Multi Drug Resistant tuberculosis (MDR-TB)

Vincent Jarlier
Pitié-Salpêtrière hospital
Paris, France

March 24th 1882: announcement of the discovery of TB bacillus
MDR-TB definition
(WHO)

2 major antituberculous drugs:
Isoniazid (INH)
Rifampicin (RIF)

MDR = resistance to INH and RIF
% MDR in new TB cases in Europe
EuroTB 2003

Israël 5%, Baltic Republics > 8 %

< 2 %
MDR-TB in the world
WHO 3rd report 2004

• Estimation : 424 000 cases/year

• (~ 4% of ~ 10 millions cases)

• **Primary** : 243 000 (3% of the **new cases**)  

• **Secondary** : 181 000 (19% of the **prev. Tt cases**)  

• China, India, Russia : 261 000 (= 62% of total MDR cases)

• > 10% MDR : Estonia (17%), Georgia (16%), Azerbaïdjan (15%), Moldavia (15%), Kazakhstan (14%), Ouzbekistan (13%)
TB drug resistance in the world
WHO 4th report 2008

- 138 countries/regions
- data on drug susceptibility tests for 91,577 patients in 81 countries, years 2002-06

n.b. previous reports 1997, 2000, 2004
MDR TB

key findings 4th report 2008 (global)

• Estimated MDR cases in 2006:
  489,139
  (95% CLs, 455,093 to 614,215)

• Global proportion of MDR among all cases:
  4.8 %
  (95% CLs, 4.6 to 6.0)
MDR-TB in new cases 1994-2007 (in %)

WHO 4th Report 2008

* Sub-national coverage in India, China, Russia, Indonesia.
MDR-TB in *previously treated* cases 1994-2007 (in %)

* Sub-national coverage in India, China, Russia, Indonesia.

WHO 4th Report

No data

< 6%

6 - 20%

20 - 40%

> 40%
Main antituberculous drugs for MDR

- Aminoglycosides
- Fluoroquinolones
- Ethionamide
- Ethambutol
- Pyrazinamide
- PAS
- Cycloserine
TB Extensive Resistance to 2\textsuperscript{nd} line Drugs (CDC, MMWR March 2006)

\textbf{XDR} = \text{resistance to :}
\textbf{INH and RIF (MDR)}
\text{and at least to}
\text{3 of the 6 main classes of second line drugs}

(“old definition”)
Revised Definition XDR-TB
October 2006

XDR = resistance to:
INH and RIF (MDR-TB)

and

amikacin, kanamycin or capreomycin
(injectable agents other than streptomycin)

and

fluroquinolones
MDR-TB and XDR-TB in France
1998 - 2007

In 10 years:
517 MDR and 13 XDR (1 to 2 XDR per year)

Kanitz 2008
submitted
XDR-TB (new definition) in % of MDR cases

WHO 4th Report 2008

* Sub-national averages applied to Russia

< 3 %
3 - 10%
> 10 %
≥ 1 case
No data
XDR-TB: key findings 4th report 2008

- Representative data for 39 countries or regions (24 in Europe)
- Data for ~5,000 MDR TB cases 2002-07

% XDR TB among MDR TB:

- 0 - 1% in 14/39 (e.g. Canada, UK, France, Denmark)
- 2 - 10% in 15/39 (e.g. USA, Australia, Netherlands, Sweden, Latvia, Romania, Moldova, Armenia, Georgia)
- > 10% in 10/39 (33% Ireland, 33% Slovenia, 31% Japan, 24% Estonia, 20% Czech, 15% H.Kong, 15% Ukraine, 14% Lithuania, 13% Azerbaijan)
XDR-TB : key findings 4th report 2008

- Representative data for 39 countries or regions (24 in Europe) for ~ 5,000 MDR TB cases 2002-07

  Only 4 countries with 10-20 cases/year:
  Japan, Estonia, Latvia, Azerbaijan

- Non representative data for South Africa 2004-07
  200 cases / year
Challenges of MDR TB
2 main endpoints:

