New recommendations for culture-based diagnostics

David Moore
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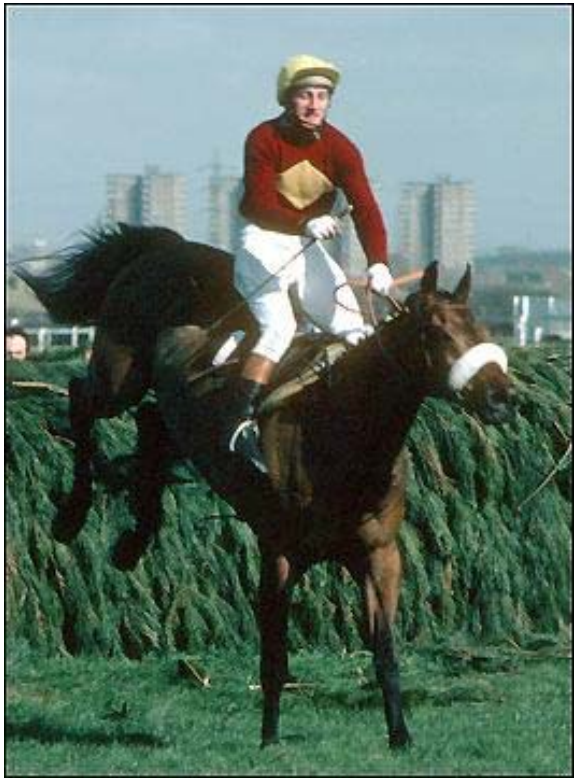
On behalf on *"Culture-based diagnostics and DST"* subgroup of STOP TB NDWG

