Introduction of new diagnostics in RNTCP: process and evidence required

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Overview of Presentation

- Current Diagnostic technologies under RNTCP
- Experience with newer diagnostic test
- Regulatory Process and Way forward

Background

- Care of TB patients starts with quality assured diagnosis
- Research on newer tools accelerated with a growing array of tests in the new diagnostic pipeline
- Unprecedented effort to improve and expand laboratory capacity (WHO/STB/GLI & partners)

Diagnostic Tests for TB

- For Drug Sensitive TB
  - Smear Microscopy
    - Conventional(Z-N), Fluorescent (LED-FM)
- For Drug Resistant TB
  - Phenotypic Culture and Drug Susceptibility Test (C&DST)
    - Conventional -Solid
    - Liquid Culture)
  - Molecular C & DST:
    - Line Probe Assay -LPA,
    - Cartridge Based – Nucleic Acid Amplification Test -CB-NAAT

High Quality DOTS Services - RNTCP

World Health Organization

THE STOP TB STRATEGY

VISION	A WORLD FREE OF TB
GOAL	To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets
OBJECTIVES	• Achieve universal access to high-quality diagnosis and patient-centred treatment • Reduce the human suffering and socioeconomic burden associated with TB • Protect poor and vulnerable populations from TB, TB/HIV and multidrug-resistant TB • Support development of new tools and enable their timely and effective use
TARGETS	• MDG 6, Target 8: Halt and begin to reverse the incidence of TB by 2015 • Targets linked to the MDGs and endorsed by Stop TB Partnership: o By 2005: detect at least 70% of new sputum smear-positive TB cases and cure at least 85% of these cases o By 2015: reduce prevalence of and deaths due to TB by 50% relative to 1990 o By 2050: eliminate TB as a public health problem (<1 case per million population)

COMPONENTS OF THE STOP TB STRATEGY

1 PURSUE
a.
b.
c.
d.
e.

2 ADDRESS
•
•
•

3 CONTRIB
•
•
• Adapt innovations from other fields

4 ENGAGE ALL CARE PROVIDERS
• Public-Public, and Public-Private Mix (PPM) approaches
• International Standards for TB Care (ISTC)

5 EMPOWER PEOPLE WITH TB, AND COMMUNITIES
• Advocacy, communication and social mobilization
• Community participation in TB care
• Patients' Charter for Tuberculosis Care

6 ENABLE AND PROMOTE RESEARCH
• Programme-based operational research
• Research to develop new diagnostics, drugs and vaccines

