Facing the Reality of Multidrug Resistant Tuberculosis: Challenges and Potential Solutions in India
April 18th – 19th 2011, New Delhi, India
RNTCP response to MDR TB

Prevention:
- Sustained high-quality DOTS implementation
- Promote rational use of anti-TB drugs
- Implement infection control measures

Stopping transmission:
- Improve laboratory capacity: Diagnosing MDR-TB
- Effective treatment of MDR-TB patients
- Initiation and rapid scale up of MDR-TB services
- Evaluate the extent of second-line anti-TB drug resistance and management strategies
Sustained high quality DOTS implementation

- India rolled out Revised National TB Control Programme (RNTCP) based on Internationally accepted DOTS Strategy in 1993 and achieved nation wide coverage in 2006
- India consistently achieved global target (>70/85 in NSP) since 2007
- India implements all components of STOP TB Strategy
- DOTS Plus (PMDT) rolled out and gradually expanded since 2007
- National Strategic Plan (RNTCP Phase III) for 2012-17 being developed

Since inception:

- >12 million TB cases initiated on DOTS;
- ~ 2 million additional lives saved;
- TB Deaths cut 6 to 7 fold (29%- 4.3%)
Trends in prevalence of culture-positive and smear-positive tuberculosis in south India (5 Blocks), 1968-2006

Impact of RNTCP

Prevalence per 100,000

Year


Pre-SCC treatment era

Prevalence per 100,000

1024
512
256
128

Culture +ve

Smear +ve

SCC treatment era

RNTCP era
RNTCP: Studies for assessment of Impact

- Nation wide ARTI Survey – 2008-10
  - Coordinated by NTI, Bangalore in association with
    - New Delhi TB Centre (North Zone)
    - MGIMS, Wardha (West Zone)
    - LRS Institute, New Delhi (East Zone)
    - CMC, Vellore (South Zone)

- Disease prevalence Surveys – 2007-09
  - TRC Chennai – MDP project
  - NTI, Bangalore
  - MGIMS, Wardha
    - Symptomatic screening + CXR
    - + Sputum Smear + Culture
  - PGI, Chandigarh
  - AIIMS, New Delhi
  - JALMA, Agra
  - RMRCT, Jabalpur
    - Symptomatic screening + Sputum Smear + Culture

- National Epidemiological Consultation recently held with WHO Experts to arrive at consensus on TB Burden estimation and Impact measurement.
Rational use of Anti-TB drugs: Problems

- In 2006, substantial quantity of FLDs and almost 100% of SLDs were sold and used outside of RNTCP
- Well documented that management of TB patients outside of RNTCP is often poor leading to risk of failure of treatment and development of drug resistance
- Large unregulated private sector
- Conflict of Interest
- Easy availability of anti TB drugs
Steps to promote rational use of anti TB drugs

n “Chennai Consensus Statement” based on ISTC developed and disseminated

n IMA on behalf of RNTCP interacting with MCI for guidelines to all healthcare providers on rational use of anti TB drugs

n Interactions with office of DCGI to draft guidelines for the regulation of anti-TB drugs, especially SLDs

n Encouragement of additional pre-qualified drug manufacturers

n GDF meeting with Indian Drug Manufacturers to advocate WHO PQ standards / SRA and share the demand in coming years
Airborne infection control measures: Problems

- Infection control considered synonymous with waste management
- Lack of National guidelines on Airborne Infection control in context of TB
- Overcrowding/lack of space at health facilities
- Lack of awareness and commitment of hospital administrators

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Airborne infection control measures: Steps taken

- National Airborne Infection Control Committee constituted
- “National guidelines for airborne infection control” developed and pilot tested
- Provision under RNTCP to upgrade IC measures at
  - DOTS-Plus site indoor facilities
  - Intermediate Reference laboratories
    - Collaboration with NACP to ensure IC measures at ICTCs and ART centres
    - Encouraging Medical Colleges to adopt infection control guidelines
    - Architects/Engineers of 6 states trained in Building Design and Eng approaches in AIC at Hyderabad
Context for airborne infection control (AIC)

