Consultation on impact of WHO-endorsed molecular diagnostics on TB and MDR-TB case- and outcome definitions: Geneva, 12-13 May 2011

Overview of rapid TB diagnostic tests – WHO endorsed and those in the pipeline

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Acceleration

- **Tools development**: At least 20 new technologies in various stages of development and evaluation
- **WHO policy formulation***
  - Liquid culture, rapid speciation, line probe assay: 2007-2008
  - LED microscopy, selected non-commercial culture and drug susceptibility testing methods: 2009
  - IGRAs, commercial serodiagnostics, Xpert MTB-RIF: 2010
- **Access** to new diagnostics and laboratory strengthening (GLI and EXPAND-TB)

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

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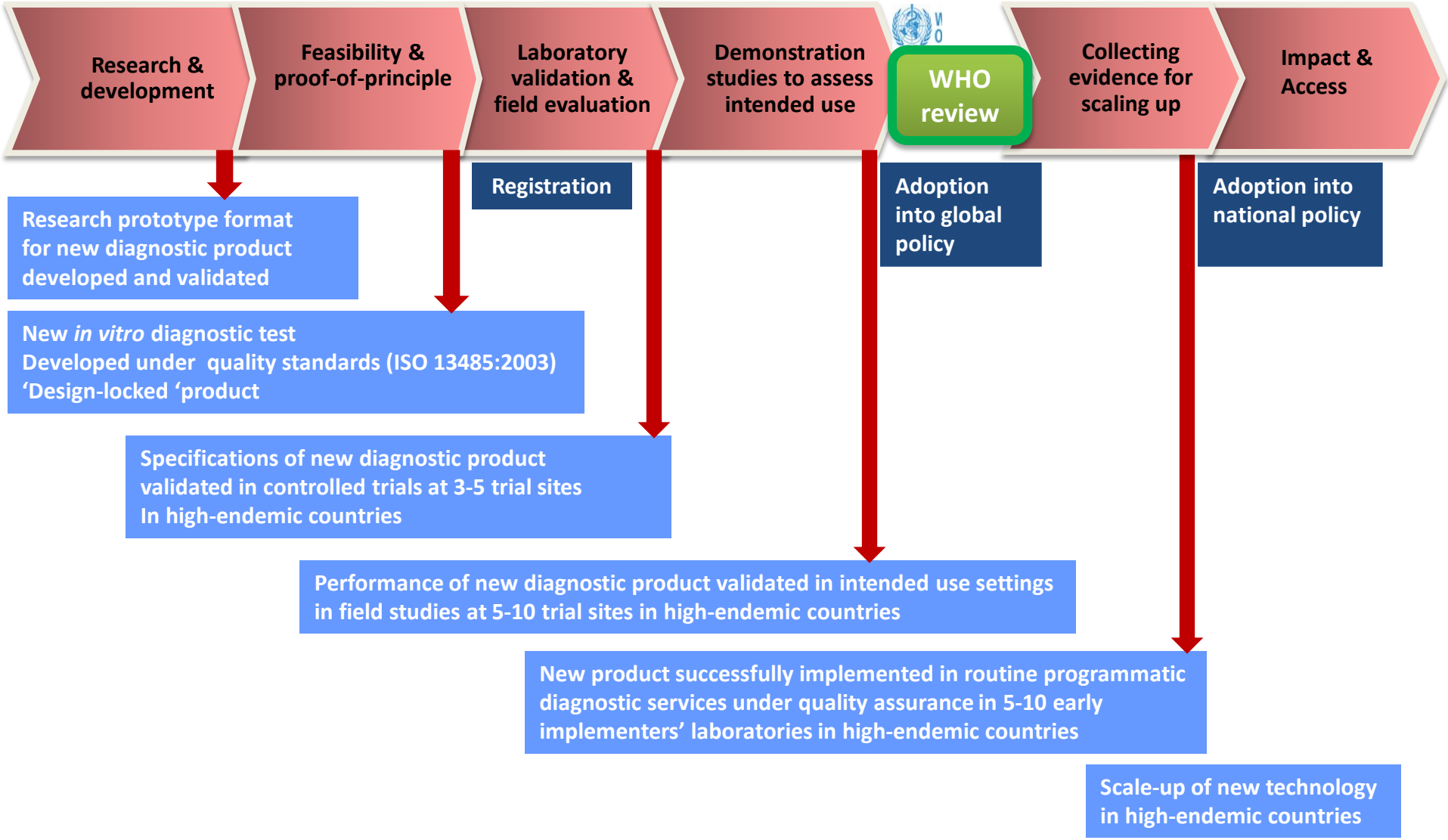
Table 1. Tuberculosis (TB) Diagnostic Tests in Use, Recently Endorsed by the World Health Organization (WHO), and in Later Stages of Development