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Stop TB Partnership

RNTCP has embraced **ALL**

ents

TOP

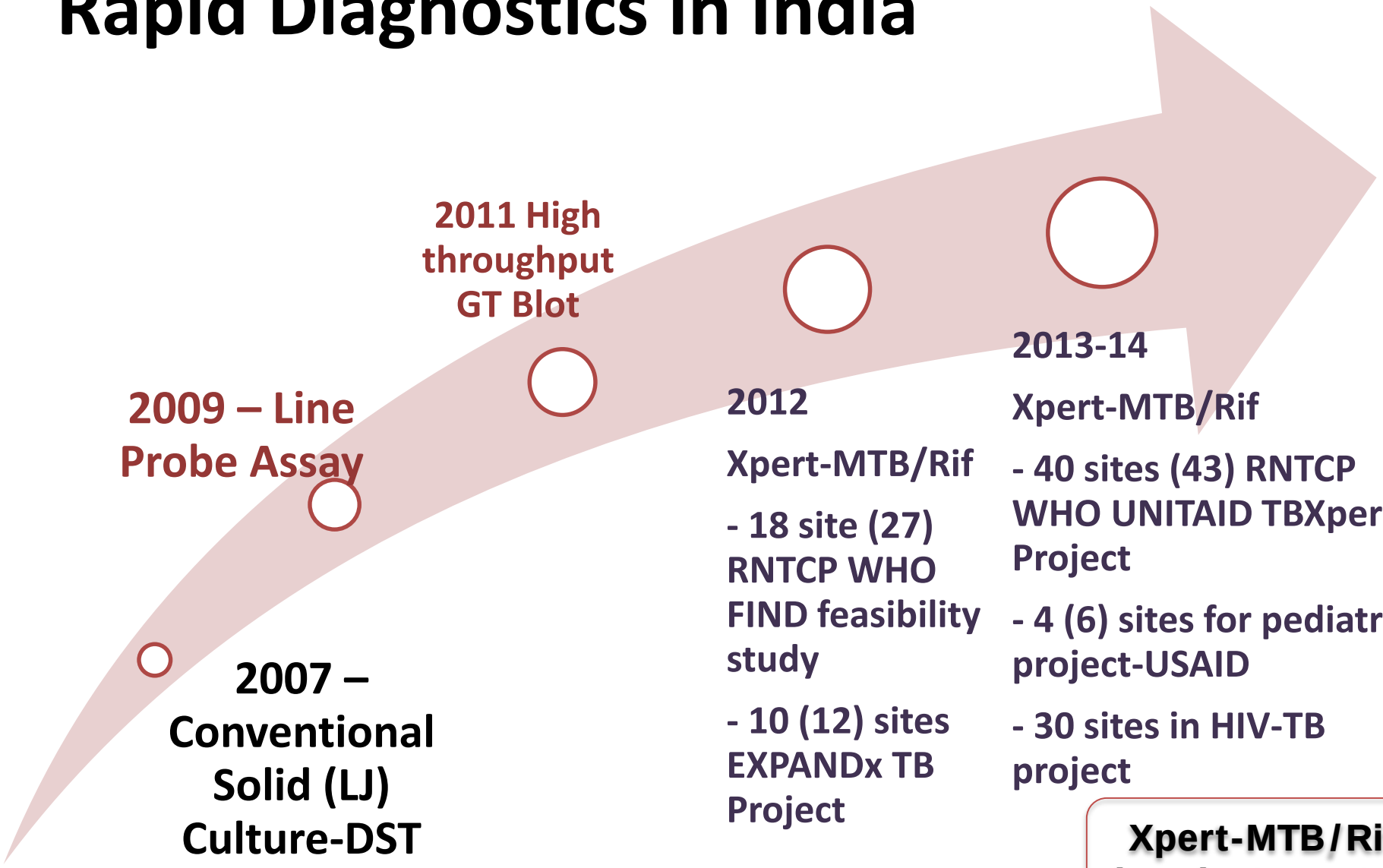
TB Strategy of WHO

RNTCP has adopted all WHO endorsed technologies e.g Smear, LC DST , LPA, GX

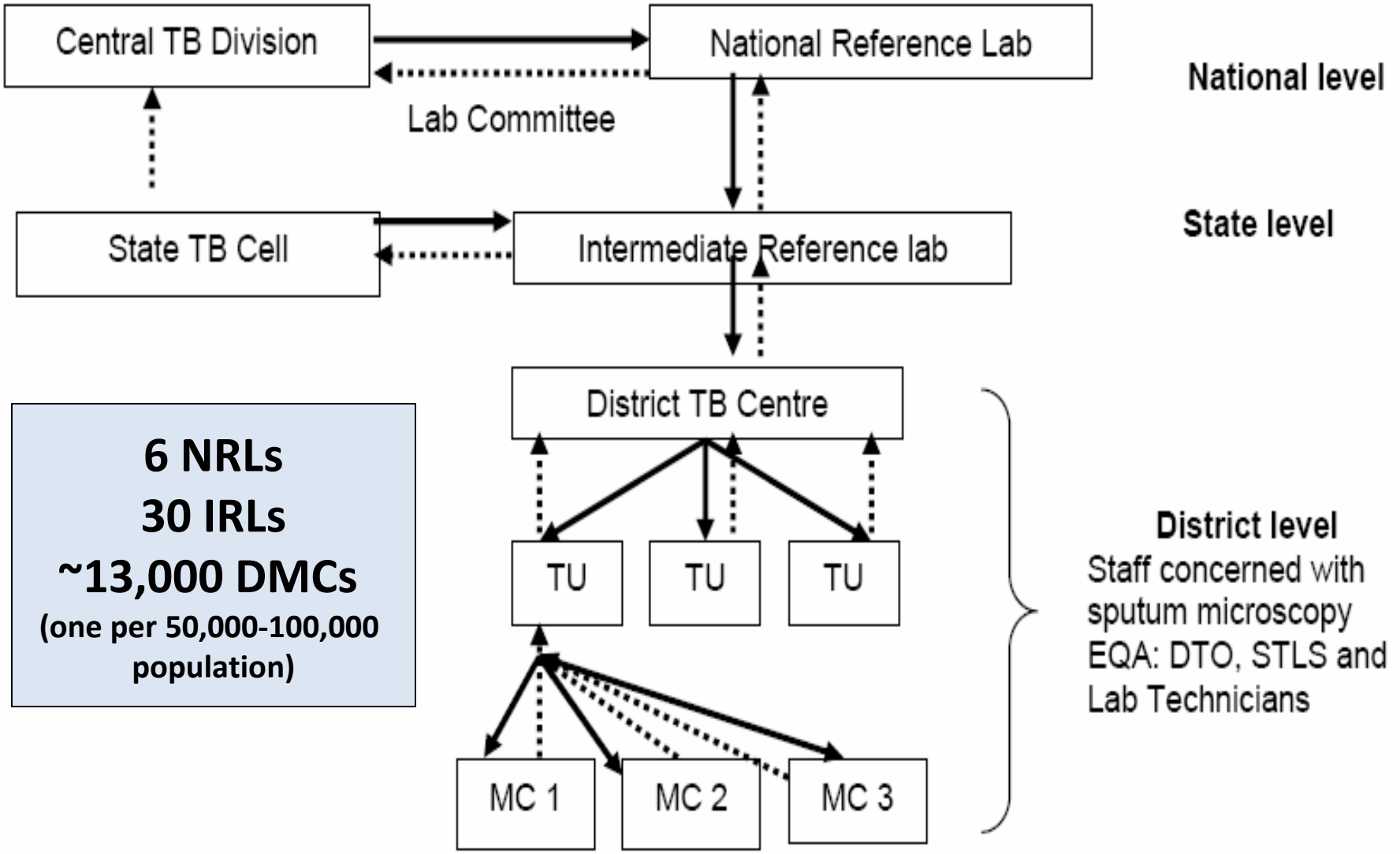
Why smear microscopy?

- Most appropriate diagnostic and reliable tool for TB control in “high burden” countries
- Simple to perform
- Easy to read
- Minimal infrastructure required
- Inexpensive
- Quick results
- Less sensitive, tedious & labour intensive
- Sensitivity difficult to improve
- Well defined quality assurance protocol