- MDR patient outcome (management of the cases)

- Number of MDR cases (genesis of cases)
Task 1
Optimize the management of MDR cases
Outcome of MDR cases background

Cure: 40 - 75%
Failure: 10 - 30%
Death: 5 - 20%
Death in HIV+: 80%
Lost to follow-up: $\geq 10\%$

Survival of MD-RTB in the 1990s

UK

Drobniewski, Thorax 2002, 90 MDRTB patients
Survival of HIV-associated MDR-TB in the 1990s
New York City, USA

Turret NEJM 1995

![Graph showing estimated percentage survival over days for patients who did and did not receive appropriate therapy. The graph indicates a significantly higher survival rate for those who received appropriate therapy compared to those who did not.]

- **Appropriate Tt**
- **No appropriate Tt**

---

**Legend:**
- Received appropriate therapy
- Did not receive appropriate therapy
# Outcome of MDR-TB France

<table>
<thead>
<tr>
<th></th>
<th>1994 (n=51)*</th>
<th>1999 (n= 45)**</th>
<th>2006 (n= 53)***</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No of tested drugs</strong> (including STR, EMB)</td>
<td>5</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td><strong>Treatment with &gt; 3 active drugs</strong></td>
<td>47%</td>
<td>84%</td>
<td>85%</td>
</tr>
<tr>
<td><strong>Success</strong></td>
<td>41%</td>
<td>67%</td>
<td>evaluated in 2008</td>
</tr>
</tbody>
</table>

* Saillour Am Resp Crit Care Med 1999: non specialized teams
** Uffredi Inter J Antibiot 2006: specialized team (lab/physicians)
*** Veziris 2008: specialized team (idem but systematic)
# Outcome (%) of MDR et XDR Lithuania (old and new definitions)

<table>
<thead>
<tr>
<th></th>
<th>cure*</th>
<th>failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR</td>
<td>67</td>
<td>13</td>
</tr>
<tr>
<td>XDR (old definition**)</td>
<td>58</td>
<td>30</td>
</tr>
<tr>
<td>XDR (new definition***)</td>
<td>28</td>
<td>55</td>
</tr>
</tbody>
</table>

- completed treatment

** R to 3 2\textsuperscript{nd} line drugs

*** R to FQs and 1 injectable

Lemaire UICT 2006
Management of MDR cases

Speeding up identification and susceptibility tests (directly on sputum)
Recommended standards for modern TB laboratory services

Laboratories should aim to identify TB and rifampicin resistance in over 90% of cases directly from smear + sputum where resources are available for this…

… rapidly within 1-2 days
Performances of genomic identification tests (classical PCR) in smear + sputum (meta-analysis by Sarmiento, JCM 2003)

- **Sensitivity**: 95-100 %
- **Specificity**: 95-98%
- **PPV**: very high due to:
  - good specificity
  - high prevalence of TB in smear + patients (> 90%)

«Typing PCR»
(ATS 1997, AJRCCM 155:1804-14)
Identification of *M. tuberculosis* in smear + sputum by using marketed DNA amplification and strip assay

- **INNO-LIPA mycobacteria (Innogenetics)**:
  - spacer 16s-23s: 16 species (including Mtb complex)
- **Genotype mycobacterium (Hain Lifescience)**:
  - 23s gene: 13 species (including Mtb complex)
- **Genotype MTBC (Hain Lifescience)**:
  - 23s, RD1, gyrB: species within Mtb complex
Resistance detection in *M. tuberculosis*

- **Rifampicin** (surrogate for MDR)
- (Isoniazid)
Genomic resistance detection in *M. tuberculosis* directly in Smear positive specimens

- DNA source: smear + specimen
- Sometimes requires additional specimen
- Often requires double PCR (nested)
- Technologies: hybridation strips, chips, others…
INNO-LiPA - Rif-TB
Sondes pour les mutations les plus fréquentes