Method	Products	Intended and/or typical use	Level of health system	Main strengths	Main weaknesses
In use					
Smear microscopy for acid-fast bacilli (light microscopy)	Noncommercial	Rapid, point-of-care test for TB case detection	Community	Requires moderate training; minimal infrastructure; minimal equipment	Low sensitivity
Culture on solid media	Many commercialized prepared media and reagents	TB case detection and as prerequisite to drug-susceptibility testing	Referral laboratory	Good sensitivity	Slow time to growth
Chest radiograph	NA	TB case detection (pulmonary TB)	Referral	Indications and use not restricted to TB	Low specificity; low sensitivity; requires equipment, trained interpreter
Tuberculin skin test	Many commercialized reagents	Detection of *M. tuberculosis* infection	Community	Extensive practical and published experience	Sensitivity decreases with increasing immunocompromise; cross-reaction with BCG vaccine
Interferon-γ release assays	QuantiFERON-TB Gold (Cellestis); T-SPOT.TB (Oxford Immunotec)	Detection of *M. tuberculosis* infection	Referral to rference laboratory	Highly specific for *M. tuberculosis*	Requires moderate training and equipment; imperfect sensitivity, especially for immunocompromised persons
Trial of antibiotics directed against routine bacterial pneumonia pathogens	NA	TB case detection for persons with suspected pulmonary TB whose sputum smear results are negative	Community	May be clinically beneficial to patients with bacterial pneumonia	Poor discriminatory power; engenders time delay in further evaluation and care for patients with TB
Automated, nonintegrated NAAT	Amplified *Mycobacterium tuberculosis* direct test (Gen-Probe); Amplicor *M. tuberculosis* test (Roche)	TB case detection (pulmonary TB)	Reference laboratory	Sensitivity between that of smear and culture; highly specific for TB	Requires moderate training and equipment; labor intensive; potential for cross-contamination among specimens
Endorsed by the WHO					
Culture in liquid media	MGIT (Becton Dickinson); BacT/ALERT (BioMérieux); others	TB case detection and as prerequisite to drug-susceptibility testing	Referral laboratory	High sensitivity (higher than culture on solid media)	Slow time to detection (although faster than culture on solid media); high contamination rates in some settings
Strip-based species identification (detects TB-specific antigen in positive cultures)	Capilia TB (Tauns)	Species identification (TB versus not TB) in cultures positive for mycobacterial growth	Referral laboratory (with culture)	Accurate; requires minimal training; minimal equipment; minimal consumables	…
Line probe manual amplification and hybridization	Genotype MTBDRplus (Hain Lifescience); INNO-LiPA Mycobacteria (Innogenetics)	TB case detection and drug-susceptibility testing	Reference laboratory	Poor sensitivity in smear-negative specimens; relatively short time to result	Labor intensive; potential for cross-contamination; requires extensive training

NOTE. Adapted from [11, 12]. BCG, bacille Calmette-Guérin; ELISA, enzyme-linked immunosorbence assay; LAMP, loop-mediated isothermal amplification; LED, light emitting diode; MODS, microscopic observation drug susceptibility; NA, not applicable; NAAT, nucleic acid amplification test.