**Challenges**
- High TB burden
- High transmission of TB and other resp. diseases in health care facilities
- Vulnerable populations, PLHA concentrated
- Scale of response & coordination required

**Opportunities**
- Massive health system strengthening investment underway
- Pandemic flu
- Growing awareness of infection control importance
- Hospitals seeking accreditation
Roadmap for AIC implementation

1. National level
   - Constitute national steering committee
   - Conduct AIC capacity building
   - Develop national operational guidelines

2. Pilot national guidelines
   - State-level advocacy and capacity building
   - Securing funds from health system
   - Baseline and follow-up assessments
National Guidelines on Airborne Infection Control

- Purpose: to provide up-to-date information about recommended methods of reducing the risk of airborne infections in health care facilities.
- Target audience:
  - Health officials (general, not just TB)
  - Health facility administrators and infection control focal points
- Elements now included in NABH hospital accreditations
- Guidelines adapted from WHO IC Policy – 2009 and covers – Managerial activities, Administrative, Environmental and Personal Protective measures, Special Settings, Household Settings, AIC Risk Assessment and Quarterly reporting systems
National AIC Guidelines Pilot Objectives

Primary

n To conduct systematic baseline assessments of AIC administrative, environmental and personal protective measures and practices at 35 selected HCF in 3 States

n To offer State & District officials, HCF administrators & IC focal points - capacity building, specific recommendations, and limited supportive supervision

Secondary

n To assess the 6-month uptake of AIC measures
Way forward – translation of pilot to practice

n Follow-up assessments

n Revision of national guidelines based on feasibility and effectiveness of measures implemented

n Integrate AIC into hospital accreditation and *routine* health system reporting (not TB)

n Implement *integrated* infection control training material for frontline HCW (RIPC)
Laboratory Scale Up Plan India: Background

- Estimated incidence of TB – 1.98 million
- Estimated incidence of MDR TB – 99,000
- DRS from 3 states in India has shown that MDR among new cases is low

<table>
<thead>
<tr>
<th>State</th>
<th>MDR among New Cases</th>
<th>MDR among previously Rx cases</th>
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<tbody>
<tr>
<td>Gujarat</td>
<td>2.4</td>
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<tr>
<td>Maharashtra</td>
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<td>Andhra Pradesh</td>
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C & DST Laboratory Network

Central TB Division, New Delhi

- Tuberculosis Research Centre, Chennai
  - State level laboratories
- National Tuberculosis Institute, Bangalore
  - State level laboratories
- LRS Institute, New Delhi
  - State level laboratories
- JALMA Institute, Agra
  - State level laboratories
National Lab Committee

- Comprises of:
  - CTD
  - NRLs
  - Other partners

- Meets once in a quarter every year

- Reviews establishment of C & DST laboratories
Universal Access to TB Care

- Major Policy decision by RNTCP 2010 – change from 70/85 targets towards:
  - early and complete case detection to include all forms of TB
  - smear negative PTB
  - pediatric TB
  - TB in HIV
  - DR TB including MDR and XDR TB and
  - TB among risk groups, etc.
RNTCP’s Vision to achieve universal access for DR TB

- By 2012:
  universal access under RNTCP to laboratory based quality assured MDR-TB diagnosis for all smear positive re-treatment TB cases and new cases who have failed an initial first-line drug treatment

- By 2015:
  universal access to MDR-TB diagnosis and treatment for all smear positive TB (new and re-treatment) cases registered under RNTCP
Diagnosis of drug resistant tuberculosis

Early diagnosis

Application of accurate chemotherapy

important because absence of the same may:

1. propagate resistance
2. cause unnecessary drug toxicity
3. decrease chances of cure
4. increase the cost of therapy
Need for laboratory capacity scale-up

