DRUG-RESISTANT TUBERCULOSIS IN RUSSIA
DEFINING THE PROBLEM

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Tuberculosis Facts

• Caused by *Mycobacterium tuberculosis*

• One third of the world’s population infected

• Kills approximately 1.8 million people each year

• Poor and/or immuno-compromised at considerable risk of disease

• TB is acquired when a person with *active untreated* TB spreads the bacteria through coughing or sneezing.

• Infection usually occurs in individuals who have **close, prolonged exposure** to someone with the disease.

• Most people who are *infected* with TB do not get TB *disease*.

• Increasing number of resistant strains

• ~400,000 cases of MDR-TB each year
## Treating tuberculosis: a crash course

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<th>First-line</th>
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### Multi-drug Resistant TB (MDR-TB):

- Resistant to at least the most effective first-line drugs: isoniazid (INH) and rifampin (RIF)

- Requires 18 to 24 months of treatment with second- and third-line medications given under direct observation and with assistance and aggressive management of side effects

### Other agents

- AMX/CLV
- Clofazamine
- Clarithromycin
Age-Standardized Mortality Rates from TB in Russia, 1965-1997

Source: INED/CHDE

Collapse of FSU
Burden of MDR-TB in World Regions

- **NORTH AMERICA**: LOW MDR
- **LATIN AMERICA**: MEDIUM MDR
- **AFRICA**: high MDR
- **FSU**: high MDR
- **ASIA**: high MDR
- **MIDDLE EAST**: MEDIUM MDR
- **WESTERN EUROPE**: LOW MDR
Eastern Europe and Central Asia

Highest proportion of MDR-TB (of all TB cases)

- > 10% among new cases
- > 50% among previously treated cases
62% of new MDR-TB cases expected in 3 countries
MDR-TB cases to be treated by Region

 Thousands of MDR-TB patients

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of Patients</th>
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<tr>
<td>African - high HIV/AIDS</td>
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<tr>
<td>African - low HIV/AIDS</td>
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<tr>
<td>Eastern Europe</td>
<td>450</td>
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<td>Eastern Mediterranean</td>
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<td>Latin America</td>
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<td>Southeast Asia</td>
<td>150</td>
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<td>Western Pacific</td>
<td>100</td>
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SCALING UP OF MDR-TB TREATMENT GLOBALLY

> 400,000 new MDR-TB cases each year

Thousands of patients

Source: Green Light Committee/WHO Geneva
TOMSK OBLAST
RUSSIAN FEDERATION
MDR-TB prevalence among all smear-positive new and re-treatment cases 2001, Tomsk Oblast (n=1303)

- MDR: 530 (40.6%)
- Non-MDR: 773
Factors associated with MDR-TB in Tomsk

Treatment Program

- Inadequate drug regimens for re-treatment
- Unsupervised therapy (no DOT)
- Unreliable drug supply
- Limited political will
- Poor management systems

Transmission

- Excessive incarceration
- High prevalence of drug resistance
- Rising HIV

Social/structural context of the post-Soviet period:

- Poverty and unemployment
- Breakdown in state structure
- Substance abuse
- Breakdown in family structure
- Anomie
Resistance patterns of Tomsk Cohort (244)

First-line drugs

- INH: 100%
- RIF: 100%
- EMB: 77%
- PZA: 66%
- SM: 99%

Second-line drugs

- KM: 49%
- CM: 10%
- CS: 2%
- FQ: 6%
- Ethio: 54%

Source: Tomsk Oblast Tuberculosis Services, Tomsk, Russian Federation, 2005.
TREATMENT OUTCOMES (N=244)

- **Cure**: 77.0%
- **Failure**: 6.6%
- **Death**: 4.9%
- **Default**: 11.5%
PROGRAM CHALLENGES

- Alcoholism
- Drug abuse
- Poverty
- Adverse events
- Long duration of treatment
- Distance from treatment sites
STRATEGIES (1)