WHO TB diagnostics policy formulation process

Diagnostic value chain



Tools/methods not recommended

- **Evidence base too weak, to be reassessed**
  - 2009: Sputum processing methods
  - 2009: TLA method for rapid DST
  - 2010: LPA for XDR-TB

- **'Negative' policy (do-not-use)**
  - 2010: Commercial serodiagnostics
  - 2010: IGRAs (high TB or HIV burden settings)

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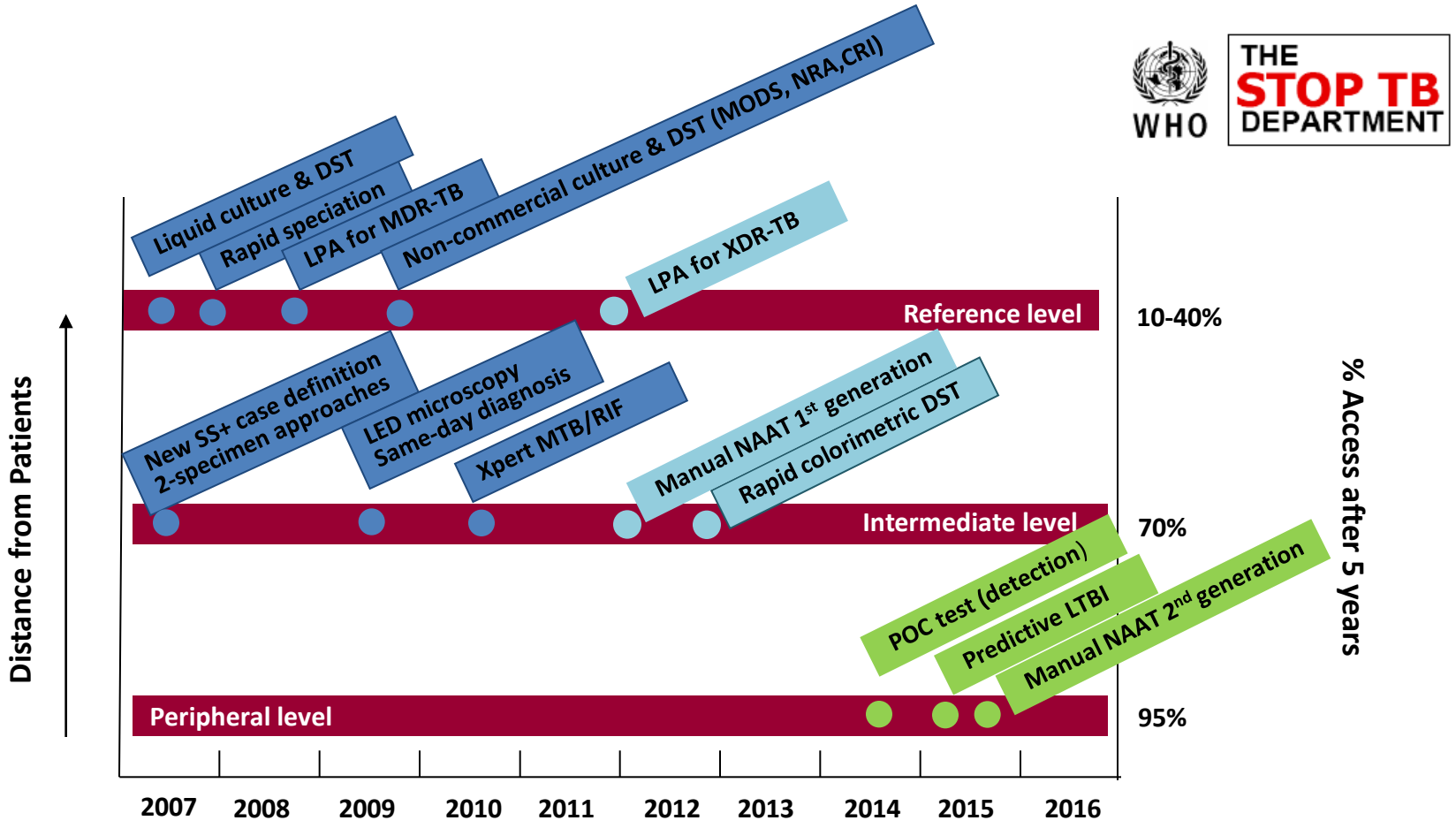