- Initially planned 27 LJ media C&DST labs is grossly insufficient

- **Annual** requirement after 2012:
  - DST for nearly 180,000 MDR-TB suspects
  - Over 330,000 follow up cultures annually (11 cultures per patient over 2 years of treatment)

- Use of solid-media only strategy for diagnostic culture/DST & follow-up culture would require an additional 124 labs of equal capacity as today’s IRLs
Strengthen Reference Laboratories and Laboratory Network

- Achieving scale-up will require major strengthening of existing NRLs in all aspects:
  - Human resources
  - Physical infrastructure and consumables
  - New technologies – liquid and molecular
  - Second-line drug susceptibility testing
  - Capacity to supervise and accredit
  - Lab information system
  - Technical and operational support

- Consider additional NRLs for support & supervision of culture & DST labs

- Laboratory networking: Support for periodic update trainings/capacity building, & TA visits
Develop lab capacity sufficient to evaluate and manage MDR in all RNTCP S+ RT patients by 2012

- Increase lab capacity several fold by:
  - Increasing through-put of existing and future labs
  - Developing many more diagnostic laboratories
  - Strengthen reference laboratories and lab networking
  - Outsource laboratory services to privates/NGOs, esp for difficult areas

- Distribution of labs for strengthening
  - Existing IRLs / accredited laboratories
  - Settings with highest patient loads
  - Willing partners
RNTCP’s Vision to address the laboratory bottleneck

- Increase throughput / unit of lab by
  - Introduction of molecular tools for diagnosis of MDR TB (48 hrs Vs 6-8 weeks)
  - Number of tests to be done per day can be increased to 48/day or more based on number of units
  - Automated Liquid culture systems

- Increase sputum processing units with additional equipments

- Additional HR
Process of Accreditation

Accreditation is being done by the RNTCP by applying the WHO standards for quality assured TB laboratories to perform Drug Susceptibility testing.

Laboratories that have the infrastructure, HR and capacity to perform TB DST are eligible for being part of the RNTCP network of accredited labs.
NGO PP Scheme

- Laboratory should be willing to sign the MoU with the State Health Society
- Sputum Culture and DST services to be provided free of charge to RNTCP patients (referral from programme)
- Rs 2000/- for smear, culture and FLD
- Rs 400/- per specimen for Culture & ID
Laboratory Scale up : an RNTCP response

- 43 laboratories proposed for C & DST

- Of these, 20 laboratories have been already accredited and are supporting the DOTS Plus activities

- Few more in the advanced stages of the accreditation process
Still Not Enough...

- Health Ministry
  - Medical Colleges
  - ICMR Institutes
- Other Sectors
  - Defence labs
  - Railways, Coal and Mining
- Private & Corporate
  - Private Labs
  - Corporate labs
More is required

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<th>New Technology</th>
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<td></td>
<td>• More refined LPA</td>
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<td>Refine approaches</td>
<td>• Better refine who requires the test</td>
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<td>• Improve algorithms</td>
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<td>More new technology</td>
<td>• DNA Chip technology</td>
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<td>• Any other new</td>
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Newer diagnostic methods

- Newer diagnostic tools – rapid progress in the past few years

- Policy for use need to be dynamic both globally and at country level

- New tools are being assessed for policy development based on systematic evidence collection and its impact on patient management
Same Day Diagnosis

- There is sufficient generalizable evidence that a same-day-diagnosis approach is equivalent in terms of diagnostic accuracy to conventional case-finding strategies by microscopy.

