Update on Epidemiology of MDR TB and XDR TB

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5 May 2008
Overview

• Global epidemiology of TB & drug resistance

• Epidemiology of MDR & XDR TB in Tugela Ferry, South Africa
Tuberculosis Worldwide

- One-third of world population infected with *M. tuberculosis*
- 9.2 million new cases, 1.8 million deaths in 2006
- 95% of cases of active TB disease and deaths occur in developing countries
- 700,000 TB cases in people living with HIV and 200,000 deaths

WHO. *Global Tuberculosis Control 2008*
Estimated numbers of new cases, 2006

60% of global TB burden in Asia

Estimated number of new TB cases (all forms)

- No estimate
- 0–999
- 1000–9999
- 10 000–99 999
- 100 000–999 999
- 1 000 000 or more

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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Estimated TB incidence rate, 2006
(per 100,000 popn.)

Estimated new TB cases (all forms) per 100 000 population

- No estimate
- 0-24
- 25-49
- 50-99
- 100-299
- 300 or more

Southern Africa: case rates over 400 / 100,000 pop.
Geographical distribution of HIV-positive TB cases, 2006

For each country or region, the number of incident TB cases arising in people with HIV is shown as a percentage of the global total of such cases.
TB Drug Resistance

- Requires laboratory diagnosis using culture and drug-susceptibility testing (DST)
- Most TB cases detected by sputum microscopy, which cannot detect drug resistance
- High resource countries provide culture and DST for all TB suspects, while low resource countries provide only to high-risk groups
- Jeopardizes effective TB treatment: Susceptible TB 95% cure, MDR-TB up to 70% cure, XDR-TB 30% cure
XDR TB is a subgroup of MDR TB

Culture-positive TB cases with drug susceptibility test results

Cases with any drug resistance

MDR TB

XDR TB
The 4th WHO/IUATLD Global Report

- 1994 WHO/IUATLD Global project on drug resistance
- DST results from 91,577 patients, from 83 countries and 2 SARs of China
- Trend data from 48 countries
Drug resistance data 1994-2007

Areas representing >50% of TB cases

India
Russia
China
Kenya
Uganda
DR Congo
Indonesia
South Africa
Ethiopia
Philippines
Viet Nam
Tanzania
Brazil
Thailand
Mozambique
Myanmar
Zimbabwe
Cambodia
Nigeria
Bangladesh
Pakistan
Afghanistan

Sub-national data
Nationwide data
No survey data
## Global Estimates

<table>
<thead>
<tr>
<th></th>
<th>Estimated No. Cases</th>
<th>Estimated No. Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB, all forms</td>
<td>9.2 million</td>
<td>1.8 million</td>
</tr>
<tr>
<td>Multidrug-resistant (MDR) TB</td>
<td>489,000</td>
<td>134,000</td>
</tr>
<tr>
<td>Extensively drug-resistant (XDR) TB</td>
<td>40,000</td>
<td>23,000</td>
</tr>
</tbody>
</table>

_Nunn P., Wright A., WHO Task Force Meeting on XDR TB, Geneva 2008_
14 settings with ≥ 6% MDR-TB among new cases 2002-2007

- Baku City, Azerbaijan
- Republic of Moldova
- Donetsk Oblast, Ukraine
- Tomsk Oblast, RF
- Tashkent, Uzbekistan
- Estonia
- Mary El Oblast, RF
- Latvia
- Lithuania
- Armenia
- Orel Oblast, RF
- Inner Mongolia Autonomous Region, China
- Heilongjiang Province, China
- Georgia
MDR-TB among new cases, 1994-2007

* Sub-national coverage in India, China, Russia, Indonesia.
16 settings with $\geq 25\%$ MDR-TB among previously treated cases 2002-2007

- Tashkent, Uzbekistan
- Baku City, Azerbaijan
- Estonia
- Republic of Moldova
- Lithuania
- Donetsk Oblast, Ukraine
- Inner Mongolia Autonomous Region, China
- Armenia
- Jordan
- Oman
- Latvia
- Thailand
- Heilongjiang Province, China
- Czech Republic
- Georgia
- Guatemala
XDR TB among MDR TB cases
2002–2007

< 3% or less than 3 cases in one year of surveillance
3 - 10%
> 10%
Report of at least one case
No data

At least 1 XDR TB case reported from 46 countries

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Tugela Ferry, South Africa
TB and HIV in South Africa

• Highest number of HIV-infected persons in sub-Saharan Africa; estimated 5.5 million PLHA in 2005

• Fifth highest TB burden in the world
  – Low TB treatment success rate: 67%
  – High treatment default rate: 12%

“We can’t fight AIDS unless we do much more to fight TB”

Nelson Mandela
International AIDS Conference, Thailand (14 July 2004)
Setting

Tugela Ferry
- Rural, resource-limited setting
- Home to 200,000 traditional Zulu people
- Poor socioeconomic status

Church of Scotland Hospital
- 355-bed rural hospital
- 40% inpatient admissions HIV+
- 25% antenatal clinic HIV+
Setting