Abbreviations

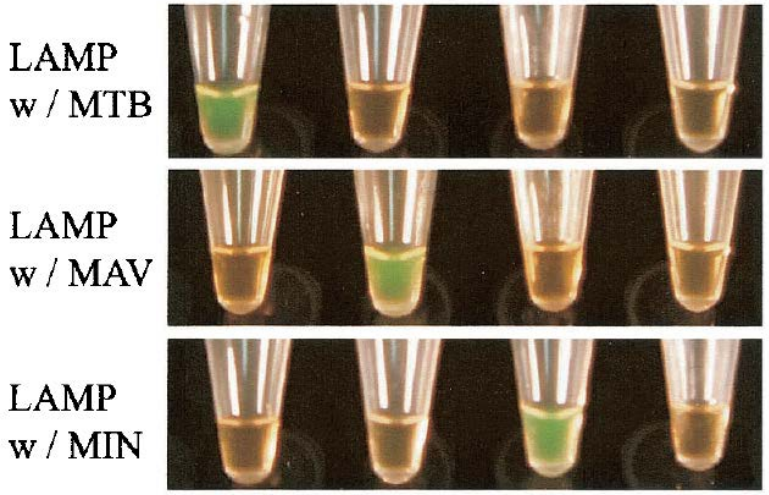
DST: Drug susceptibility test
NAAT: Nucleic acid amplification test
LTBI: Latent TB infection
POC: Point of care
MODS: Microscopic observation drug-susceptibility
NRA: Nitrate reductase assay
CRI: Colorimetric redox indicator assay
LED: Light-emitting diode
LPA: Line probe assay

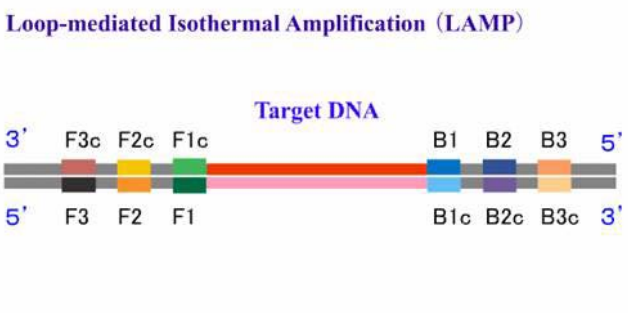
Technologies or methods endorsed by WHO
Technologies at late stages of development
Technologies at early stages of development

Manual NAAT

EIKEN CHEMICAL CO.,LTD.

- Closed system
- Isothermal
- Rapid
- Multiprimer
- Visible readout
- Detect TB, not resistance