Mtb identification

Wild

Mutant
Performances of 
InnoLiPA RIF. TB® (Innogenetics)

95-100 % of detection 
in RIF-R strains

Rossau 1997, Cooksey 1997, Marttila 1898, 
Hirano 1999, Traore 2000………. 
DNA strip assay MTBDR®

Rifampicin & rpoB

Mtb identification

INH & katG 315

## Strip DNA assay MTBDR® for detecting rifampicin resistance (77 R strains, France)

<table>
<thead>
<tr>
<th>Région étudiée</th>
<th>Mutations MTBDR</th>
<th>Séquençage</th>
<th>N souches (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MUT WT&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MUT&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>511-513</td>
<td>MUT WT1</td>
<td>Q513K</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q513P</td>
<td>1</td>
</tr>
<tr>
<td>514-516</td>
<td>MUT WT2</td>
<td>D516Y</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>MUT1:D516V</td>
<td>M5151+D516Y</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>D516V</td>
<td></td>
<td>4 (5%)</td>
</tr>
<tr>
<td>522</td>
<td>MUT WT3</td>
<td>S522L</td>
<td>2</td>
</tr>
<tr>
<td>526</td>
<td>MUT WT4</td>
<td>H526A</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H526L</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H526R</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>MUT2B:H526D</td>
<td>H526D</td>
<td>8 (10%)</td>
</tr>
<tr>
<td></td>
<td>MUT2A:H526Y</td>
<td>H526Y</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>531-533</td>
<td>MUT WT5</td>
<td>S531L</td>
<td>37 (48%)</td>
</tr>
<tr>
<td></td>
<td>MUT3 :S531L</td>
<td>S531W</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>S531T</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>L533P</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>531-533</td>
<td>MUT WT5+WT1</td>
<td>S531C+L511P+F505L</td>
<td>1</td>
</tr>
</tbody>
</table>

100% detection of rifampicin-R

Brossier 2006 JCM
Brossier Int J Tub Lung Dis 2008
### Strip DNA assay MTBDR® for detecting INH resistance (96 R strains, France)

<table>
<thead>
<tr>
<th>% mutation among Inh&lt;sup&gt;R&lt;/sup&gt;</th>
<th>Inh&lt;sup&gt;R&lt;/sup&gt; high level</th>
<th>Inh&lt;sup&gt;R&lt;/sup&gt; low level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>katG</strong>:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S315</td>
<td>68 %</td>
<td>60</td>
</tr>
<tr>
<td>-15c-&gt;t</td>
<td>19 %</td>
<td>3</td>
</tr>
<tr>
<td>Other inh&lt;sub&gt;A&lt;/sub&gt; or kat&lt;sub&gt;G&lt;/sub&gt;</td>
<td>13 %</td>
<td>4</td>
</tr>
</tbody>
</table>

With KatG 315 only only 68 % detection of INH-R

Brossier 2006 JCM
Strip DNA assay **MTBDR® plus** for detecting INH resistance (96 R strains, France)

<table>
<thead>
<tr>
<th></th>
<th>% mutation among Inh^R</th>
<th>Inh^R High level</th>
<th>Inh^R Low level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>katG</strong>: S315</td>
<td>68 %</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td><strong>inhA promoter</strong>: -15c-&gt;t</td>
<td>19 %</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Other inhA or katG</td>
<td>13 %</td>
<td>4</td>
<td>9</td>
</tr>
</tbody>
</table>

KatG 315 and InhA promoter 87 % detection of INH-R (NPV still too low if high prevalence)  

Brossier Int J Tub Lung Dis 2008
Strip DNA assay MTBDR® plus directly in Smear + sputum (MDR context, South Africa)

- 536 consecutive specimens
- 97 % of results interpretable in 2 days
- Rifampicine:
  - Sensitivity 99 %
  - Specificity 99 %
- Isoniazid:
  - Sensitivity 94 % (but many clonal strains!)
  - Specificity 99 %