• Creating an administrative structure to treat MDR-TB that builds on the current health system, and integrates both the civilian and penal sectors

• Ensuring a reliable drug supply

• Training physicians, nurses, and community health workers in both rural and urban areas

• Improving facilities

• Providing transportation assistance for patients and health workers
STRATEGIES (2)

- Food assistance for patients
- Choice of treatment site
- Improved side effect management
- Improvement of working hours at medical facilities to make it more convenient for patients
- Treatment at home for patients who are unable to ambulate or who live too far
- Volunteers (e.g. neighbors) for observation of therapy
- Rapid search for non-adherent patients and defaulters
- Social support for patients
Next Cohort (N=386)

- Cure rate lower in the civilian sector but not in the prison sector

- Findings:
  - Worse adherence
  - Increased substance abuse
  - More difficult cases being addressed now
  - Longer delays to treatment
  - Increasing resistance due to exposure to 2nd line drugs
Overcoming socio-economic factors: “Sputnik Initiative” for non-adherent patients

- Started in December 2006
- Non-adherent patients selected by clinical committee
- Patient-oriented approach
  - Place and time preferred by patient
  - Attempts to help in health and social problems
  - Few patients per nurse
- Daily supervision
- Administrative support
Sputnik Initiative results: first 3 months

- **Success in 13 of 16 patients (81%):**
  - 1 patient refused treatment
  - 1 patient transferred to observation
  - 1 patient defaulted
  - 3 out of 5 (60%) patients who initially were registered as defaulters, continued treatment with 100% adherence rate
  - Adherence increased from 42% to 83%
MAIN LESSONS LEARNED FROM TOMSK

1. Ambulatory care can play a crucial role in successful TB control
2. There are socio-economic barriers to successful treatment that can be overcome
XDR-TB: CAUSE FOR CONCERN?

5 SEPTEMBER 2006 | GENEVA -- The World Health Organization is concerned over extreme drug-resistant TB strains of tuberculosis. The emergence of virulent drug-resistant strains of tuberculosis has strengthened and implemented to prevent the global spread of the disease. Research showing the extent of XDR-TB, a newly identified strain, has alarmed WHO. Many people living with HIV are virtually untreatable using currently available drugs.

Later this week, WHO will join other TB experts at a two-day meeting in South Africa (7-8 September) to assess the situation.
XDR-TB

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- **Weak Agents**
  - ETH
  - MOXI
  - PAS

- **Other agents**
  - AMK/CLV
  - Clofazamine
  - Clarithromycin

- Resistant to at least the two most effective first-line drugs: isoniazid (INH) and rifampin (RIF)

- Also resistant to at least the most effective second-line drugs: a fluoroquinolone and an injectable agent
Number of MDR TB and XDR TB Cases by Region, 2000–2004 (N=347)

**FSU**
- MDR 406 (14%)
- XDR 55 (14%)

**U.S.**
- MDR 1814
- XDR 74 (4%)

**Latin America**
- MDR 543
- XDR 32 (6%)

**Asia**
- MDR 274
- XDR 4 (1%)

**Africa, Middle East**
- MDR 156
- XDR 1 (<1%)

*Country unknown, MDR= 102; XDR= 2 (2%)*

Source: Abigail Wright, WHO, Geneva; Sarita Shah, Albert Einstein College of Medicine, New York
Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa

Neel R Gandhi, Anthony Moll, A Willem Sturm, Robert Pawinski, Thiloshini Govender, Umesh Laloo, Kimberly Zeller, Jason Andrews, Gerald Friedland

Summary
Background The epidemics of HIV-1 and tuberculosis in South Africa are closely related. High mortality rates in co-infected patients have improved with antiretroviral therapy, but drug-resistant tuberculosis has emerged as a major cause of death. We assessed the prevalence and consequences of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis in a rural area in KwaZulu Natal, South Africa.