Introduction of WHO Endorsed Rapid Diagnostics in India



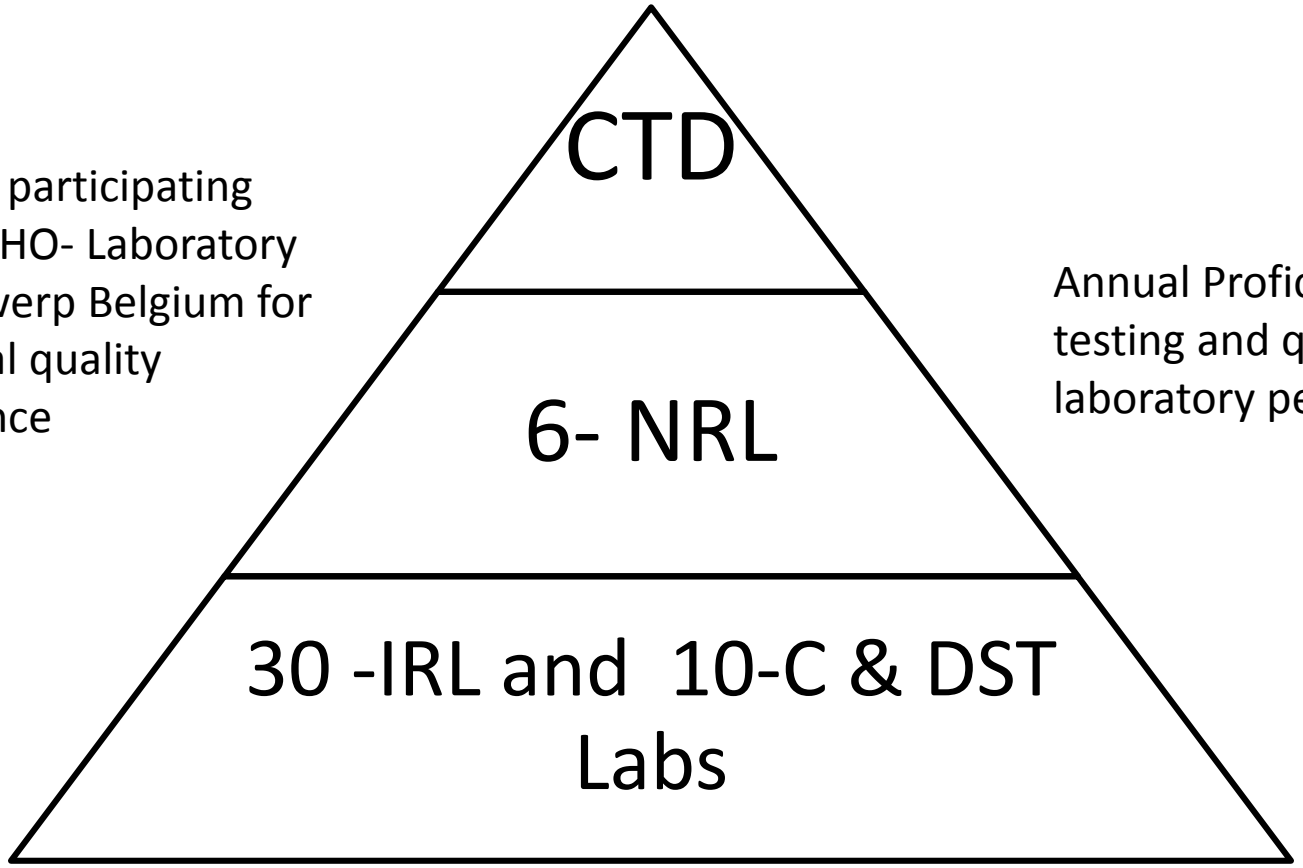
RNTCP Laboratory Network



6 NRLs
30 IRLs
~13,000 DMCs
(one per 50,000-100,000 population)

RNTCP- Quality Assurance Network for C & DST laboratory

All NRL participating with WHO- Laboratory at Antwerp Belgium for external quality assurance



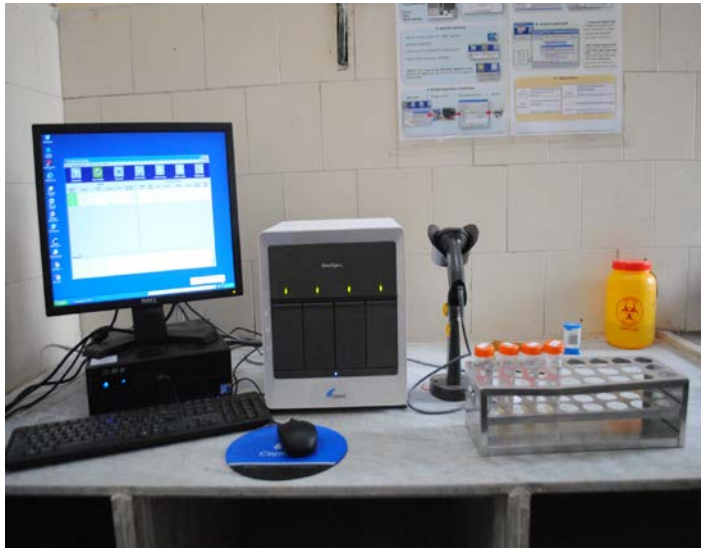
Annual Proficiency testing and quarterly laboratory performance

