MDR, XDR and Untreatable TB from a Laboratory Perspective

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MDR, XDR and Untreatable TB from a Laboratory Perspective

Short background
Shortage of labs - and shortcomings of labs
Examples from Belarus, Iran and Sweden
Role of the TB-lab in MDR-TB control
Rapid detection of MDR/XDR-TB
Priorities for the TB-lab service
MDR/XDR-TB

- MDR (res to rifampicin + isoniazid)
- XDR (MDR + res to FQs + 2nd line injectables)

Stops (standard) chemotherapy of TB and of drug resistant TB respectively.
TDR, Untreatable TB

TDR – a strain of *M. tuberculosis* resistant to all at the time and place available drugs. More resistant than XDR-TB

Untreatable TB – a clinical definition of a case with so severely drug resistant TB that the patient cannot be cured with any existing drug therapy

There are no official definitions of these terms.
TDR, Untreatable TB

The name is not important.

These strains do exist – and are transmitted.

They constitute an increasing public health threat, which must be recognized and international guidelines urgently modified to address this problem.

They must be detected promptly and our efforts to limit (or stop) further development and transmission of such strains should be maximized.
Proportion of MDR among new TB cases
Latest available data, 1994-2011

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Countries that had reported at least one XDR-TB case by Oct 2012
Shortage of labs - and shortcomings of labs
Culture laboratories for TB per 5 million population
Countries with high burden of TB, MDR-TB or both, 2011

* 2010 data for Azerbaijan, Lithuania, Rep Moldova, Ukraine

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The proportion of laboratory-confirmed TB cases is extremely low

- In 2009, only seven EU/EEA Member States achieved the target of ≥80% culture confirmation among new pulmonary cases.

**Figure 4:** Proportion of laboratory-confirmed new pulmonary TB cases diagnosed in 2009, EU/EEA
Diagnostic DST for rifampicin and isoniazid (2)

DST coverage for new (red) and retreated (blue) TB patients, by region and globally 2011
Diagnostic DST for rifampicin and isoniazid (1)
Among new bacteriologically-positive TB cases, 2009-2011
(& projections 2011-15 as per Global Plan)
DST coverage for second-line drugs among MDR-TB cases, 2011

[Bar chart showing DST coverage for second-line drugs among MDR-TB cases for different regions, with AFR having the highest coverage.]

% tested

AFR | AMR | EMR | EUR | SEAR | WPR | All Regions
Publications from Iran and Belarus


The DRS in Minsk 2010-11 – The Study team

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Evgeni Sahalchyk
Andrey Astrauko
Settings with highest % of MDR-TB among new TB cases (2001-2008: WHO)

- Minsk city, Belarus (2010): 35.3%
- Belarus- preliminary (2011): 29.2%
- Murmansk Oblast, Russian Federation (2008): 28.3%
- Pskov Oblast, Russian Federation (2008): 27.3%
- Arkhangelsk Oblast, Russian Federation (2008): 23.8%
- Baku city, Azerbaijan (2007): 22.3%
- Ivanovo Oblast, Russian Federation (2008): 20.0%
- Republic of Moldova (2006): 19.4%
- Kaliningrad Oblast, Russian Federation (2008): 19.3%
- Belgorod Oblast, Russian Federation (2008): 19.2%
- Dushanbe city and Rudaki district, Tajikistan (2009): 16.5%
- Mary El Republic, Russian Federation (2008): 16.1%
- Donetsk Oblast, Ukraine (2006): 16.0%
- Estonia (2008): 15.4%
- Tashkent, Uzbekistan (2005): 14.8%
Drug susceptibility of *Mtb* strains isolated from new and previously treated patients

<table>
<thead>
<tr>
<th>Category</th>
<th>Susceptible</th>
<th>MonoDR</th>
<th>PolyDR</th>
<th>MDR</th>
<th>XDR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>New</strong></td>
<td>44.2%</td>
<td>8.3%</td>
<td>11.5%</td>
<td>35.3%</td>
<td>2.0%</td>
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<tr>
<td><strong>Previously treated</strong></td>
<td>17.6%</td>
<td>4.5%</td>
<td>1.5%</td>
<td>76.5%</td>
<td>19.4%</td>
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</tbody>
</table>
49% !
High degree of clustering
High degree of clustering

→ Improved infection control needed
Direct Smear Microscopy Room
Shiraz Regional TB-lab, Iran
TB Culture Room
TB Antibiogram Room
TDR in Iran

Two years material (2006-08) – 146 MDR isolates

Among those: **XDR-TB 5.4% and TDR 10.2%**

15 TDR patients were described with isolates resistant to all tested 13 drugs: INH, RIF, SM, EMB, PZA, OFL, CIP, AMI, KAN, CAP, ETH, CS and PAS.

Of the patients 11/15 were men and 7/15 immigrants from the neighboring countries Afghanistan and Azerbaijan.