- Countries that have successfully implemented the 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.
Rapid Methods of Diagnosis

- Light-emitting diode (LED) fluorescent microscopy
- Liquid Cultures: MGIT 960
- Molecular tests:
  1. Line probe assay
  2. Gene xpert
  3. LAMP TB- Manual NAAT (Loop Mediated Isothermal)
Recommended that conventional fluorescence microscopy be replaced by LED microscopy and that LED microscopy be phased in as an alternative for conventional ZN light microscopy in both high- and low-volume laboratories
MGIT 960 AUTOMATED LIQUID CULTURE SYSTEM

**STRENGTHS:**

- Capacity to incubate & monitor 960 tubes every 60 minutes
- Can handles 8000 Cult/year
- System alerts when tubes +ve,
- No radioactive material used
- Results available -7-14 days

**WEAKNESS:**

- Continuous Electricity
- • Reagent costs
- • High Contamination rates
- • Training
- • ID required for positive
Capilia TB Assay

- Immunochromatographic assay based on detection of MPB64, present in M. tb complex but not MOTT or some BCG strains
- Consists of nitrocellulose membrane with anti-MPB64 mouse antibodies conjugated with colloidal gold
- With antigen-antibody reaction, see red-purple band within 15 mins.
- Evaluated for 172 mycobacterial isolates (119 M.tb complex): 92% sensitivity, 100% specificity*
- 3 false negatives with MPB64 gene mutation

Molecular Methods

Good performance characteristics

Rapid

Sensitive (approaching culture)

Specific

Expensive and requires sophisticated technology
The Line Probe Assay (LPA)

Use of LPA under the program

Integrated national plan for LPAs with MDR-TB management and lab capacity strengthening

Use of LPAs on smear-positive sputum and cultures (insufficient evidence on smear negatives)

LPAs do not replace culture + DST

Commercial assays recommended
Lab infrastructure, procedures and biosafety

Human resources, Training, technical support and supplies
EQA
Newer tools in the pipeline
GeneXpert- MTB RIF Test

Automated NAT, specific for TB, RIF resistance through rpoB multiplex PCR, as sensitive as culture
One tube reaction
Only one step sputum processing
1-2 hrs for results
16 samples/day/module
One day training for technologists
GeneXpert

Major advantages in workflow

- no bio-safety cabinet
- closed system (no contamination risk)

Performance

- specific for *M. tb*, sensitivity close to culture
- detection of rif-resistance via rpoB gene
Loop Mediated Isothermal Amplification (TB LAMP)

Simplified NAAT
Does not require a thermocycler
Detection by fluorescence
Rapid (90 mts) High throughput
Sensitivity 97%
Specificity 99% (culture reference)
High sensitivity for smear negative specimens (HIV)
TB LAMP

Major advantages in workflow:
- no bio-safety cabinet
- closed system (no contamination risk)

Performance:
- specific for MTB, sensitivity close to culture
detection of rif-resistance via rpoB gene

Useful in:
- high MDR-TB settings
- high HIV prevalence settings
Effective DOTS Plus implementation

Component of DOTS Plus:

- Sustained political and administrative commitment
- Diagnosis of MDR-TB through quality assured culture and drug susceptibility testing
- Appropriate treatment strategies that utilize second-line drugs under proper management conditions
- Uninterrupted supply of quality assured anti-TB drug
- Recording and reporting system designed for DOTS-plus programme that enable performance monitoring and evaluation of treatment outcome
Effective DOTS Plus implementation

Treatment:

- Referral of confirmed MDR TB case to DOTS plus site

- DOTS plus committee reviews and decide to put the patients on Cat IV after evaluation

- Patients admitted for at least one week and then discharged with maximum of 7 days drug supply after informing DTO

- DTO in consultation with MOPHI identifies the DOT provider and sends drug boxes and patients records

- Patient’s progress monitored and reported as per guidelines

- Required education and support to patient provided as per need
The DOTS Plus guidelines have been prepared.

All states provide DOTS Plus services by 2012.

Rational use of anti TB drugs- advocated.

Uninterrupted supply of good quality drugs has been ensured.

Resistance to second line drugs is being monitored at the NRLs.

Efforts are on to prevent transmission of DR TB.
Provision of Good quality DOTS

Ensuring Airborne Infection Control Measures

Laboratory Scale up for the diagnosis of MDR TB

Use of Rapid diagnostic tools for fast tracking of MDR TB patients

Effective DOTS Plus implementation.