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>
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<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>
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<tr>
<td>2008*</td>
<td>113</td>
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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></th>
<th>Population (Millions)</th>
<th>Est. MDR cases</th>
<th>% MDR among TB cases</th>
<th>MDR incidence /100,000</th>
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</thead>
<tbody>
<tr>
<td>South Africa</td>
<td>43.8</td>
<td>14034</td>
<td>2.6</td>
<td>32.1</td>
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<td>Russian Federation</td>
<td>140.7</td>
<td>36037</td>
<td>19.4</td>
<td>25.6</td>
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</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

Bar chart:
- 61 cases started on treatment
- 10 cases died before treatment
- 3 cases could not be located
- 3 cases still to be started on treatment
- 1 case refused treatment
- 2 cases transferred to another district

80 DR-TB cases diagnosed in Q1 & 2, 2008
Genotype MTBDR test impact?

Cases diagnosed between September 2007 and June 2008

- **Smear Negative, DST on positive culture**: N=19, Median days to treatment initiation = 88
- **Smear Negative, PCR on positive culture**: N=25, Median days to treatment initiation = 69
- **Smear Positive, DST on positive culture**: N=16, Median days to treatment initiation = 59
- **Smear Positive, PCR on sputum**: N=17, Median days to treatment initiation = 37

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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