Perceptions versus Realities


Washington, DC, November 5, 2008
STEMMING THE TIDE OF MULTIDRUG-RESISTANT TUBERCULOSIS:

MAJOR BARRIERS TO ADDRESSING THE GROWING EPIDEMIC

SALMAAN KESHAVJEE, MD, PHD

HARVARD MEDICAL SCHOOL
BRIGHAM AND WOMEN’S HOSPITAL
PARTNERS IN HEALTH

INSTITUTE OF MEDICINE
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“The Emerging Threat of Multidrug-Resistant Tuberculosis: Global and Local Challenges and Solutions”

Pretoria, South Africa

March 3-4, 2010
“The New Profile of Drug Resistant TB: A Global and Local Perspective”
Magnitude of Problem  Grossly Underestimated

Certain to exceed 500,000 new cases estimated to occur each year

Only half of 22 countries with highest TB burden participate in WHO MDR-TB survey

Surveys most often represent data at least four to five years old

Data from many countries are derived by modeling not laboratory based surveillance

Few countries have capacity for testing susceptibility to second line drugs

Less than half of African Region population represented in surveillance data
Pediatric MDRTB

- Children usually not included
- When included lumped 0-14 years & 5-14 years

- 8.8% of Children with TB in South Africa have MDR-TB (limited survey 140 cases, 2008)
- 15.4% Argentina & 23.6% Peru
Number Patients Receiving Treatment Small and Ineffective

< 10% of new MDR-TB cases are treated each year

< 2% receiving verifiable, quality assured, second-line anti-TB drugs

Even in the small proportion of patients that are being treated, many are not receiving drugs that actually address their drug resistance profile, and therefore their treatment is ineffective.
Human-to-Human Spread More common than Previously Appreciated

Until recently assumed drug resistant strains too weak to achieve human-to-human transmission

Therefore, infection control was not a public health priority

Unlike pattern in 1970s and 1980s, wherein most MDR-TB appeared to result from lack of patient compliance or sequential treatment regimens, today transmission of MDR and XDR-TB strains appears to dominate, ie Shanghai; South Africa, Tomsk and Lima experience.
Pediatric MDRTB

South Africa – Gary Reubenson (2008 140 culture confirmed cases)
- 85% no previous TB treatment
- None with history of adult MDRTB contact
- 49% HIV +
- 30% mortality

Columbia-Carlos PerezValez (128 Culture Confirmed Cases)
- 97.7% new cases, ie never treated and most with no history of adult MDRTB contact
Infection Control High Priority:

• Prior to report of XDRTB in 2006 infection control rarely mentioned and is still given low priority

• Institutionalized vs community based treatment programs
Enhancing laboratory capacity may improve surveillance but not likely to impact individual patient treatment and thus failure to impact epidemic spread of drug resistant strains.

Unrealistic to think in countries where there are currently fewer than one laboratory per 10 Million population (which is the case in most high-burden countries), that sufficient resources and time are available to scale up quickly enough to have a major impact upon rapid diagnosis and treatment, especially given that most patients are in remote settings.

Recently introduced diagnostics and those in late stage development increase speed and sensitivity unfortunately they still require laboratory infrastructure and limited capacity for detection of multiple drug resistant genes and detection of infection other than in sputum.

Technology for detection of MDR and XDR-TB at point of care is available but requires further development.
Countries need **one culture facility per 5 million population** and **one DST facility per 10 million population**.

- Out of 22 select high-burden countries:
  - only six had **one culture facility per 5 million population** (China, South Africa, the Russian Federation, Brazil, Thailand and Cambodia)
  - only nine had **one DST facility per 10 million population** (China, Indonesia, South Africa, the Russian Federation, Viet Nam, Uganda, Brazil, Thailand and Cambodia)
Pediatric MDRTB:

South Africa
128 culture proven cases
• 75% pulmonary
• 30% sputum culture +
• 33% gastric aspirates culture +
Bottlenecks in Procurement and Distribution of High Quality Drugs

- Procurement problems
- Drug Quality Issue
- Need for Better Data on Drug Quality
- Quality Enforcement
- Quality Strategies
- Need for Accurate Demand Forecasting
Need for Urgency:

Currently there are no consistent policies to deal with patients whose TB is untreatable.

What we do know is that proof that disease in these patients is untreatable may take months during which time they may spread their resistant organisms to family members and others in the community, including health care workers.
Treatment of Totally Drug Resistant TB (TDR)

Even under the best of circumstances (Tomsk and Peru) 30 to 40% of cases of XDRTB are untreatable with existing drugs. Do they represent TDR?

