Rapid culture and drug susceptibility testing using non-commercial methods

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Global TB Case Detection

- 2.6 million new smear + cases notified in 2007
- 64% of the estimated 4.1 million cases

- 5.3 million new cases overall notified in 2007
- 57% of the estimated 9.3 million cases
Conclusions:

- **Highest rates ever recorded** of MDR-TB
- **Highest rates** are in countries of the former Soviet Union and China
- **Severely limited laboratory capacity** has meant limited data availability in Africa
- **Insufficient efforts** in many areas of the world to treat and control MDR-TB
- Equipment to **rapidly diagnose** MDR-TB in 1 week instead of 3 months exists but most patients cannot access such services
- **XDR-TB in 45 countries** threatens to derail 10 years of progress in TB control and HIV management
- **Extraordinary measures** are needed in Eastern Europe: rapid detection, effective care, access to drugs
Current Policy Recommendations

- **2007**
  - Liquid medium for culture and DST

- **2008**
  - Line probe assays for rapid MDR-TB screening
Initiatives to Expand Access

FIND prices for BACTEC and MGIT and Country List

Enhancement of diagnostic capacity for TB and MDR-TB is urgently needed to scale up access to care and treatment of MDR-TB. To help meet this challenge, FIND has collaborated in the development and evaluation of new TB diagnostic tools, including TB liquid culture and DST, rapid species identification, and line probe assay. WHO has officially endorsed the use of these technologies based on the thorough evaluation of the evidence of their effectiveness under actual program conditions. As part of its role in the development and evaluation process of these tools, FIND has successfully negotiated with three of the manufacturing partners to obtain significant price reductions in order to facilitate access to these diagnostic technologies. These discounts average 50% on diagnostic instruments, and 75% on reagents, and are available to high TB burden countries that wish to procure TB diagnostics for use in the public and non-profit health care sectors and who procure these tools with funding from the government, UNITAID, or the Global Fund. Furthermore, the FIND-negotiated agreements contain provisions for further discounts as procurement volumes of reagents increase. As these become available FIND shall communicate the new prices to the TB community. In the case of the BBL MGIT Tubes List Nr. 245122 reagents it is expected that price shall be reduced in the second quarter of 2008.

Current FIND-negotiated prices, along with the list of countries eligible for the discounts, as with BD are listed below.

<table>
<thead>
<tr>
<th>Product Description</th>
<th>Price</th>
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<tbody>
<tr>
<td>BD BACTEC™ MGIT™ 960 System</td>
<td>US$ 38,950.00</td>
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<tr>
<td>BBL MGIT Tubes List Nr. 245122 Reagents</td>
<td>US$ 205.00/100</td>
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Expanding and accelerating access to diagnostics for patients at risk of MDR-TB

A. Project title: Expanding and accelerating access to diagnostics for patients at risk of multi-drug resistant tuberculosis (MDR-TB)

B. Timeframe: Project duration: 2009-2011, starting on the date of the final signature of the Memorandum of Agreement.

C. Amount committed by UNITAID: US$ 25,129,897

D. Lead partner: Global Laboratory Initiative (GLI), Stop TB Department, World Health Organization

E. Other partner(s): - Global Drug Facility (GDF), Stop TB Partnership, World Health Organization - Foundation for Innovative New Diagnostics (FIND)
Are there non-commercial options for detection and DST that could serve as temporary solutions during capacity building?