Barnard Am J Resp Crit Care Med 2008
Phenotypic susceptibility test directly from Smear + specimen

- Possible when > 1 afb/microscopic field
- Source of bacilli: specimen itself (homogenized and decontaminated)
- Dilutions according to afb count
- Requires technical training
- Results obtained at the same time as primo-cultures

Particularly important for 2\textsuperscript{nd} line drugs (can be done as soon as genotypic test proves RMP-R)
Management of MDR cases

Design and organize treatment
Actions and recommendations

• Implement WHO *Guidelines for the programmatic management of drug-resistant tuberculosis*

• Green Ligth Committee (GLCs) to facilitate access to high-quality second-line drugs
<table>
<thead>
<tr>
<th>rank</th>
<th>Amino Glycosides</th>
<th>activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AMINOGLYCOSIDES</td>
<td>Bactericidal</td>
</tr>
<tr>
<td>a</td>
<td>Streptomycine</td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>Kanamycine/ Amikacine</td>
<td></td>
</tr>
<tr>
<td>c</td>
<td>Capreomycine</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>ETHIONAMIDE</td>
<td>Bactericidal</td>
</tr>
<tr>
<td>3</td>
<td>PYRAZINAMIDE</td>
<td>Bactericidal acidic pH</td>
</tr>
<tr>
<td>4</td>
<td>OFLOXACINE</td>
<td>Bactericidal</td>
</tr>
<tr>
<td>5</td>
<td>ETHAMBUTOL</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>6</td>
<td>CYCLOSERINE</td>
<td>Bacteriostatic</td>
</tr>
<tr>
<td>7</td>
<td>P.A.S.</td>
<td>Bacteriostatic</td>
</tr>
</tbody>
</table>
« Simple » MDR cases
(susceptible to all second line drugs)

At least 3 months of initial intensive phase:

- Amikacin or kanamycin
- Moxifloxacine
- Ethionamide
- Pyrazinamide
- +/- Ethambutol

At least 12 months of continuation phase (stop aminoglycoside after culture negativation)
Moxifloxacin in MDR TB treatment in the mice
amikacin + ethionamide + pyrazinamide (AEtZ)
+ fluoroquinolone

Mean UFC in lungs

Moxifloxacin

Veziris AAC 2003
Sterilizing activity in MDR TB (mice): relapse 3 months after end of treatment

% relapses

6 months: 58%
Not long enough!

9-12 months required

Gold standard
suscept TB

11%

2RHZ + 4RH

2AEtMZ + 4EtM

2JMZ + 2JM

2JMZ + 4JM

Veziris ICAAC 2008
« Complicate » MDR cases (e.g. R to ethionamide, pyrazinamide..) and XDR cases

• « Hand tailored » treatment designed by an expert team
  • Last chance for patient survival
Management
of MDR cases

Discover and evaluate
new antituberculous agents
Discover and evaluate new antituberculous agents

• Screening of drug libraries
• (design based on new targets identified by genomics or proteomics)
• In vitro testing
• Target identification
• Identification of acquired mechanisms of resistance
• In vivo testing : animal model (mice)
• Trials in human
Nitro-imidazoles: PA-824
(PathoGenesis Corp.
>> global Alliance against TB)
MIC on \textit{M. tuberculosis}: 0.06 - 0.1 \text{mg/L}

Target unclear

\textit{Stover Nature 2000}
Nitro-imidazoles: OPC-67683
(Otsuka Pharmaceutical, Tokushima)

MIC on *M. tuberculosis*: 0.01 mg/L

Target unclear

Matsumoto PLoS Medicine 2006
Diarylquinoline: R207910 (TMC207)

Inhibition of ATP synthase

Subunit c (atpE)

ADP + Pi > ATP

Andries Science 2005
Task 2
Decrease the number of MDR cases:

Curb the genesis of new cases
Curb the genesis of new cases

Prevent cross transmission
South Africa (Tugela Ferry)
XDRTB and HIV

Gandhi Lancet 2006

Fears of ‘extreme’ TB strain
New drug-resistant infection is ‘nightmare’ say health experts

by Robin McKie
Science Editor

Health experts are to hold an emergency meeting in Johannesburg this week, following the discovery of a deadly new strain of tuberculosis.