• TB wards crowded, 30-40 bed congregate settings
• TB case rate: 1000 / 100K pop, >80% HIV co-infected
• Sputum AFB microscopy available on-site
• Culture and DST in Durban; 6-8 weeks for results
XDR TB in Tugela Ferry

• Jan 2005–Mar 2006 cross-sectional study of TB suspects (n=1,539)
  – Culture and DST for all suspects
  – Molecular fingerprinting (spoligotyping) on XDR TB isolates

• Major findings:
  – 53 cases of HIV-associated XDR TB (10% of culture-positive cases)
  – 51% never previously treated for TB, suggesting primary transmission
  – 52 of 53 (98%) died, median survival of 16 days

Gandhi et al. Lancet 2006; 368: 1575-80
Update from Tugela Ferry

- Routine culture and DST for TB suspects since June 2005

- June 2005 – August 2007
  - 232 MDR TB cases (excluding XDR TB cases)
  - 307 XDR TB cases

- HIV status
  - MDR TB: 93% co-infected with HIV
  - XDR TB: 99% HIV co-infected

Drug Resistance Pattern of XDR TB Isolates

Updated Survival for MDR & XDR TB

![Survival curve graph showing MDR TB and XDR TB survival probabilities over days.](image-url)
Updated Survival for MDR & XDR TB

Log rank $p < .001$

MDR TB

XDR TB
Summary of Current Situation

• Number of MDR & XDR TB patients continues to increase in Tugela Ferry
  – XDR TB now more common than MDR TB

• XDR TB isolates resistant to increasing number of drugs tested
  – 6-drug pattern in XDR TB predominates

• Continued high, rapid mortality for MDR and XDR TB patients
TB Drug Resistance in South Africa

- Current prevalence of MDR/XDR TB not known
  - XDR TB cases reported from all 9 provinces

- Routine culture and DST not performed in South Africa
  - Reserved for treatment failures or re-treatment cases
  - Reported cases are only minimal estimates

- Last systematic drug resistance survey in 2002
KwaZulu-Natal Province

- Centralized TB culture and drug-susceptibility testing (DST)
- Complete 6-drug DST on all positive cultures: INH, RIF, EMB, SM, CIP, KM
- Methods:
  - Data reviewed from Jan 2005 – Dec 2007
  - Patient (not isolate) based case counting

<table>
<thead>
<tr>
<th>Year</th>
<th>MDR TB</th>
<th>XDR TB (% of MDR TB)</th>
<th>XDR TB from COSH (% of all XDR TB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>2472</td>
<td>199 (8.1%)</td>
<td>116 (58%)</td>
</tr>
<tr>
<td>2006</td>
<td>2572</td>
<td>230 (8.9%)</td>
<td>134 (58%)</td>
</tr>
<tr>
<td>2007</td>
<td>3040</td>
<td>285 (9.4%)</td>
<td>139 (49%)</td>
</tr>
</tbody>
</table>
Fig 5: Distribution of health care facilities in KZN with XDR-TB cases

April – June 2007
Mortality and XDR TB

- Majority of MDR & XDR TB patients die before diagnosis made
- Additional deaths during delay between diagnosis and referral to central drug-resistant TB hospital
  - Only 686 (28%) of 2476 MDR/XDR TB cases started on second-line TB therapy
- HIV co-infection: 93% of MDRs, 99% of XDRs
  - May account for survival difference compared with other cohorts

How did this happen?
**Acquired Resistance or Transmission?**

**Acquired resistance:** Due to incomplete or inappropriate treatment regimen, malabsorption, poor quality drugs

**Response:** Standardized treatment regimens, Directly observed therapy, Fixed dose combinations

**Primary Transmission:** Patient develops resistance to transmission of drug-resistant strain

**Response:** Infection Control
Acquired Resistance or Transmission?

• Acquired (amplified) resistance may explain original genesis of first XDR TB strains
• Current magnitude of XDR TB epidemic difficult to explain by acquired resistance alone
• Conditions in hospital similar to those seen in U.S. during MDR TB outbreaks and favor transmission
  – High HIV prevalence
  – Poor infection control
Primary Transmission of MDR & XDR TB?

• Genotyping to determine acquired vs. primary resistance

• Patients who developed MDR or XDR TB after initial treatment for TB from 6/2005–6/2006
  – e.g., Susceptible TB → MDR TB
  – Susceptible TB → XDR TB

• Genotyping on initial and follow-up isolates
  – If same, then acquired resistance (ineffective therapy)
  – If different, then primary resistance (new infection)

Multiple Episodes of Reinfection

Three episodes of re-infection with a new strain appearing approximately every 70-90 days
Exogenous Reinfection with MDR TB strain

Spoligotypes of initial and follow-up isolates among patients re-infected with MDR TB strains
Exogenous Reinfection with XDR TB strain

Spoligotypes of initial and follow-up isolates among patients re-infected with XDR TB strains