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

- nicolasdurier@hotmail.com
- davidajmoore@msn.com

Remit

- Facilitate
  - Info sharing
  - Collaboration
  - Research
  - Implementation

Focus

- Non-commercial methods

Subgroup activities

Completed or underway

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

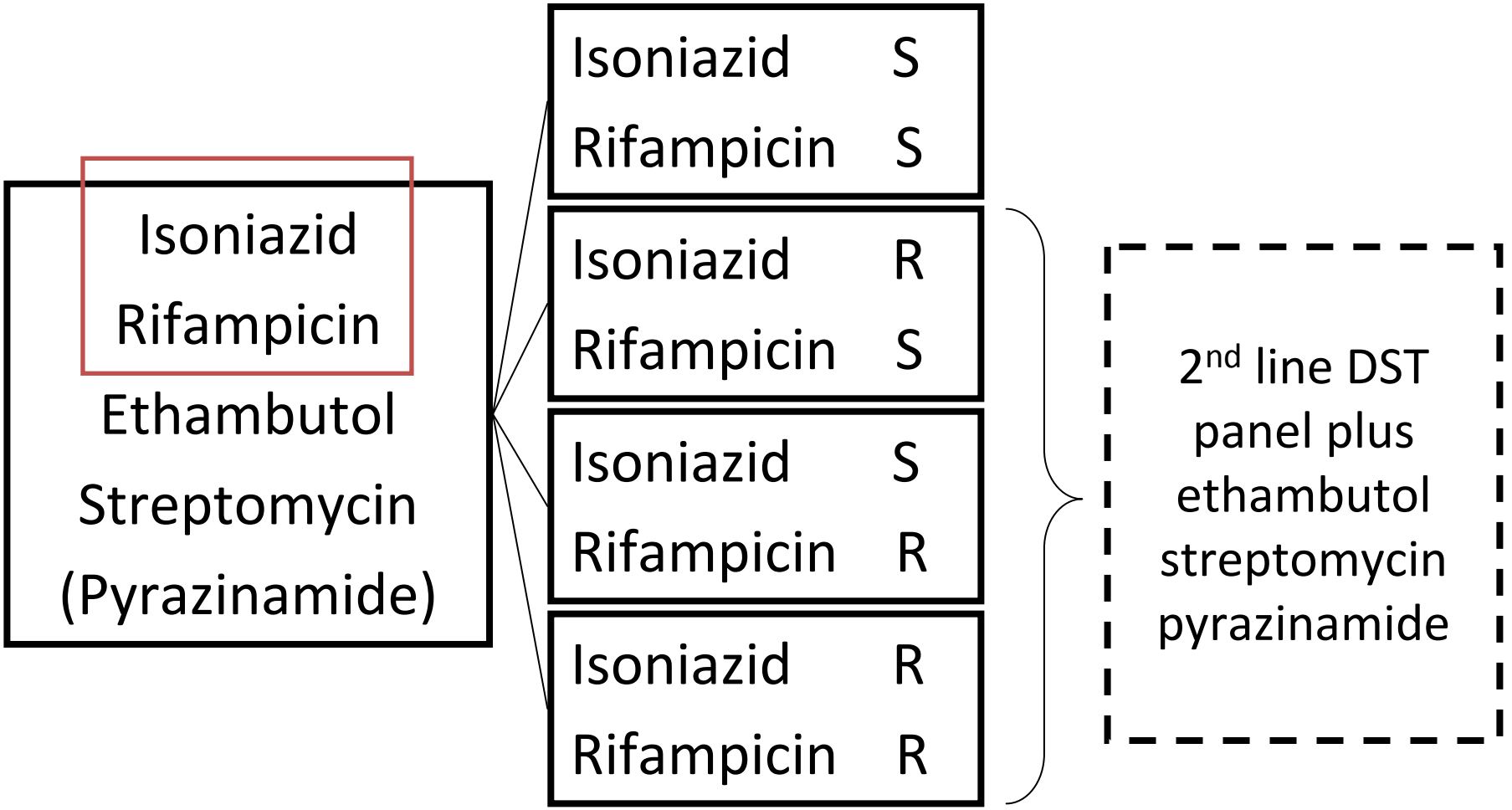
- www.tbevidence.org

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



Non-commercial methods

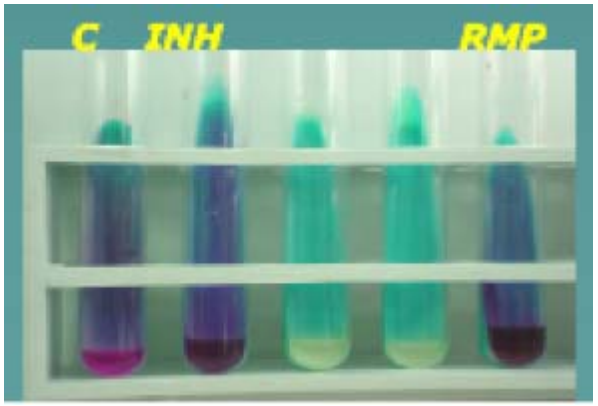
Conventional

- 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

April 2009

Postponed to September 2009

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

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

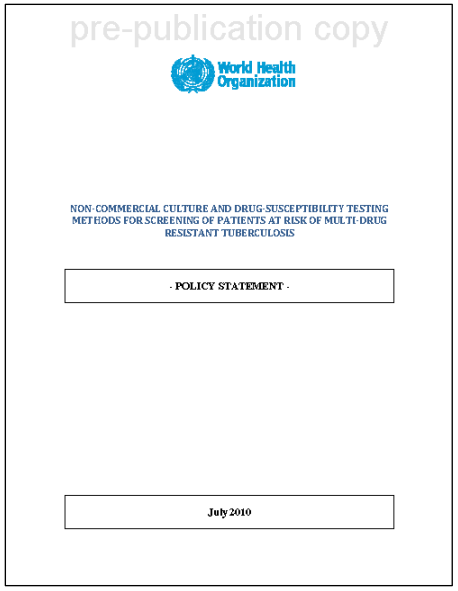
www.GRADE.org

World Health Organization

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

- POLICY STATEMENT -

July 2010



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

Key recommendations

TLA, phage-based assays – insufficient evidence for recommendation

MODS and NRA

- As direct or indirect tests

CRI

- As indirect test

"...for screening of patients suspected of having MDR-TB"

So who would you *not* test?