- 2009
  - Microscopically Observed Drug Susceptibility (MODES)
  - Thin Layer Agar (TLA)
  - Nitrate Reductase Assay (NRA)
  - Colorimetric Redox Indicators (CRI)
  - Phage-based Assays (including FASTPlaque™)
Review Questions

• “To perform systematic reviews of the literature and meta-analysis (where appropriate) of data examining the diagnostic accuracy and performance characteristics [of the assay] for the detection of drug resistance in MTB”
Microscopically Observed Drug Susceptibility (MODS)

- Direct or indirect inoculation of patient specimens for detection & DST

- Liquid media – increased sensitivity and faster growth

- Microcolony detection – faster turnaround time
Results of Systematic Review (MODS)

- 9 studies identified
  - 6 direct inoculation
  - 3 indirect inoculation

- Overall (Rifampin, n=8)
  - Sensitivity = 98.0% (94.5, 99.3)
  - Specificity = 99.4% (95.7, 99.9)

- If more stringent exclusion criteria (n=5)
  - Sensitivity = 98.7% (89.4, 100)
  - Specificity = 100% (95.8, 100)
Results of Systematic Review (MODS)

- **Direct only (n=6)**
  - Sensitivity = 96.8% (92.4, 98.7)
  - Specificity = 99.0% (94.3, 99.8)

- **Contamination Rates (n=7)**
  - MODS: 6.3%
  - vs. solid media comparisons: 10.4%
  - vs. liquid media comparisons: 4.1%

- **Turnaround Time (n=6)**
  - Direct Inoculation: 11.6 days (range 6 – 21)
  - Indirect Inoculation: 6.5 days (range 6 – 7)
Thin Layer Agar (TLA)

- Direct or indirect inoculation of patient specimens for detection & DST
- Solid media – easier to manipulate
- Microcolony detection – faster turnaround time
Results of Systematic Review (TLA)

- 3 studies identified
  - 2 direct inoculation
  - 1 indirect inoculation

- All reporting 100% accuracy
Results of Systematic Review (TLA)

- Contamination Rates (n=9)
  - TLA: 11.8%
  - vs. solid media comparisons: 5.5%
  - vs. liquid media comparisons: 9.7%

- Turnaround Time (n=2)
  - 11.1 days (range 11 – 11.2)
Nitrate Reductase Assay (NRA)

- Based on MTB’s ability to reduce nitrate to nitrite

- Simple, direct or indirect inoculation of patient specimens for detection & DST

- Sensitive detection of small amounts of metabolic biproduct improves turnaround time

KNO₃-containing media
Add reagent to drug-free slant day 7 (repeat day 10, 14)
Color development = growth
Results of Systematic Review (NRA)

- Overall (n=20)
  - Sensitivity = 97.0% (95.0, 98.0)
  - Specificity = 100% (99.0, 100)
Results of Systematic Review (NRA)

- Direct only (n=5)
  - Sensitivity = 96.0% (92.0, 98.0)
  - Specificity = 99.6% (98.7, 100)

- Contamination Rate
  - 4.8%

- Turnaround Time
  - 7 – 14 days
Colorimetric Redox Indicators (CRI)

- Based on reduction of indicator by metabolically active MTB

- MIC determination using microdilution

- Sensitive detection metabolic activity improves turnaround time

Incubate microdilution plate 7 days

Add indicator to all wells, incubate overnight

Color change = growth
Results of Systematic Review (CRI)

- Overall (n=31)
  - Sensitivity = 98.0% (96.0, 99.0)
  - Specificity = 99.0% (99.0, 100)
Results of Systematic Review (CRI)

- Direct only (n=2)
  - Sensitivity = 90.0% (68.3, 98.8)
  - Specificity = 100% (98.7, 100)

- Contamination Rate
  - 5%

- Turnaround Time
  - 7 days
Mycobacteriophage Assays: 
FASTPlaque™, in-house amplification, in-house luciferase reporter phage (LRP)

- Uses bacteriophage viruses to infect and detect viable MTB
- Amplification approach or luciferase light production
- 2 day turnaround time, direct or indirect detection & DST

Plaques – viable MTB cells present  
No plaques – no viable MTB cells present
Results of Systematic Review (Phage)

- Overall (FASTPlaque\textsuperscript{TM}, n=15)
  - Sensitivity = 95.0% (91.5, 97.1)
  - Specificity = 95.3% (91.1, 97.6)

- Overall (in-house amplification, n=11)
  - Sensitivity = 98.7% (96.3, 99.6)
  - Specificity = 98.2% (94.9, 99.4)