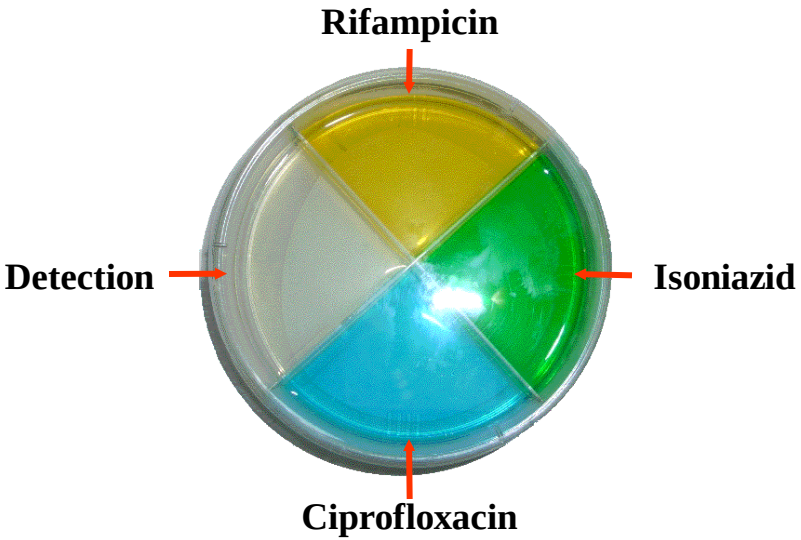


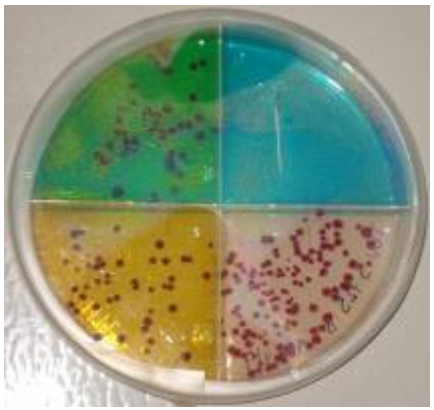


Colorimetric DST

(Carlton Evans, Welcome Trust)

- **Sputum processing in transport medium at room temp**
- **Two drops on selective thin-layer agar**
- **Colour growth detection and colony morphology my microscopy**





MDR

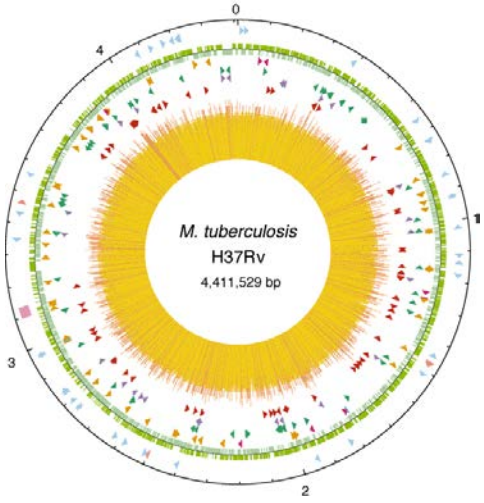
Novel antigen and antibody detection

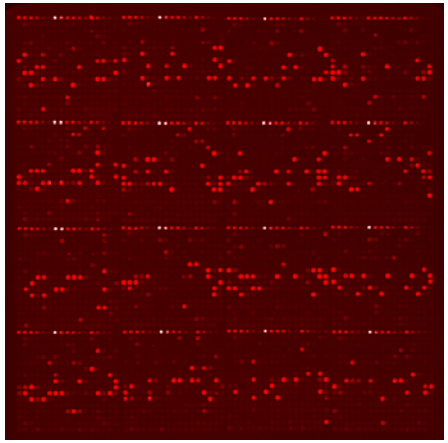
Antigen detection

- LAM – several prototypes in development

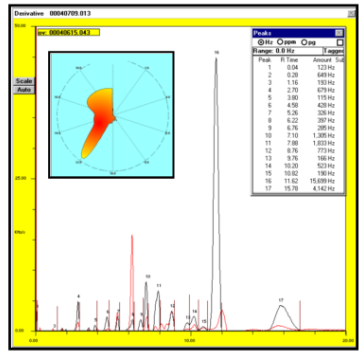
Antibody detection

- Antigen array chip with ~4,000 proteins
- Whole M.tb proteome screen to identify a set of diagnostic antigens for seroprofiling
- 19 top-rank proteins targeted for purification
- New serological tests





New frontiers: VOC detection



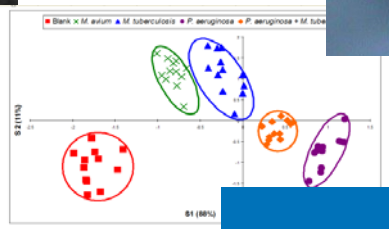


Figure 3: DFA plot showing separate cluste
aeruginosa, mixed infections (P. aeruginos
unspiked sputum. The concentration of the spik

