XDR and MDR and TB Urgent Research Priorities

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**TB Drug resistance**

- Worldwide surveillance indicates substantial and rising rates and numbers of M.TB resistant to existing medications
- Multiple drug resistant MDR-TB
  - ~ 400,000 cases of MDR-TB a year
  - 10,000 MDR patients under treatment in GLC programs
  - Global goal – treat 800,000 MDR cases by 2015
- Highest rates in Former Soviet Union and China
- Limited information from Africa
- Well known association of outbreaks with HIV co-infection in industrialized world
- Relationship between TB drug resistance and HIV not well defined
Emergence of XDR TB

- 17,690 isolates worldwide 2004-5, 20% MDR, 2% XDR
  - Latvia- 19% of MDR TB cases
  - S. Korea- 15% of MDR TB cases
  - Latin America-6% of MDR TB cases
  - USA-4% MDR TB cases
  - Africa-<1% MDR TB cases
  - India?, China?
Countries with XDR-TB
Confirmed cases to date

Argentina
Armenia
Bangladesh
Brazil
Chile
Czech Republic
Ecuador
Georgia
Germany
Rep of Korea
Latvia
Mexico
Peru
Portugal
Russian Federation
South Africa
Spain
Thailand
UK
USA

Based on MMWR March 2008 data, and information provided to WHO Stop TB Department. December 2008
TB/HIV Integration Study
Tugela Ferry, Rural KwaZuluNatal

- TB/HIV concomitant therapy
- TB cult and DST available
- ddI+3TC+EFV
- Mortality: 14 of 119 (12%)
- Analysis of deaths demonstrated good virologic response to ARV with Non Detectable HIV viral loads at time of death
- 10 due to suspected or confirmed MDR TB
  - 6 of these patients had XDR TB
- 4 patients had 2nd episode of TB after successful TB treatment completion
  - All 4 died of XDR TB
544 patients
Culture-Positive for \textit{M.tbc}

323 (59%)
Not Resistant to both Isoniazid & Rifampicin

221 (41%)
Resistant to Isoniazid & Rifampicin (MDR TB)
(14% of total TB suspects)

53 (24%)
Resistant to all tested drugs (XDR TB)
(10% Culture-Positive)
(3.4% of total TB suspects)

347 cases of XDR TB Worldwide
Nosocomial Transmission of XDR TB

• No prior TB treatment 51%, completion/cure 30%

• Genotyping reveals similar strains

• 28/42 (67%) of patients hospitalized in prior 2 years

• Community contact tracing of XDR patients revealed no additional cases (>1,600 contacts)

• 2 healthcare workers died with confirmed XDR TB
  – 4 other workers died with suspected XDR TB
Mortality

- 52 of 53 (98%) XDR TB patients have died
- Median survival from sputum collection 16 days (range 2-210 days)
Summary

• Multidrug-resistant TB substantially more common in a rural district of KwaZulu Natal compared with previously published rates

• An extensively drug-resistant strain of TB accounts for nearly one-quarter of all MDR TB cases found and 10% of all M.TB
  – Recent transmission in both hospital and community
  – All patients tested were HIV-infected
  – Rapidly fatal
Epidemiologic Update

• Continued appearance of cases in TF
  – Total MDR / XDR TB >400
  – Total XDR TB 217 (55%)

• More widespread distribution
  – Retrospective lab surveillance review from January 2005, 34 sites in KZN with total >100 additional XDR TB isolates
    • No epidemiologic data
  – MRC / NHLS review of specimens last 18months – >100 XDR TB isolates from all provinces
    • No epidemiologic data

• Suspected but not yet documented isolates from neighboring countries
Total no. of contacts traced = 1646
  - Total no. of contacts with MDR TB = 12
  - Total no. of contacts with XDR TB = ?2

2+ HIV- patients with XDR

Total MDR TB Deaths = 112/166 (68%)

Total XDR TB Deaths = 171/203 (84%)
Survival by level of resistance

NonDR=57  MDR=52  XDR=61

Survival Functions

1= non-MDR
2 = MDR
3 = 4/5 XDR
4 = 6 XDR

Cum Survival
observation period

0.0 0.2 0.4 0.6 0.8 1.0
1 2 3 4
1-censored 2-censored 3-censored 4-censored
## Risk Factors for Mortality from Time of Diagnostic Sputum Collection

### Cox Proportional Hazards Model

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<th></th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
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<tbody>
<tr>
<td>Male Sex</td>
<td>1.09</td>
<td>0.64-1.54</td>
<td>0.718</td>
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<tr>
<td>Treatment in Last Year</td>
<td>1.29</td>
<td>0.78-1.80</td>
<td>0.321</td>
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<tr>
<td>Hospitalized in Last Year</td>
<td>1.24</td>
<td>0.76-1.72</td>
<td>0.378</td>
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<td>Sputum Smear Positive</td>
<td>2.36</td>
<td>1.88-2.84</td>
<td>&lt;0.001</td>
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<tr>
<td>XDR-TB</td>
<td>4.31</td>
<td>3.71-4.91</td>
<td>&lt;0.0001</td>
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<tr>
<td>MDR-TB</td>
<td>3.09</td>
<td>2.47-3.71</td>
<td>&lt;0.001</td>
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<tr>
<td>CD4 less than 200/mm3</td>
<td>4.69</td>
<td>3.59-5.79</td>
<td>0.006</td>
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Global 7-point Action Plan to Combat XDR TB