- Overall (LRP, n=8)
  - Sensitivity = 99.6% (35.6, 100)
  - Specificity = 99.4% (93.4, 99.9)
Results of Systematic Review (Phage)

- Direct only (n=5, FASTPlaque™ only)
  - Sensitivity = 93.0% (88.0, 96.7)
  - Specificity = 96.3% (91.6, 98.4)
Results of Systematic Review (Phage)

• Large range of contaminated or indeterminate results: 0 – 36% (mean = 5.8%)

• Primarily a problem for studies using direct specimens: 3 – 36% (mean = 20.4%)
  ▫ 18 out of 28 arms using indirect specimens did not report any contaminated/indeterminate results

• 3 studies with arms using antibiotic supplement (NOA) showed decreased contamination by 36 – 94%
  ▫ No statistically significant difference in accuracy
# Summary Findings

<table>
<thead>
<tr>
<th>Diagnostic (Reference)</th>
<th># Studies (Participants)</th>
<th>Pooled Accuracy Estimates from Meta-Analyses</th>
<th>Turnaround Time (direct)</th>
<th>Contamination Rates (direct)</th>
<th>Quality of Evidence</th>
<th>Costs (as per NDWG)</th>
<th>Resources (as per NDWG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MODS</td>
<td>9 studies (n=1474)</td>
<td>Sens 0.980 Spec 0.994</td>
<td>11.6 days</td>
<td>6.3%</td>
<td>Moderate</td>
<td>Equipment: ++ Consumables: ++</td>
<td>Training: extensive Infrastructure: ++/+/-</td>
</tr>
<tr>
<td>TLA</td>
<td>3 studies (n=439)</td>
<td>Sens 1.00 Spec 1.00</td>
<td>11.1 days</td>
<td>11.8%</td>
<td>Low</td>
<td>Equipment: + Consumables: ++</td>
<td>Training: extensive Infrastructure: ++/+/-</td>
</tr>
<tr>
<td>Phage – FASTPlaque</td>
<td>12 studies (n=2945)</td>
<td>Sens 0.950 Spec 0.953</td>
<td>1 – 2 days</td>
<td>20.4%</td>
<td>Very Low</td>
<td>Equipment: ++ Consumables: +++</td>
<td>Training: moderate Infrastructure: ++/+/-</td>
</tr>
<tr>
<td>CRI</td>
<td>31 studies (n=2498)</td>
<td>Sens 0.980 Spec 0.990</td>
<td>7 days</td>
<td>5%</td>
<td>Moderate</td>
<td>Equipment: + Consumables: ++</td>
<td>Training: extensive Infrastructure: +++</td>
</tr>
<tr>
<td>NRA</td>
<td>19 studies (n=2304)</td>
<td>Sens 0.970 Spec 1.00</td>
<td>7 – 14 days</td>
<td>4.8%</td>
<td>Moderate</td>
<td>Equipment: + Consumables: ++</td>
<td>Training: moderate Infrastructure: ++/+/-</td>
</tr>
</tbody>
</table>

**WHO-endorsed rapid test for DST (for comparison)**

| LPA                    | 12 studies (n=4937)      | Sens 0.981 Spec 0.987                      | 1 – 2 days               | Moderate                   | Equipment: +++ Consumables: +++ | Training: moderate Infrastructure: ++/+/-|
Concerns and Issues

- Lack of data on outcomes other than accuracy

- Quality of primary studies
  - Case control vs. Cross-sectional designs
  - Convenience sampling vs. Consecutive/Random
  - Retrospective vs. Prospective data collection
  - Reporting of blinding
Concerns and Issues

• Non-commercial methods generally suffer from lack of standardization

• Large scale demonstration studies have not been performed, and are not likely to be performed

• Limited data using direct patient specimens, even though this would be the most important application

• Setting of implementation? Peripheral vs. central laboratories

• Biosafety concerns

• Specificity of species identification
STAG Meeting - November 2009

• Final policy recommendations to be determined
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