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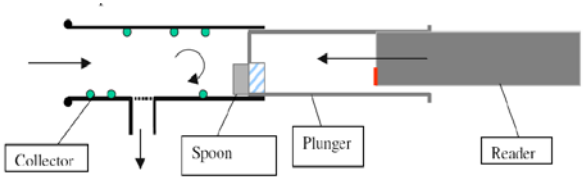

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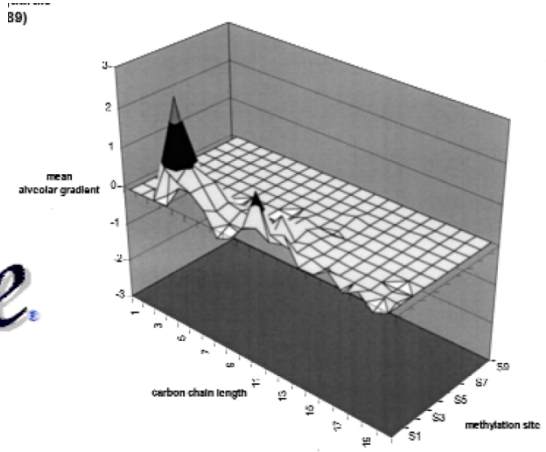

Back to the future

"*Many subject the purulent sputa to diagnostic tests - they place the phlegm over hot coals and note its odor when it has burned; for a* ***foul odor*** *always characterizes the product of physical decomposition*."
Caelius Aurelius, Roman physician 130 BC

"*In persons affected with phthisis, if the sputa which they cough up have* ***a heavy smell*** *when poured upon coals, and if the hairs of the head fall off, the case will prove fatal*."
Hippocrates, Greek physician 460-410 BC

Test-specific recommendations

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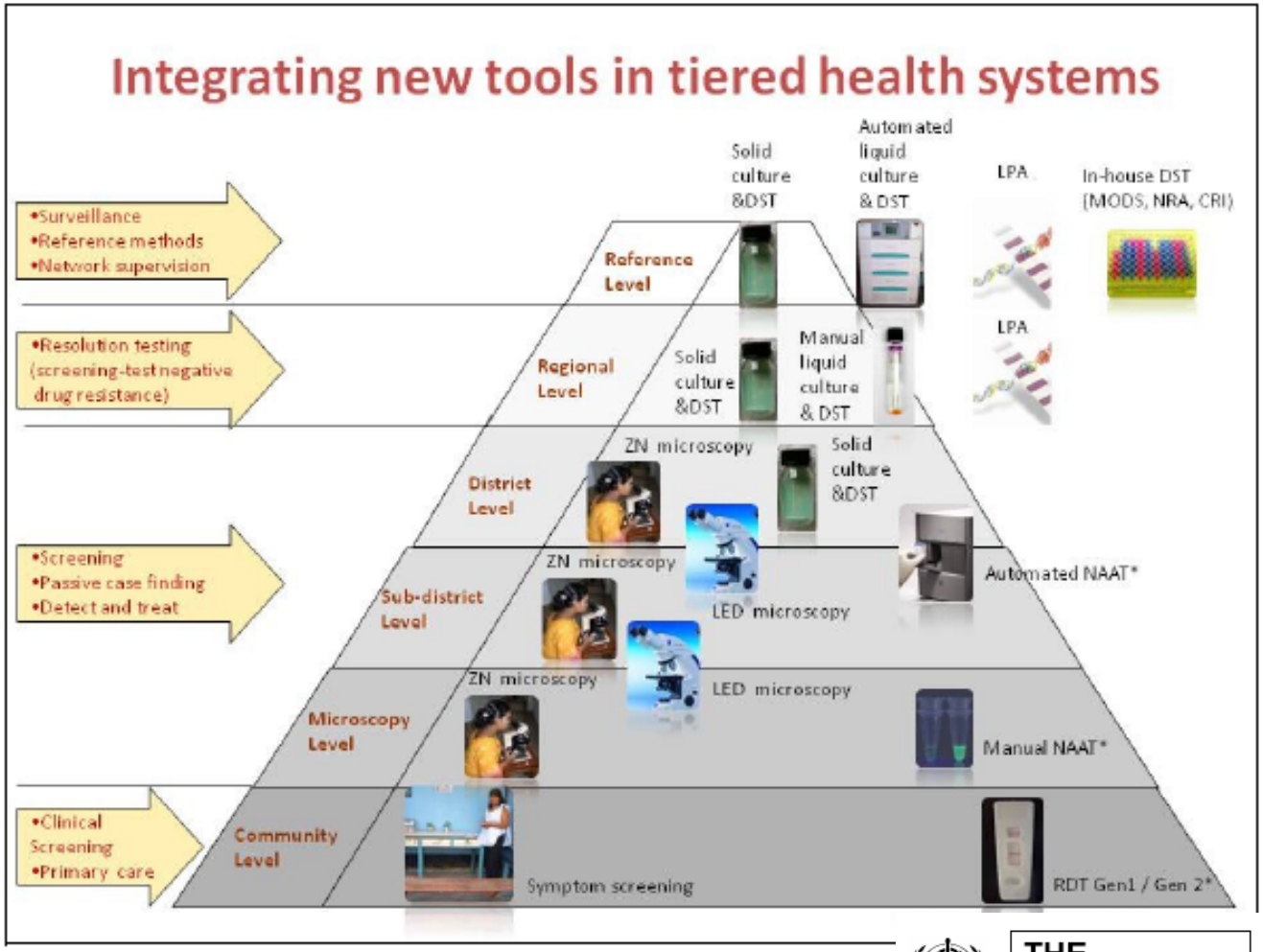
- **Different technologies**
- **Different targets**
- **Different performance characteristics**