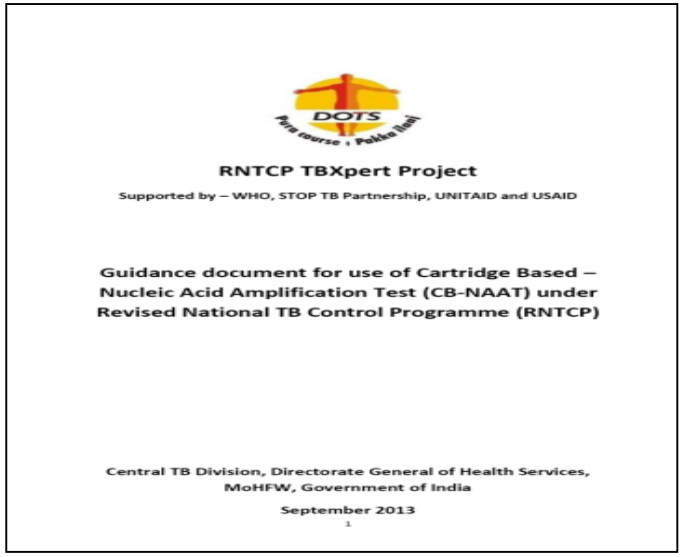
Line Probe Assay-Demonstration study

- Demonstration project was carried out at selected sites across the country (2008) based upon WHO recommendation of LPA policy in 2007
- The results was presented to the National Committee and endorsed for using LPA under programme (2009)
- As on November-2014, 50 LPA labs providing services to programme

CB-NAAT Feasibility study

- Feasibility study was conducted at 18 Sub-district level (2012)
- Finding of study lead formulation of RNTCP guideline on use of CBNAAT
- Currently, 89 CBNAAT GeneXpert labs providing services to programme





RNTCP TBXpert Project

Supported by – WHO, STOP TB Partnership, UNITAID and USAID

Guidance document for use of Cartridge Based – Nucleic Acid Amplification Test (CB-NAAT) under Revised National TB Control Programme (RNTCP)

Central TB Division, Directorate General of Health Services, MoHFW, Government of India

