Primary considerations:

individuals at risk of MDR-TB

Ernesto Jaramillo / Dennis Falzon
Outline of presentation

• Update on global MDR-TB indicators
• The new PMDT guidelines & use of rapid R testing
• Xpert MTB/RIF algorithm to test MDR-TB suspects
  - Individuals at risk for MDR – different groups
Update on latest global MDR-TB indicators
DR surveillance indicators (1)
Characteristics of available data on drug resistance, 2010

Data available from 119 out of 193 countries (62%)
• 48 countries rely on surveillance systems
• 71 countries rely on periodic surveys
Trends data from 83 settings
DR surveillance indicators (2)
Distribution of proportion of MDR among new TB cases, 1994-2010

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. © WHO 2011. All rights reserved.
### DR surveillance indicators (3)

<table>
<thead>
<tr>
<th>TB case</th>
<th>Best MDR-TB estimate</th>
<th>95% CLs</th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>3.3%</td>
<td>3.0% - 3.6%</td>
</tr>
<tr>
<td>Retreated</td>
<td>21%</td>
<td>19% - 22%</td>
</tr>
</tbody>
</table>
69 countries reported at least one XDR-TB case by March 2011
Diagnostic DST for new and retreated TB cases by WHO Region, 2009*

Number of countries reporting data in each region shown in brackets beneath bars **
Reported MDR-TB versus MDR cases expected among notified TB by WHO Region, 2009

<table>
<thead>
<tr>
<th>WHO Region</th>
<th>2009</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>Reported</td>
<td>Ratio</td>
</tr>
<tr>
<td>African</td>
<td>27,000</td>
<td>10,735</td>
<td>40%</td>
</tr>
<tr>
<td>American</td>
<td>6,000</td>
<td>2,795</td>
<td>47%</td>
</tr>
<tr>
<td>East Med.</td>
<td>13,000</td>
<td>480</td>
<td>4%</td>
</tr>
<tr>
<td>European</td>
<td>58,000</td>
<td>28,240</td>
<td>49%</td>
</tr>
<tr>
<td>S-E Asian</td>
<td>95,000</td>
<td>2,549</td>
<td>3%</td>
</tr>
<tr>
<td>West Pacific</td>
<td>80,000</td>
<td>2,057</td>
<td>3%</td>
</tr>
<tr>
<td>Global</td>
<td>280,000</td>
<td>46,856</td>
<td>16%</td>
</tr>
</tbody>
</table>
Enrolments and treatment outcomes

- A total of 30,475 MDR-TB patients in 91 countries (24 of the high MDR burden countries) were reported to have been started on treatment in 2009.

- The median value of success among MDR-TB patients started on treatment in 2007 in 92 countries was 54%.
The new PMDT guidelines & use of rapid R testing
The new PMDT guidelines (1)

- Guidelines on PMDT updated between 2009-2011
- Systematic reviews / modelling work
- Wide consultation of content and methodology experts
- GRADE Methodology to develop recommendations and assign strength
The new PMDT guidelines (2)

Quality of evidence

<table>
<thead>
<tr>
<th>Quality</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is very unlikely to change confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the effect and may change the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain.</td>
</tr>
</tbody>
</table>

Guyatt GH et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008 Apr 26;336(7650):924-6
The new PMDT guidelines (3)

Strength of recommendations

<table>
<thead>
<tr>
<th>Strength</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>The Guideline Development Group is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.</td>
</tr>
<tr>
<td>Conditional</td>
<td>The Guideline Development Group concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects.</td>
</tr>
</tbody>
</table>
## The new PMDT guidelines (4)

### Meaning of recommendations

<table>
<thead>
<tr>
<th>Perspective</th>
<th>Strong recommendation</th>
<th>Conditional recommendation</th>
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</thead>
<tbody>
<tr>
<td>For patients</td>
<td>Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.</td>
<td>The majority of individuals in this situation would want the suggested course of action, but many would not.</td>
</tr>
<tr>
<td>For clinicians</td>
<td>Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.</td>
<td>Recognize that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.</td>
</tr>
<tr>
<td>For policy-makers</td>
<td>The recommendation can be adapted as policy in most situations.</td>
<td>Policy making will require substantial debate and involvement of various stakeholders.</td>
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Rapid drug susceptibility testing for early start of appropriate treatment (1)

« Rapid drug susceptibility testing for resistance to isoniazid and rifampicin or to rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB subject to available resources »

Conditional recommendation, ⊕⊕⊕⊕⊕ / very low quality evidence
Rapid drug susceptibility testing for early start of appropriate treatment (2)

- Optimal timing and method of DST determined through modelling work.
- Outcomes of interest were reduced mortality, improved cure rates, decreased development of resistance, and reduced likelihood of failure and relapse.
- The model did not take into consideration secondary transmission.
- Sensitivity analyses showed that the results were fairly robust.
Rapid drug susceptibility testing for early start of appropriate treatment (3)

- Rapid DST for both H&R on all patients pretreatment was the best strategy for averting deaths and preventing acquired MDR.
- Rapid testing at the time of diagnosis was the most cost-effective testing strategy for any patient group or setting even at very low levels of resistance among TB patients - MDR in >1% and isoniazid resistance (other than MDR) in >2%.
- For new patients, DST at start of treatment was a better strategy than waiting to test only those patients who remain sputum-smear positive later in the course of their first-line treatment.
Rapid drug susceptibility testing for early start of appropriate treatment (4)

- Rapid DST for rifampicin alone did not have the same benefit as the rapid testing for both isoniazid and rifampicin resistance. This is because detection of patients with isoniazid resistance alone provides the opportunity for their effective treatment and can prevent the development of additional resistance to rifampicin.
Xpert MTB/RIF algorithm to test MDR-TB suspects
« Person at high risk of MDR-TB, known or suspected of having TB »
A. Individuals at risk of MDR-TB
- Diagnosed with TB or
- Suspected of having TB

B. HIV (+) individuals (or HIV unknown in high HIV settings) suspected of having TB

HIV (-) individuals not at risk of MDR-TB with either:
- Abnormal CXR
- Sputum smear (-) but still suspected of having TB

Individuals accessing health centre

Xpert MTB/RIF

- TB, Rif resistance
- TB, no Rif resistance
- No TB detected

- Enrol on MDR-TB regimen
- DST FLD and SLD
- ART if HIV +
- Treatment regimen based on patient history
- ART if HIV +
- Appropriate further clinical management
- IPT if HIV +
Individuals at risk for MDR
High risk groups for MDR-TB (1)

Primarily:
- All previously treated for TB
- Any person at high risk of MDR-TB as per national policy
- Other MDR-TB risk groups
High risk groups for MDR-TB (2)

- Exposure to known DR-TB case
- Failure of initial FLD regimen ("Cat 1")
- Treatment failure in the private sector
- SS+ at months 2 or 3
- Relapse & return after default
- Exposure in institutions with high DR-TB prevalence or outbreaks
High risk groups for MDR-TB (3)

- Residence in areas of high DR-TB prevalence
- Use of anti-TB drugs of poor/unknown quality
- $R_x$ in poorly performing programmes
- Malabsorption or diarrhoea
- HIV (in some settings)