Table 1: Pooled values (95% CI) of sensitivity and specificity of five commercial NAATs for pulmonary TB in 60 published studies (Greco, Girardi et al. 2006)

Test	AFB+		AFB-	
	Sensitivity	Specificity	Sensitivity	Specificity
Amplicor (PCR)	96 (94-97)	83 (80-86)	61 (57-65)	97 (96.8-97.4)
Cobas Amplicor (PCR)	96 (95-97)	74 (68-8)	64 (59-69)	99 (99.2-99.4)
BDP (SDA)	98 (96-99)	89 (84-93)	71 (66-76)	97 (96.4-97.4)
E-MTD (TMA)	97 (95-98)	96 (93-97)	76 (70-80)	97 (96.6-97.4)
LCx (LCR)	96 (94-98)	71 (64-78)	57 (50-64)	98 (97.8-98.5)

PCR: polymerase chain reaction; SDA: strand displacement amplification; TM: transcription mediated amplification; LCR: ligase chain reaction.

Tools in tiered laboratory services



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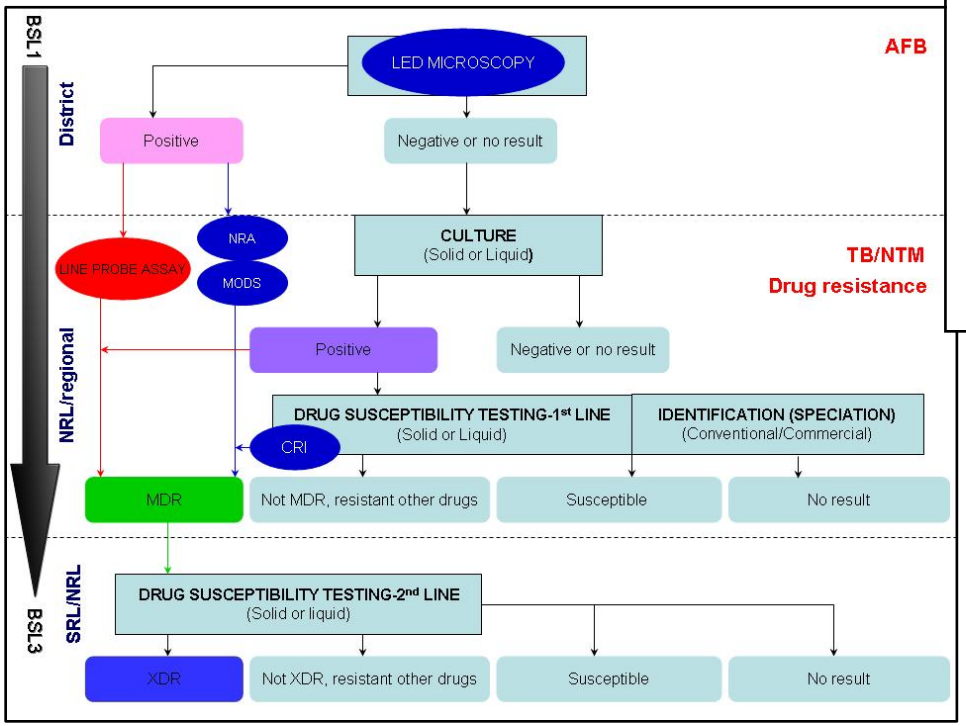
