Molecular methods for TB drug resistance testing: what is needed?

Experience from Khayelitsha, Cape Town, South Africa

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Khayelitsha

- Peri-urban township
- Population 0.5 million
- Antenatal HIV prevalence ~30%
- Patients on ART: 10,000 started, >9000 in care
- MTCT HIV+ rate: 4.5%
- TB case notification rate 2007: ~1,500/100,000/year
- 10 health facilities providing TB diagnosis and treatment
- TB outcomes (76% cure rate and 83% success rate)
Rapid Molecular Screening for Multidrug-Resistant Tuberculosis in a High-Volume Public Health Laboratory in South Africa

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GenoType® MTBDRplus
Molecular Genetic Test System for the Detection of the Mycobacterium tuberculosis Complex and its Resistance to Rifampicin and/or Isoniazid from Culture Samples or pulmonary smear-positive patient material

- simple
- safe
- fast
- easy to combine
- can be automated

CE-labelling
Quality management certified to ISO 9001/13485
DR-TB in Khayelitsha

~ 2.4% of TB cases

<table>
<thead>
<tr>
<th>Year</th>
<th>No. DR-TB cases diagnosed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003/04</td>
<td>12</td>
</tr>
<tr>
<td>2005</td>
<td>57</td>
</tr>
<tr>
<td>2006</td>
<td>110</td>
</tr>
<tr>
<td>2007</td>
<td>146</td>
</tr>
<tr>
<td>2008*</td>
<td>113</td>
</tr>
</tbody>
</table>
### MDR burden?

- Routine DST only for previously treated and high MDR risk TB cases
- Therefore likely to be poor overall case detection
- Case detection of 150-200 cases/year = incidence 30-40/100,000/year

<table>
<thead>
<tr>
<th>Country</th>
<th>Population (Millions)</th>
<th>Est. MDR cases</th>
<th>% MDR among TB cases</th>
<th>MDR incidence /100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>43.8</td>
<td>14034</td>
<td>2.6</td>
<td>32.1</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>140.7</td>
<td>36037</td>
<td>19.4</td>
<td>25.6</td>
</tr>
</tbody>
</table>

Source: WHO 2008
The need for rapid diagnosis

80 DR-TB cases diagnosed in Q1 & 2, 2008

76% of diagnosed cases started on treatment

Median 57 days between sputum sample and treatment start

Median 30 days between sputum sample and death
Genotype MTBDR test impact?

Cases diagnosed between September 2007 and June 2008

<table>
<thead>
<tr>
<th>Condition</th>
<th>Median Days to Treatment Initiation</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear Negative, DST on positive culture</td>
<td>88</td>
<td>19</td>
</tr>
<tr>
<td>Smear Negative, PCR on positive culture</td>
<td>69</td>
<td>25</td>
</tr>
<tr>
<td>Smear Positive, DST on positive culture</td>
<td>59</td>
<td>16</td>
</tr>
<tr>
<td>Smear Positive, PCR on sputum</td>
<td>37</td>
<td>17</td>
</tr>
</tbody>
</table>

Only 30% of cases are smear positive.
Need to test ALL TB cases not just the smear positives…

• Up to 100 TB suspects seen every week in just one clinic
• Of these, preliminary data suggests that more than 30% are culture positive
• A point of care test for all suspects could be feasible and cost effective in this setting
Laboratory burden

• 18 MGIT machines
• ~18,000 cultures a month
• Culture not offered to all TB cases
• Reliance on culture requires centralised laboratory
Current constraints to PCR (Hain genotype)

• Logistically not straightforward
• Requires 3 rooms, preferably one with negative pressure to reduce the risk of cross contamination
• Not a closed system, thereby increased risk of cross-contamination
• As yet, no reliable systems to assess cross-contamination
• Lack of clinical trust
• User-dependent, lack of human resources
Clinical trust in PCR

Case: 16 year student

- Negative smear at the end of regimen 1 in March 2008
- Symptoms reappear in April, sputum taken 10th April.
- DST requested as previously treated case
- PCR result from pos culture on 19th May shows MDR
- Started on MDR treatment on 2nd June by clinic doctor, after counselling
- Referred to specialist MDR clinic and seen a week later
- Patient told doctor that he had no symptoms now and X-ray findings inconclusive
- Treatment stopped on the 9th June by specialist doctor, request new sputum and to see again in 2 months
- Patient failed to attend clinic despite repeated attempts to recall; lack of trust in clinic doctor
- Patient died after massive haemoptysis on 16th July
Conclusions

• Culture is not the answer in this setting
  – Too slow and too burdensome on lab

• Molecular rapid test has reduced the time to treatment initiation and appears feasible in this setting
  – But, there are some drawbacks…
What is needed for a molecular test?

• Robust technology
• Able to be decentralised to some extent
• Not reliant on highly trained (and motivated) personnel
• High throughput required, whilst reducing the risk of cross-contamination during amplification

Needs to work directly on all sputum specimens!
Is it possible?

• PCR tests for TB have been around for a decade, why are they only now starting to be used routinely in high burden settings?
  – Lack of commitment
  – Lack of understanding of real needs
• Promising developments
• Need to be trialled in terms of programmatic impact
Acknowledgments

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