Methods We undertook enhanced surveillance for drug-resistant tuberculosis with sputum culture and drug susceptibility testing in patients with known or suspected tuberculosis. Genotyping was done for isolates resistant to first-line and second-line drugs.

Results From January, 2005, to March, 2006, sputum was obtained from 1539 patients. We detected MDR tuberculosis in 221 patients, of whom 53 had XDR tuberculosis. Prevalence among 475 patients with culture-confirmed tuberculosis was 39% (185 patients) for MDR and 6% (30) for XDR tuberculosis. Only 55% (26 of 47) of patients with XDR
XDR-TB – KwaZulu Natal, Republic of South Africa

- **January 2005 – March 2006: 1539 Patients**
  - 221 MDR-TB (14.4%)
  - 53 of MDR-TB patients had XDR-TB (3.4% of total; 24% of MDR-TB patients)

- **Of the XDR-TB patients:**
  - 55% had never been treated for TB
  - 67% had had a recent hospital admission
  - All tested were HIV positive (44/53 were tested)
  - Median survival from XDR-TB diagnosis: 16 days
  - 85% had similar strains (by genotyping)
  - 98% case fatality

Determinants for the Frequency of HIV-Associated Tuberculosis in a Community

- Total population
- Infected with *M. tuberculosis*
- Infected with HIV

Prevalence and incidence of infection with *M. tuberculosis*

Prevalence and incidence of HIV infection

Overlap of the two respective population segments

Adapted from: John R. Mansoer MD, MPH, U.S. Centers for Disease Control
Impact of HIV Infection on Tuberculosis Notifications in Chiang Rai, Thailand, 1985 - 1994


Adapted from: John R. Mansoer MD, MPH, U.S. Centers for Disease Control

End 2006: 39.5 million

From: Jennifer Kates, KaiserEDU.org
People Living with HIV/AIDS by Region, as Percent of Global Total, 2006

Total = 39.5 million

- Sub-Saharan Africa: 62.5%
- South/South-East Asia: 19.7%
- Eastern Europe/Central Asia: 4.3%
- Latin America: 4.3%
- North America: 3.5%
- East Asia: 1.9%
- Western/Central Europe: 1.9%
- Middle East/North Africa: 1.2%
- Caribbean: 0.6%
- Oceania: 0.2%

People Newly Infected with HIV by Region, as Percent of Global Total, 2006

Total = 4.3 million

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<thead>
<tr>
<th>Region</th>
<th>Percentage</th>
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<tr>
<td>Sub-Saharan Africa</td>
<td>65.1%</td>
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<tr>
<td>South/South-East Asia</td>
<td>20.0%</td>
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<tr>
<td>Eastern Europe/Central Asia</td>
<td>6.3%</td>
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<tr>
<td>Latin America</td>
<td>3.3%</td>
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From: Jennifer Kates, KaiserEDU.org
Young People, Aged 15–24, as Share of People Living with HIV/AIDS by Region, 2003

Global: 28%
Eastern Europe/Central Asia: 48%
Latin America: 38%
East Asia: 38%
Carribean: 32%
South & South-East Asia: 29%
sub-Saharan Africa: 27%
North Africa & Middle East: 26%
Oceania: 23%
North America: 13%
Western/Central Europe: 10%

Note: As a share of 15-49 year olds
Antiretroviral (ART) Use among People with HIV/AIDS in Low & Middle-Income Countries, 2006

Percent on Anti-retroviral Therapy (of those who need them):

- **All**: 24%
- **Latin America/Caribbean**: 75%
- **Sub-Saharan Africa**: 23%
- **East/South/South-East Asia**: 16%
- **Europe/Central Asia**: 13%
- **North Africa/Middle East**: 5%

From: Jennifer Kates, KaiserEDU.org
In a cohort of 611 patients enrolled between 9/2000 and 9/2004, the percentage with XDR-TB at start of treatment: 5.1% (31 patients)

- Associated with: previous tuberculosis treatments, previous fluoroquinolone exposure, previous injectable agent exposure, and alcoholism
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