New recommendations for culture-based diagnostics

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On behalf on “Culture-based diagnostics and DST” subgroup of STOP TB NDWG
Declaration of interest

Declaration of disinterest
Culture and phenotypic DST sub-group

Membership
• Open to all – join today!
• 90 is not enough
• Needs wider global distribution

Remit
• Facilitate
  – Info sharing
  – Collaboration
  – Research
  – Implementation

Focus
• Non-commercial methods

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• davidajmoore@msn.com
Subgroup activities

Completed or underway

- Inventory of methods
- Gathering of SOPs
- Gathering of QA plans
- Collection of bibliography

- [www.tbevidence.org](http://www.tbevidence.org)

Planned

- “Box-ing” of materials for non-commercial methods
- Establishment of training centres – Africa and Asia
- [coordination of field evaluation proposal]
Actionable information and need-driven DST

Isoniazid  S
Rifampicin  S

Isoniazid  R
Rifampicin  S

2nd line DST panel plus ethambutol, streptomycin, pyrazinamide
Non-commercial methods

**Conventional**
- Culture detection
  - LJ
  - Middlebrook media etc.
- Indirect DST
  - proportion method
  - resistance ratio
  - absolute concentration

**New**
- Detection and direct DST
  - MODS
  - NRA
  - Phage-based assays
  - TLA
- Indirect DST
  - Colorimetric redox indicator (CRI) assays
    - MABA, TEMA, resazurin etc.
• Detection and direct DST
  – MODS
  – NRA
  – Phage-based assays
  – TLA

• Indirect DST
  – Colorimetric redox indicator (CRI) assays
Steps to WHO endorsement

**Expert Group Committee**
- Convened, meet for 1 day
- Review evidence
  - systematic reviews
  - meta-analyses
- GRADE approach
- Report and recommendation sent to STAG-TB of WHO

**STAG-TB**
- Review EGC recommendations
- Make recommendation to WHO
  - June 2007
    - DST/liquid culture
    - 2 smears, 1 AFB
  - June 2008
    - Line probe assays
    - 3Is

*November 2009*
*Cancun UNION meeting December 2009*

**WHO**
- Issue policy statement

*April 2009*
*Postponed to September 2009*

*July 2010*
GRADE

Quality of evidence

How confident are we that research estimates of pros and cons (harms and cost) are correct?

1. Study design
2. Limitations
3. Directness
   - patient-important outcomes
   - accuracy studies usu. LOW quality evidence for this
4. Unexplained variability
5. Imprecise or sparse data
6. Reporting bias

Strength of recommendation

STRONG or WEAK

Determined by

1. Quality of evidence
2. Balance of desirable vs. undesirable effects
3. Costs
4. Values and preferences

www.GRADE.org
NON-COMMERCIAL CULTURE AND DRUG-SUSCEPTIBILITY TESTING METHODS FOR SCREENING OF PATIENTS AT RISK OF MULTI-DRUG RESISTANT TUBERCULOSIS

- POLICY STATEMENT -

July 2010

1. Background .......................................................................................................................... 1
2. Evidence base for policy formulation .................................................................................. 2
   2.1 Process for evidence synthesis ....................................................................................... 2
   2.2 Management of Declaration of Interest ....................................................................... 3
3. Premise for adopting new diagnostic tools/methods ............................................................ 3
4. Summary of results .............................................................................................................. 4
   4.1 Colometric redox indicator (CRI) methods ................................................................... 4
   4.2 Microscopically observed drug susceptibility (MODS) ............................................... 5
   4.3 Nitra reductase assay (NRA) ......................................................................................... 6
5. Policy recommendations .................................................................................................... 6
6. Target audience .................................................................................................................. 7

http://www.who.int/tb/dots/laboratory/whopolicy_noncommercialculture_and_dstmethods_july10.pdf
Key recommendations

MODS and NRA

- As direct or indirect tests

CRI

- As indirect test

TLA, phage-based assays – insufficient evidence for recommendation

“...for screening of patients suspected of having MDR-TB”
So who would you *not* test?

<table>
<thead>
<tr>
<th></th>
<th>New cases</th>
<th>Retreatment cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H  R  MDR</td>
<td>H  R  MDR</td>
</tr>
<tr>
<td>1999</td>
<td>9.0% 4.0% 3.0%</td>
<td>16.2% 14.6% 12.3%</td>
</tr>
<tr>
<td>2006</td>
<td>11.6% 5.8% 5.3%</td>
<td>30.3% 26.4% 23.6%</td>
</tr>
</tbody>
</table>
“Issues”

Apples and oranges

• Pooled data from studies with different SOPs
  – Different drug concentrations
  – Different reading timetables
  – Direct and indirect together

“...as an interim solution”

Speciation

Cost and indeterminate samples
Antibiotic stock solutions were diluted and added to MODS liquid medium to give the following critical concentrations: INH, 0.1 μg/ml (MODS INH medium), and RIF, 2.0 μg/ml (MODS RIF medium).

Also argues for “locked down” SOPs and integrated QA programme
“Issues”

Apples and oranges

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Cost and indeterminate samples

- MGIT
  - can ill-afford indeterminate or contaminated samples
- NRA
  - 17% (Solis 2005)
  - 17% (Affolabi 2007)
  - 30% in programmatic implementation (Asencios 2008)

“…as an interim solution”

- Pending arrival of molecular tools and automated liquid culture...

Speciation

- MODS
  - Cording / PNB well
Liquid vs. solid culture for tuberculosis: performance and cost in a resource-constrained setting

V. N. Chihota,* A. D. Grant,† K. Fielding,† B. Ndibongo,* A. van Zyl,* D. Muirhead,*†
G. J. Churchyard*†

Table 3  Sensitivity and specificity of microscopic cording and the anti-MPB64 TB assay in identification of Mycobacterium tuberculosis complex, compared with standard biochemical tests as the gold standard

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 341)</th>
<th>Smear-positive (n = 128)</th>
<th>Smear-negative (n = 213)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N (%)</td>
<td>95%CI</td>
<td>n/N (%)</td>
</tr>
<tr>
<td>Cording</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>199/201 (99.0)</td>
<td>96.5–99.9</td>
<td>99/100 (99.0)</td>
</tr>
<tr>
<td>Specificity</td>
<td>137/140 (97.9)</td>
<td>93.9–99.6</td>
<td>26/28 (92.9)</td>
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<td>MPB64</td>
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<tr>
<td>Sensitivity</td>
<td>199/200 (99.5)</td>
<td>97.2–100</td>
<td>99/99 (100)</td>
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*One sided, 97.5%CI.
CI = confidence interval.

Performance of cording equivalent to MPB64 assay
“Issues”

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**Speciation**

- **MODS**
  - Cording / PNB well
- **NRA**
  - *M kansasii, M szulgai, M fortuitum, M smegmatis* all NRA +
  - Some (few) MTB NRA-negative
  - NRA PNB tube?
  - Otherwise BSL-3 for NRA (like MGIT)
  - BSL-2 for MODS
- CONTENTIOUS!
Culture and phenotypic DST sub-group

Join today

• Nicolas Durier (nicolasdurier@hotmail.com)
• David A. Moore (davidajmoore@msn.com)

Get involved

• “Box-ing” of materials for non-commercial methods
• Establishment of training centres – Africa and Asia
• Field evaluation proposal

Thank-you for your attention