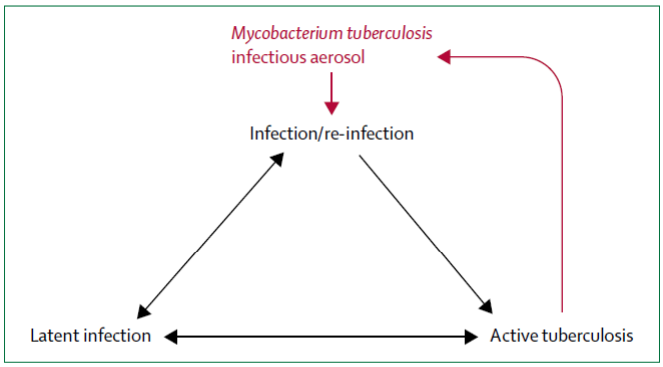

Figure 1: Clinical stages or states of *Mycobacterium tuberculosis* infection

Wallis R, Pai M et al. Lancet 2010

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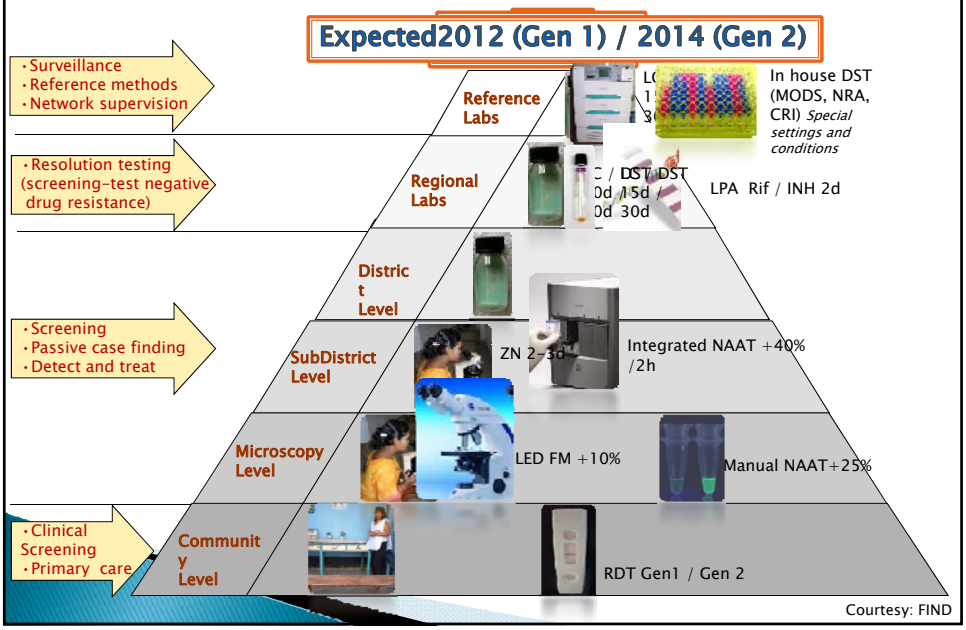
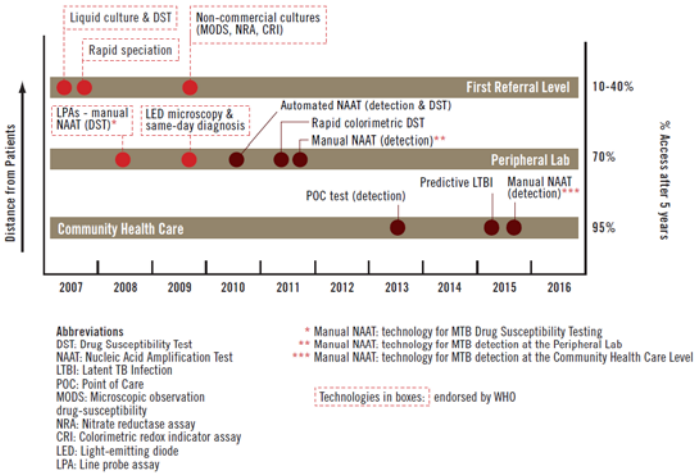
What we hope to see in the next few years



Updated NDWG pipeline for diagnostics



http://www.stoptb.org/global/plan/

www.tbevidence.org