All 15 strains (mainly Harleem and Beijing genotypes) had different VNTR/Spoligotype profiles.
A case of XDR-TB in Sweden

Middle-aged man from former USSR
Asylum seeker – former prisoner
Pulmonary TB since 2001
Several episodes of treatment
Arrival in Sweden Summer 2012
Strain not earlier seen in Sweden
Early laboratory test-results

Smear positive +++
Screening with LPA showed resistance to RIF, INH, EMB, FQ, and 2nd line injectables
DST results July 2012

Resistant to 12 of 15 tested agents

- Streptomycin  R
- Kanamycin    R
- Amikacin     R
- Ofloxacin    R
- Moxifloxacin R
- Rifampicin   R
- Rifabutin    R
- Ethambutol   R
- Etionamid    R
- Capreomycin  R
- Isoniazid    R
- PAS          R

Pyrazinamid  S
Linezolid    S
Cyklooserin  S
Treatment since August 2012

- PZA S
- Cycloserin S
- Linezolid S
- TMC 207 ? (likely S)
- Clofazimin ?
- Spektramox ?
- Moxifloxacin R
## Laboratory follow-up

<table>
<thead>
<tr>
<th>Weeks</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>14</th>
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<tr>
<td>AFS a</td>
<td>***</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>AFS b</td>
<td>***</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MGIT pos</td>
<td>10 d.</td>
<td>22 d.</td>
<td>31 d.</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Management of drug resistant TB in Sweden

- Prompt detection of patients with MDR-TB
- Optimisation of therapy based on individual DR data
- Infection control
- Recording/reporting
- Follow up – monitoring of treatment outcome
- National MDR-TB expert group
The TB-lab role in MDR-TB control

- For correct \textbf{classification} and control of \textbf{MDR-TB} a specific and sensitive identification of strains \textbf{resistant to rifampicin and isoniazid} is crucial.
Not so long ago.....
The TB-lab role in MDR-TB control

• **Rapid** detection of resistance to RIF and INH is needed for **timely** modification of drug regimens to ensure **early non-infectiousness and cure** of patients with MDR-TB.
Drug susceptibility testing (DST)

- Solid medium 4 weeks
- Liquid medium 1 week
- Molecular testing 1 day

Indirect (testing isolates) vs direct (clinical specimens) testing.
Today
Mycobacterial Growth Indicator Tube (MGIT 960)

Courtesy: A. Martin
Today –
Molecular detection of *M. tuberculosis* and resistance related mutations

Steps in Hain test for molecular MDR screening with PCR and line probe hybridization

- Process specimen, extract DNA, amplify DNA targets with PCR
- Hybridize amplified DNA to oligonucleotide probes on strips

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An early warning system for MDR-TB is needed

A prompt identification of patients with resistant strains makes it possible to:

- Early modify drug regimens to ensure non-infectiousness and cure
- Increase and direct the infection control measures
- Reduce the development and spread of MDR-TB
Why is rapid detection of MDR/XDR/TDR so important?
Developement of drug resistance

- Bacteria: drug susc. → MDR
- M tub → MDR
- M tub → Res → More res → MDR → XDR
Developement of drug resistance

- Bacteria: drug susc. → MDR
- M tub → MDR
- M tub → Res → More res → MDR → XDR

Potential blocks
Infectiousness

- Patient with susc TB – weeks
- Patient with MDR/XDR-TB – up to years
**Time to DST results – what’s acceptable?**

- **Direct DST**
  - NAAT
  - DST NRA
  - DST MGIT

- **Indirect DST**
  - Isolation MGIT
  - NAAT
  - DST MGIT
  - Isolation Solid media
  - NAAT
  - DST NRA
  - DST MGIT
  - DST Solid media
Rapid testing is costly?

If you consider rapid detection of resistant *M tuberculosis* is too expensive – try not to do it!
Priorities for the TB-laboratory service - 1

• A new algorithm should be developed taking into account new diagnostic possibilities.
  – The role of Microscopy, Culture, DST, Molecular rapid tests should be optimized to allow sensitive, specific and timely detection of MDR/XDR-TB.

• Necessary resources should be made available for implementing more rapid tests as soon, and as wide, as possible.
  – Which tests are most suitable in different parts of the diagnostic service of a national lab-network?

• Un-necessary routine examinations should be discontinued
  – To keep down the overall costs and make financial and physical space for improved techniques – old routines should be questioned.
Priorities for the TB-laboratory service - 2

- A plan is set up for the future organization of the national lab network, taking into consideration that new techniques will be implemented
  - How many microscopy centers, culture/DST labs, how many molecular units?

- A set of basic quality criteria should be established, and a licensing system introduced to assure the high quality service. Standard Operating Procedures (SOPs) should be developed and implemented.
  - Laboratories failing to meet quality standards should be offered training, and if necessary closed.

- Methods for determining susceptibility to new drugs introduced should be developed.
  - Could include both phenotypic and genotypic testing
Priorities for the TB-laboratory service - 3

- A HR development plan should be established.
  - Both for replacement of people leaving and to guarantee relevant knowledge in new techniques.

Infection control in TB labs must be improved
- A risk assessment of all diagnostic units and tests carried out should be done

- Need of training should be analyzed and gaps filled

- Operational research should be strengthened.
what is worth doing - is worth doing well
"There is more to tuberculosis than the tubercle bacillus."

Robert Koch 1843-1910