Currently there are NO good data on TDRTB. We all know it exists but no one systematically looks for it and no one talks about it. One of the most urgent needs is to get accurate data so we can realistically address the challenge. Recent data from KZ indicate that 80% of XDR patients are untreatable.

Treatment of drug sensitive TB requires a cocktail of 3 or more antibiotics. “Successful treatment of XDR and TDR TB requires not one or two new antibiotics but 3-4 new classes of antibiotics simultaneously thus representing a HUGE technical and financial challenge.”
Putting Challenges into Perspective: The Realities of Drug Discovery

• 90% failure rate from target identification to regulatory approval

• 50% failure approval rate even in Phase III. Thus to get a single new drug the pipeline must be full at each stage.

• Average time for drug discovery and development from target ID to approval 10-14 years (probably considerably longer for TB due to follow-up).

• Average costs for a single new drug from discovery to approval and not including post-launch surveillance for adverse events, manufacturing compliance, drug delivery, etc = >$1.5billion (probably higher for TB due to lack of infrastructure, point of care diagnostics, surrogate markers)
Realities of New TB Drug Development:

Technical and financial challenges in development of new drugs are so large that no one government, institution, or company has enough resources or expertise to adequately address the challenges. To put it in perspective, the total R&D budget for large companies on average across therapeutic areas is $2-3 billion with average launch of a single new product of 1 in 4 years. **Total global investment in TB drug R&D, including the Gates Foundation in 2009 was $176 million.**
Preception: TB remains a problem but we have drugs to successfully treat it. Some countries have almost eliminated it using existing tools.

Reality: MDR and XDR are increasing at a rapid rate.

Preception: Only 500,000 new cases of MDR-TB per year which is not large compared to other unmet medical needs besides these are caused by inappropriate treatment, lack of patient compliance, and impure drugs.

Reality: Less than 2% new cases being treated each year and most are due to person-to-person spread; therefore a minimum of 5 million cases of MDR
Key Messages…

Failure to acknowledge the new realities of drug resistant TB and to act rapidly will be catastrophic for many countries and will greatly jeopardize the public health of all others (immigration and international travel).

We must start communicating the realities of drug resistant TB and translating the data into policies commensurate with the magnitude and urgency of the challenges we face.
Opportunities to Collaborate

2011

India IOM/Indian Academies
China IOM/NAS and CAS

NIAID preceding workshop on TB Research Priorities
MDR-TB Prevention and Control in China

Mingting Chen
Vice Director/Researcher
National Center for Tuberculosis Control and Prevention of China CDC
Main Content

- Current Situation
  - MDR-TB Epidemic Situation
  - Progress on MDR-TB control

National Action Plan

- MDR-TB Prevention Plan
- MDR-TB Control Plan
### MDR-TB Epidemic Situation -- National Level

<table>
<thead>
<tr>
<th>Case category</th>
<th>MDR-TB rate</th>
<th>XDR-TB rate</th>
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<tbody>
<tr>
<td>New cases</td>
<td>5.71%</td>
<td>0.47%</td>
</tr>
<tr>
<td>Retreatment cases</td>
<td>25.64%</td>
<td>2.06%</td>
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<tr>
<td>All cases</td>
<td>8.32%</td>
<td>0.68%</td>
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- Occur MDR-TB cases 120,000 annually estimated
- Occur XDR-TB 9,000 annually estimated
MDR-TB Epidemic Situation
Provincial Level

11 provinces has got DRS results

- MDR-TB rate among all TB cases: 3.5~23.3%
  - New TB cases: 2.1~10.8%
  - Previous treated cases: 11.7~41.9%
Progress on MDR-TB control -- GF pilot Project

Explore MDR-TB service system
- Prefecture level is core
- County level is pivot
- Community is base
- Incorporate hospital, CDC and district.

Explore management mechanism
- Strict admission mechanism: prefecture apply, provinces first review, national final review and approve

Ideal preliminary results
Progress on MDR-TB control
--GF pilot Project

Till 31Dec, 2010

• Cover 41 prefectures in 12 provinces

• Confirmed 1978 MDR-TB cases and enrolled 1049 cases in treatment;

• Bacteriology conversion rate at the end of 6 months
  - Sputum conversion rate: 75.6%
  - Culture conversion rate: 65.2%
## Progress on MDR-TB control
--- Gates MDR-TB Project

<table>
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<tr>
<th>Explore rapid diagnosis</th>
<th>• Genechip</th>
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<tr>
<td>Standardized medical service package</td>
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| Multiple streams funding mechanism | • Health insurance  
                                 | • Government funding  
                                 | • Project fee et al          |
| Disburse model and supervise mechanism |                                 |
| Hospital-CDC collaboration model  | • Multi-sector cooperation including Hospital, CDC and community |
Progress on MDR-TB control
--
major national science and technology project