September 2013

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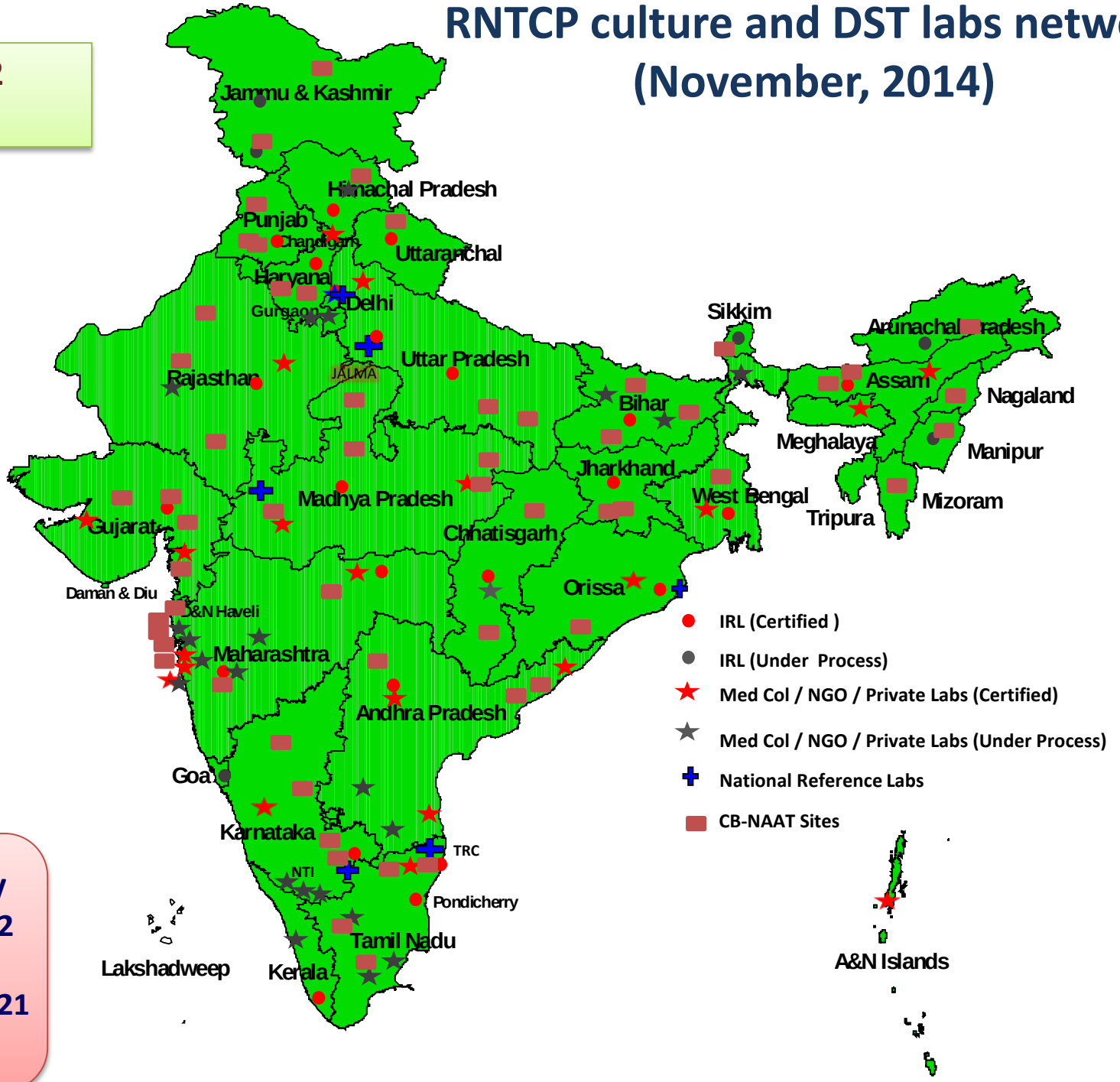
RNTCP culture and DST labs network (November, 2014)

C-DST labs: 62
SL-DST: 11



By technology
- **Solid culture: 42**
- **LPA: 50**
- **Liquid culture: 21**
- **CB-NAAT: 89**

Comparison of Microscopy Technologies

Technology	Strengths	Weaknesses
Ziehl-Neelsen Microscopy	• Required 5000 bacilli per ml • Cheap	• Low out-put laboratory (only 20-25 smear examination per day) • Less sensitive compared to FM • Strict Quality Assurance required
Fluorescent Microscopy (Light Emitting Diode -FM)	• Ease of operation • Higher sensitivity (> 15% from ZN Microscopy) • User friendly • Ideal for high load settings (> 25 smear per day) • Require less power, and very long half-life (> 10,000 hrs)	• Costly compared to ZN Microscopy