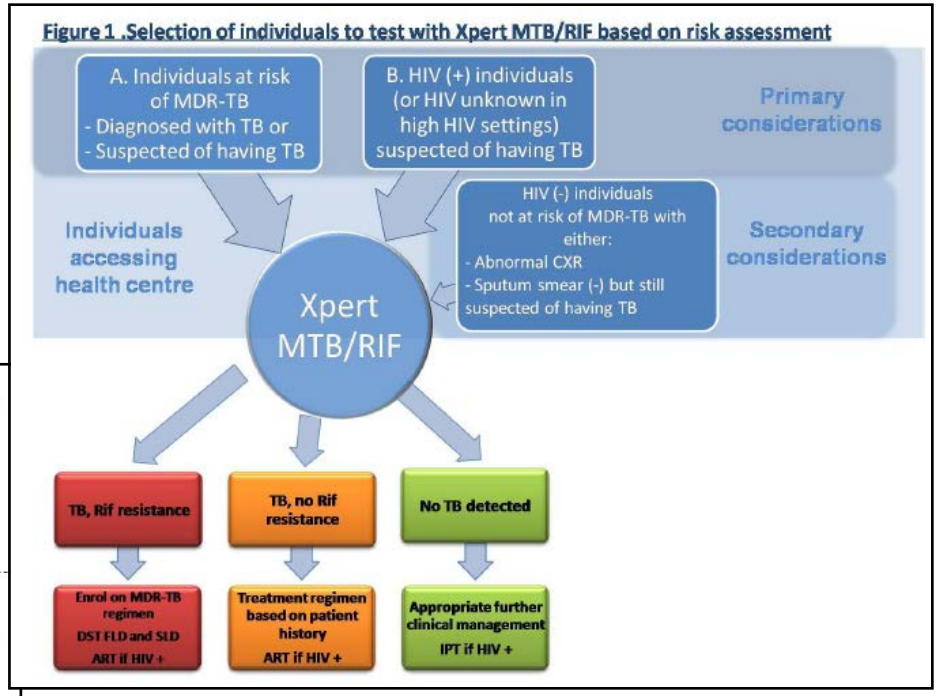
Tools in different algorithms





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Tools in different combinations

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New diagnostics dictating change

- New molecular tests now recommended for rapid diagnosis of TB and rifampicin resistance in high-burden MDR-TB and TB-HIV settings
- New molecular tests will be used for diagnosis in place of conventional bacteriology in defined patient groups
- New molecular tests (and future other rapid tests) do not readily fit with existing case definitions and treatment outcomes
- Danger of increased complexity → opportunity to improve case and outcome definitions

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