1. Conduct rapid epidemiologic surveys of XDR TB (determine location, extent and burden)
2. Enhance laboratory capacity (emphasis on rapid DST)
3. Improve technical capacity of clinical and public health practitioners to effectively respond to XDR TB outbreaks and manage patients
4. Implement infection control precautions (PLHA focus)
5. Increase research support for anti-TB drug development
6. Increase research support for rapid diagnostic test development
7. Promote universal access to ARVs under joint TB/HIV activities
First Global XDR TB Task Force
WHO Geneva 8-9 October 2006

• Define key issues, make recommendations and identify urgent action steps required in next 3-6 months:
  - Management of XDR TB suspects in high and low HIV settings
  - Programmatic management of XDR TB treatment and Rx design
  - Laboratory XDR TB definitions
  - Infection control and protection of health care workers, with emphasis on high HIV settings
  - Immediate XDR TB surveillance activities and needs
  - Advocacy, communication, social mobilization strategies

• Develop plans for appropriate global response, and within countries, including designation of roles and responsibilities
MDR and XDR TB Urgent Research Priorities

- **Further Epidemiologic characterization**-
  - Rapid, organized, widespread investigation and ongoing surveillance
  - Epidemic or Outbreak?
  - Characterization of transmission risk
    - Acquired vs Primary Infection
    - Critical collision of TB and HIV
      - Contrast of countries of FSU and SSA
    - Nosocomial and community
    - Relationship to HIV
  - Relationship between strains and resistance?
    - What is known about KZN strain?
    - Virulence and drug resistance?
  - Full understanding of the etiology of current disaster
MDR and XDR TB Urgent Research Priorities

• **Diagnostics**
  
  – Need for M. TB identification and drug susceptibility testing
  
  – Very short term, better case detection through revised diagnostic algorithms, improved microscopy, and widespread expansion of available facilities and technologies
    
    • Rapid mycobacterial culture and DST- MODS.
  
  – In the longer term novel technical approaches
    
    • antigen detection, molecular detection, diagnostic humoral and cellular immune responses, sensing volatile organic compounds and other biomarkers
MDR and XDR TB Urgent Research Priorities

**Therapeutics**

- Basic research in drug development
- Multiple new drugs in development
  - Speeding drug evaluation and approval process
  - Trial designs that allows individualization, yet provides rigorous evaluation of a new drug (s)
  - MDR and XDR TB provide opportunity-large effect size, smaller sample sizes, quicker answers
- PK and PD interactions
- Expansion and development of novel treatment delivery strategies for SLD-treatment-
MDR and XDR TB Urgent Research Priorities

- Need to immediately focus work on transmission reduction:
  - Rapid diagnosis
  - Community based treatment to reduce sputum positive prevalence
  - **Infection control strategies**
    - Implement existing strategies
      - Administrative, facilities, personal
    - Monitoring
    - Operational research
MDR and XDR TB Urgent Research Priorities

• Need to immediately focus work on transmission reduction:
  – Rapid diagnosis
  – Infection control strategies
    • Implement existing strategies
      – administrative, facilities, personal
    • monitoring
  – pilot community based treatment to reduce sputum positive prevalence
MDR and XDR TB Urgent Research Priorities

- TB and HIV
  - Universal access to antiretroviral therapy
  - Strengthening TB programs
  - Operational research to promote successful programmatic collaboration and integration
    - TB and HIV identification
    - When to start HIV Rx?
    - Where, how and by whom?
    - What drugs?
    - Cost and effectiveness
Tuberculosis and HIV Disease and TB Drug Resistance-A Perfect Storm

- Enormous cost of worldwide neglect of TB
- Lack of resources, basic research, modern diagnostics and new treatments, applied and operational research
  - Estimated $20 billion needed in next decade
- Areas of high TB and HIV prevalence particularly vulnerable
  - Failing TB programs
  - Poverty/crowding/migration
  - Primitive infection control
- The collision of HIV and TB and need for collaboration
Evolution of the extensive drug resistant (XDR) KZN strain of M.TB in KwaZulu-Natal

- Majority of patients infected with the same KZN strain
- Databases 1994 to 2005 searched for resistance patterns in isolates of M.TB with KZN strain fingerprint.
- In 1994, KZN strain cases with MDR TB, with some STM resistance
- From 1994, MDR isolates found with resistance to additional drugs
- First XDR isolate in 2001
- Resistance to up to 7 drugs developed in a decade.
Evolution of the extensive drug resistant (XDR) KZN strain of M. tuberculosis in KwaZulu-Natal

Coincided with:

• High TB prevalence and weak TB control program

• Explosive HIV epidemic
  • Dramatic TB increase and overwhelming of TB services

• Introduction of the DOTS based TB control program
  • Standardized treatment in absence of drug susceptibility testing or resistance surveillance
  • Adding of single drug to failing regimen - STM

• Widespread antibiotic use for non-TB disease