Comparison of Conventional DST Technologies

Technology	Strengths	Weaknesses
Solid Culture (LJ)	• Sensitivity 80-85% & Specificity 98%. • Colony morphology useful for presumptive ID & growth with contamination • Applicable for diagnosis and follow-up • Applicable for MDR-TB & XDR-TB	• Growth is slow and takes 6-8 weeks • AMC of instruments • Lengthy time for certification • Trained Manpower
Liquid Culture (MGIT)	• More sensitive & can be positive even when bacterial load is low(10-100 bacilli/ml) • Rapid detection (4-21 days) and DST (15-28 days) • Applicable for diagnosis and follow-up • Applicable for MDR-TB & XDR-TB	• BSL-III facility essential • Continuous power supply • Trained Manpower • Higher contamination

Comparison of Molecular DST technologies

Technology	Strengths	Weaknesses
Molecular DST (LPA)	• Rapid turnaround time (TAT), within 5 days • Highly sensitive and specific (99% RIF &80 % INH) • High Out-put laboratory with GT-BLOT (40 test per day)	• Trained manpower • Only applicable for smear positive TB patients • Labour Intensive • Detects only for first line Drug (H&R) • Only for diagnosis
CB-NAAT	• Rapid turn around time within 90 min • require bio-safety conditions similar to the conventional sputum smear microscopy sample • Minimal Training for LT • Inbuilt quality control for process	• Stable electricity supply • Require ambient operating temperatures max. 30C • Only detects R resistance • Annual Calibration • Only for diagnosis

Regulatory authority for diagnostic tests in India

- The In Vitro Diagnostic kits/reagents (IVD) are regulated in India under the provisions of the Drugs & Cosmetic Act 1940 & Rules 1945.
- The Drugs Controller General (India),Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services , Ministry of Health and Family Welfare, Government of India
- The test is classified
  - Notified e.g. IVD for HIB, HBV, HDV, Blood grouping
  - Non-Notified e.g. TB, Dengue

Regulatory authority for diagnostic tests

- There is guidelines available at http://www.cdsco.nic.in for medical diagnostic
- The act clearly indicate a norms for validation of the new test with sample size should be statistically significant to establish/demonstrate the clinical sensitivity & specificity of the proposed kits/reagents in Indian population.

RNTCP's Decision making committee

- National Expert Committee on diagnosis and management of tuberculosis: Decision making body for the programme
- National Referance Laboratory coordination committee: Review and submit recommendations to national expert committee
- National Operational Research Committee: approve the research project

Expert Group under Chairmanship of Secretary DHR & Director General ICMR

- Joint venture of Department of Bio-technology (DBT), Indian Council of Medical Research (ICMR) and Ministry of Health & Family Welfare (MOH & FW),
- The objective of this initiative is to learn the status of the Indian indigenous technologies developed by the Indian researchers and discuss the way forward so that these can be made available/commercialized for larger use for TB MDR/XDR–TB

Format for application for evaluation of newer diagnostic test

Name of the Company	
Name of Test/Technology	
Initial Fixed cost	
Is it for TB or MDR/XDR-TB	
Sensitivity/specificity	
Whether internal/external validation done	
Whether Point of care or needs sample transportation	
Whether each test to be done individually or in a batch	
Time taken from sample collection to results	
Cost per test/ per unit cost	
Volume based cost for use in National programme	
Present status of technology for use	
Expected time taken for commercialization	

The current need of programme

- More sensitive and specific technologies
- Address challenge of
  - Drug Sensitive TB
  - Drug resistance TB
  - Extra-pulmonary TB
  - Smear negative TB
  - NTM
  - Comorbid conditions e.g. HIV, Diabetes

Point-of-care diagnostic tests (POCT)

- Point-of-care diagnostic tests (POCT) can provide access to state of the art diagnostic support even in settings where health care infrastructure is minimal.
  - High accuracy (sensitivity and specificity),
  - Speed (a few hours at most),
  - Robustness (non–instrument-dependent, temperature- and humidity-tolerant),
  - Ease of use (noninvasive specimens, usable by nonskilled individuals)
  - Safety
  - Affordability

Karin Weyer, Susanne Carai, and Paul Nunn. The Journal of Infectious Diseases 2011;204:S1196–1202

Many thanks to all