- Operational research
- Biological research
- Epidemiological research

Popularized technique

Testing and evaluating platform of MDR-TB new diagnosis technique

- Guidelines for carding and intervention of regular work in TB control
- Multi-channel financing mechanism
- Rapid diagnostic technology for MDR-TB patients
- Evaluation system for the model of MDR-TB patients diagnosis, treatment, management and funding mechanism
Progress on MDR-TB control

--- Others

Damien:
Tibet, guizhou, ningxia et al pilot MDR-TB treatment use domestic TB drugs

Local government investment:
Beijing, shanghai, jiangsu, wuhan, guangdong, henan et al pilot MDR-TB treatment use domestic TB drugs
建议增加BD、美里埃、礼来项目在MDRTB预防控制和新技术的内容
Progress on MDR-TB control --Technical Preparation

- Developed and issued
  - Guideline for MDR-TB Chemotherapy
  - Guideline for Infection Control of Tuberculosis

- Draft and will issue
  - National Framework for Drug Resistant TB prevention and Control
  - National Action Plan for MDR-TB Prevention and Control
  - Guideline for programmatic Management of Drug Resistant TB
  - National Tuberculosis Laboratory Network Developing Plan
  - Second line Anti-tuberculosis Drug Management Manual
“turning off the tap” of MDR-TB

MDR-TB prevention

Supporting measures

MDR-TB control

Diagnosis, treatment, management and care

Reduce the burden of MDR-TB
Adopt new tools to enhance MDR-TB standardized treatment and management

Ensure Quality TB Service

Improving basic DOTS

PPM DOTS

TB control in vulnerable populations

Re-education centers and prisons

TB/HIV

Laboratory capacity building

Reduce the incidence and mortality of TB

Control of MDR-TB

Adopt new tools to enhance MDR-TB standardized treatment and management

Case detection

Treatment

Management

Infection control

Procurement and supply management

Human Resource development

Monitoring & Evaluation

Operational Research

ACSM, community care

Supporting systems

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Supporting systems
MDR-TB Prevention Plan

Consolidate and Enhance achievement of DOTS strategy implementation

Increase accessibility and equalization of general TB control services

Produce quality assured anti-TB drugs and standardize the use and management of TB drug

Reinforce infection control measures
MDR-TB Control

- Diagnosis
- Treatment
- Management
- Care

Supporting Measures

Reduce the morbidity and mortality of MDR-TB
• Guarantee the government counterpart funding of GF to ensure the expansion of GF consolidated project

• Explore and pilot model of Gates MDR-TB project, then modify and expand in phase 2
Establish National and provincial PMDRT Review Committee

- Strict approval procedures
  - Set up Basic Requirements for PMDRT sites
- Training
- Supervise

Integrate the MDRTB component into current internet-based TB reporting system
MDR-TB Control Plan
---PMDRT Service system

Patient centered system

Provincial designated hosp. -
• Hospitalization for severe MDR and XDR-TB;
• Provide training, TA

Prefectural designated hosp. -
• Diagnosis, treatment and hospitalization

District TB dispensary -
• Suspect recommend, transfer and ambulatory case management

Community health service center -
• Ambulatory case management
MDR-TB Control Plan
--Technique Strategies

Case finding
- Focus on MDR-TB high risk group and expand to all SS+ cases gradually
- Transfer from traditional DST to rapid diagnosis stepwise

- Standardized regimen:
  6 Z Km(Am,Cm) Lfx (Mfx)
  PAS (Cs) Pto / 18 Z Lfx (Mfx) PAS(Cs) Pto

Case management
- Hospitalization
- Outpatient follow up
- District management

Patient care
- Transport subsidy
- Nutrition subsidy
- Psychology support et al
Laboratory Capacity Strengthening

- Strengthening the laboratory network
  - To fulfill the National Development Plan on TB laboratory
  - To implement laboratory accreditation
  - To establish the regional reference laboratory
  - To strengthen training and increase eligible staffs

- Technical
  - To expand culture at county level and DST at prefecture level gradually
  - To introduce the new diagnostics at different level
  - To scale up the EQA coverage for culture and DST
Supporting Mechanism

- Sustained political commitment
  - funding mechanism for MDR-TB under development through insurance and government investment
- Multi-sector cooperation and international cooperation
- Enhance TB control system and HR development
- Uninterrupted supply of quality-assured anti-tuberculosis drugs
- Operational research and new tools validation and demonstration mechanism
Thank you!