<table>
<thead>
<tr>
<th>Initial Isolate</th>
<th>Follow-up Isolate</th>
</tr>
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<tbody>
<tr>
<td>ST 60</td>
<td>ST 1218</td>
</tr>
<tr>
<td>ST 26</td>
<td>ST A4</td>
</tr>
<tr>
<td>ST A4</td>
<td>ST A3</td>
</tr>
<tr>
<td>ST 244</td>
<td>ST 244</td>
</tr>
<tr>
<td>ST 172</td>
<td>ST 53</td>
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<tr>
<td>ST 4</td>
<td>ST 4</td>
</tr>
<tr>
<td>ST 1</td>
<td>ST A2</td>
</tr>
<tr>
<td>ST A2</td>
<td>ST 33</td>
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</table>
Addressing MDR/XDR TB epidemics
Addressing MDR/XDR TB epidemics

Strengthen TB DOTS program to curb generation of drug resistance

Create Infection Control programs to prevent transmission

Prevention
Addressing MDR/XDR TB epidemics

Strengthen TB DOTS program to curb generation of drug resistance

Create Infection Control programs to prevent transmission

Needed to facilitate IC and prompt MDR/XDR TB treatment

Evaluate rapid diagnostics in field settings

Diagnosis
Addressing MDR/XDR TB epidemics

- Strengthen TB DOTS program to curb generation of drug resistance
- Create Infection Control programs to prevent transmission
- Needed to facilitate IC and prompt MDR/XDR TB treatment
- Evaluate rapid diagnostics in field settings
- New drug development and clinical trials
- Decentralize to reduce referral delay, increase capacity, and improve treatment completion

Treatment
Strengthening TB DOTS Program

- TB DOTS staff increased from 3 to 30
- Creation of 13 field teams (contact tracing, treatment administration, tracing of defaulters)
- 7 Vehicles allocated to TB program
- TB culture and drug-susceptibility testing to 1\textsuperscript{st} and 2\textsuperscript{nd} line TB drugs for all TB suspects
Strengthening TB DOTS Program

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- Creation of 13 field teams (contact tracing, treatment administration, tracing of defaulters)
- 7 Vehicles allocated to TB program
- TB culture and drug-susceptibility testing to 1st and 2nd line TB drugs for all TB suspects

*Treatment completion improved from 55% to 70%*
Transmission of MDR & XDR TB
Creation of Infection Control Program

• Administrative: policies, training, cough triage, reduced inpatient admission and length of stay

• Environmental: natural and mechanical ventilation, isolation wards, outdoor waiting areas

• Personal: N95 mask, HIV testing of staff, ARVs for HIV+ staff, annual CXR screening
Improving Survival

• Early Diagnosis
  – Liquid culture (MGIT): diagnosis in 4-6 weeks
  – Rapid diagnostics demonstration projects underway (MTBDR assay, MODS)
  – Contact tracing for all MDR & XDR TB cases

• Decentralized treatment program
  – Opening of 7 satellite MDR TB centers
  – Continue with inpatient model for intensive phase
  – Community-based treatment pilot project
Summary

• Global epidemiology shows concerning increases
  – Coverage of high burden countries expanding
  – Highest rates ever reported, drug resistance severe
    an widespread in FSU and China
  – Limited trend data from high-burden countries
  – Laboratory strengthening urgently needed
Summary

• Global epidemiology shows concerning increases
  – Coverage of high burden countries expanding
  – Highest rates ever reported, drug resistance severe
    and widespread in FSU and China
  – Limited trend data from high-burden countries
  – Laboratory strengthening urgently needed

• South Africa MDR/XDR TB epidemic continues to expand
  – Fueled by transmission of drug-resistant TB strains
    in high HIV prevalence setting
  – Significant mortality in MDR & XDR TB patients
  – Full extent unknown due to limited laboratory
    capacity, but appears widespread in KZN province
Implications

• Comprehensive approach to TB control needed
• Focus on infection control and laboratory capacity long overdue
• Long term strategy must include:
  – Culture and DST for all TB suspects
  – Rapid TB drug-resistance assays for resource-limited settings
  – New medications to reduce treatment duration of susceptible TB & latent TB, improve cure rates in MDR TB, and provide efficacy against XDR TB
Acknowledgements

- World Health Organization
- Tugela Ferry Care & Research Collaboration
- Church of Scotland Hospital
- Nelson Mandela School of Medicine
- Inkosi Albert Luthuli Hospital Microbiology Lab
- KZN Department of Health
- Albert Einstein College of Medicine
- Patients and families
- Doris Duke Charitable Foundation & Irene Diamond Fund
“If the number of victims which a disease claims is the measure of its significance, then all diseases, particularly the most dreaded infectious diseases, such as bubonic plague, Asiatic cholera, et cetera, must rank far behind tuberculosis.”

- Robert Koch, 1882
DEADLY AFRICAN XDR-TB STRAIN

Cough!
Cough!
Cough!

OTHER COUNTRIES

!!!
Objectives of Global Project

• Estimate magnitude globally
• Implement standard methods to compare data and evaluate trends
• Inform policy
• Evaluate program performance

• Principles:
  – Ensure sample represents population of interest
  – Differentiate resistance among new vs. previously treated cases
  – Quality assured laboratory results