	New cases			Retreatment cases		
	H	R	MDR	H	R	MDR
1999	9.0%	4.0%	3.0%	16.2%	14.6%	12.3%
2006	11.6%	5.8%	5.3%	30.3%	26.4%	23.6%

“Issues”

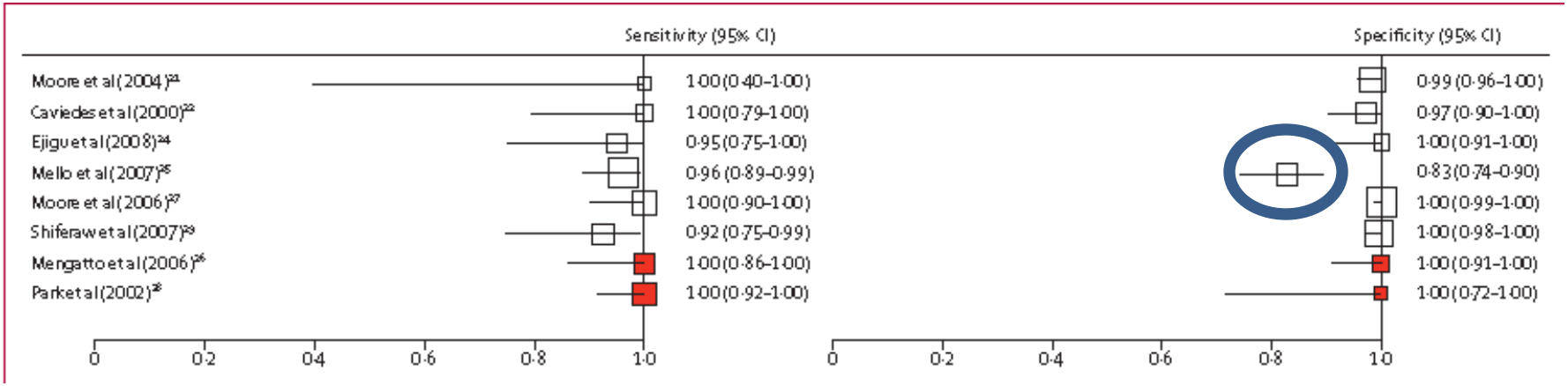
Apples and oranges

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

Cost and indeterminate samples

“...as an interim solution”

Speciation



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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  - Direct and indirect together

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

INT J TUBERC LUNG DIS 14(8):1024–1031

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

	Overall (N = 341)		Smear-positive (n = 128)		Smear-negative (n = 213)	
	n/N (%)	95%CI	*n/N* (%)	95%CI	*n/N* (%)	95%CI
Cording						
Sensitivity	199/201 (99.0)	96.5–99.9	99/100 (99.0)	94.6–100	100/101 (99.0)	94.6–100
Specificity	137/140 (97.9)	93.9–99.6	26/28 (92.9)	76.5–99.1	111/112 (99.1)	95.1–100
MPB64						
Sensitivity	199/200 (99.5)	97.2–100	99/99 (100)	96.3–100*	100/101 (99.0)	91.6–100
Specificity	137/140 (97.9)	93.9–99.6	26/28 (92.9)	76.5–99.1	111/112 (99.1)	95.1–100

*One sided, 97.5%CI.
CI = confidence interval.

Performance of cording equivalent to MPB64 assay

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"...as an interim solution"

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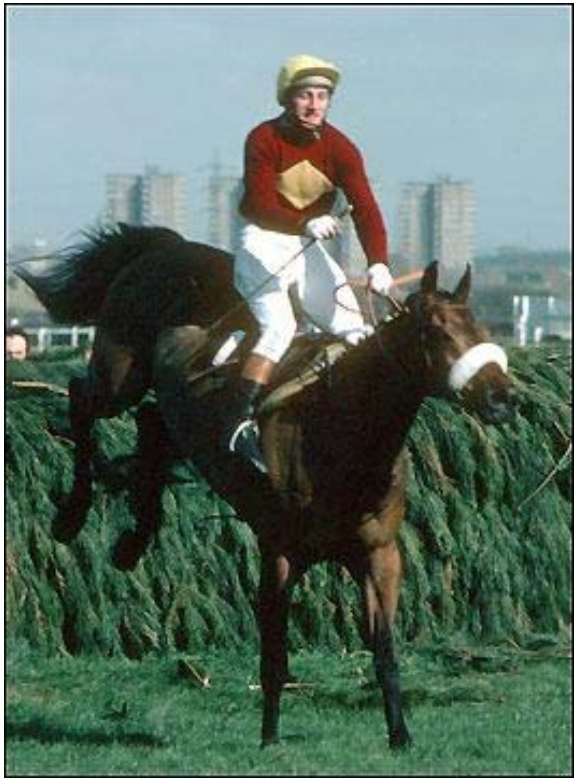
Speciation

- 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!



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Get involved

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- field evaluation proposal

Thank-you for your attention