The strain, known as extreme drug-resistant TB, has horrified health organisation doctors. In one outbreak in South Africa, 82 of 83 patients died within weeks of becoming infected.

‘This new strain leaves us facing a nightmare,’ said Paul Nunn, coordinator of the WHO's drug-resistance unit. ‘It is resistant to nearly every drug in our arsenal. We are on the threshold of the appearance of a strain of TB that is resistant to every medicine known to science.’

The strain was originally discovered by scientists earlier this year. They looked at cases of multiple drug-resistant TB, which has developed over the past decade in many parts of the world – and discovered that among these a worrying new ‘extreme’ strain had evolved.

‘Mainstream drugs are ineffective against multiple drug-resistant TB, said Nunn. However, there are half a dozen second-line medicines that can be used to tackle it. Now this new extreme resistant strain has appeared. It is not only resistant to our principal anti-TB drugs, but to many of our second-line defences. In short, we are now on the last line of our defences against tuberculosis.’

Among the areas found to have been affected by extreme drug-resistant TB are Latvia and South Africa. Scientists discovered the strain last month among HIV-infected patients in the KwaZulu-Natal region. Fifty-one of the 53 infected people are already dead, and the last may well have died by now, added Nunn.

As a result, WHO is to hold its emergency meeting to help set up measures that will lead to the rapid diagnosis of the new strain.

It appears to kill within a few weeks and that does not give us a lot of time to spot it and treat it with the right drugs,’ added Nunn. The few classes of drugs that are still effective against this strain of TB are expensive and can be toxic.

As a result, WHO is to hold its emergency meeting in Johannesburg to help establish measures that will lead to the rapid diagnosis of the new strain.

It appears to kill within a few weeks and that does not give us a lot of time to spot it and treat it with the right drugs,’ added Nunn. The few classes of drugs that are still effective against this strain of TB are expensive and can be toxic.

The meeting will be attended by officials from WHO and its partners, including the South African Medical Research Council and the US Centers for Disease Control and Prevention.

A new super-TB is threatening Latvia.
South Africa XDR-TB 2006

• Majority: no previous treatment
• Suggests newly infected with XDR
• 26 of 30 (87%) XDR isolates = genetically similar
• Nosocomial transmission in hospitals likely
• Transmission in community possible for 36% of the patients who had no prior hospitalizations
• 52 of 53 patients died
• All patients tested for HIV (n=44) : HIV +

Gandhi Lancet 2006
Prevent cross transmission of MDR-TB

• Out-patients dispensaries
• Hospital
• Prisons
• ...........
Curb the genesis of new cases

Prevent transformation of MDS-TB in MDR-TB
(and of MDR-TB in XDR-TB)
Stepwise resistance in strain F15/LAM4/KZN in South Africa

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRET</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IREttT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRSEEttT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRSETCa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRSEEttK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRSEEttFq</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRSEEttKFFq</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IRSEEttKFFq</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **1994 INH-S**
- **1994-5 INH-R**
- **1994-7 RIF-R : MDR**
- **1999-03 MDR + R FQ or AMG**
- **2003 XDR**
Prevent transformation of MDS-TB in MDR-TB

• TB program
• Resources and expertise
• Standardized protocols (DOT, combined drugs)
• Organization
• Training
• Evaluation (indicators: % completed treatment, % cases with previous treatment, resistance rates...)

Commitment: health authorities, medical community
Conclusion
When your boat is sinking... 

Drain the water (diagnose and treat MDR)
...but most crucial

Seal the hole
(do not generate new MDR cases)