Summary of Report to WHO on Liquid Culture and DST

Heather Alexander Konopka, PhD

Foundation for Innovative New Diagnostics
Centers for Disease Control and Prevention

FIND MGIT Demonstration Projects

- Large-scale implementation and assessment of MGIT culture (and DST) in high TB-burden, low- to middle-income programmatic settings

- Objectives:
  - Demonstrate the feasibility, impact, and costs of performing MGIT culture and DST in low- to middle-income settings
    - TB/HIV case finding
    - MDR TB detection
  - Provide information to inform WHO guidance and policy

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TB/HIV Case Finding

- CREATE projects
  - ZAMSTAR (Zambia, South Africa)
  - Thibela (South Africa)
  - THRio (Brazil)
- AMPATH
  - Kenya
  - Nested assessment of WHO smear-negative diagnostic algorithm
- Include assessment of Capilia TB assay

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MDR TB Detection

- Four sites:
  - Nukus, Uzbekistan (MSF)
  - Kathmandu, Nepal (GENETUP)
  - Samara Oblast, Russian Federation (HPA/UK)
  - Manila, Philippines (TDF)

- Common Standard Operating Procedures (SOPs)
- On- and off-site training provided by outside consultants and BD
- Standardized protocols for phased validation and implementation of MGIT culture and DST
- Include rapid species identification methods (Capilia or molecular methods)
- Detailed cost analysis

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Preliminary Data Analysis and Report to WHO

- Performance data through February 2007
- Background document prepared by FIND and collaborators
- Presented to ad hoc review group convened by WHO (March 2007)
- Recommendations presented to and endorsed by STAG TB (June 2007)
- Issued as WHO policy (October 2007)

Background Document

- Background
- Performance data on liquid culture and DST
- Assessment of Capilia TB assay
- Costing data
- Implementation issues – lessons learned
- Patient impact
- Draft recommendations for STAG TB

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Performance Data on MGIT Culture and DST

- Culture positivity rates by smear status
- Contamination
- Time-to-detection by smear status
- DST data
- CDC Thailand data

Culture Positivity and Contamination

Total Smear positive Smear negative	LJ Positive	LJ Negative	LJ Cont.	Total
MGIT Positive	849 630 219	444 100 344	29 17 12	1322 747 575
MGIT Negative	43 24 19	895 13 882	3 0 3	941 37 904
MGIT Cont.	58 44 14	119 14 105	18 9 9	195 67 128
Total	950 698 252	1458 127 1331	50 26 24	2458 851 1607

- Overall MGIT positivity rate:
  - 55%
- Overall LJ positivity rate:
  - 31%
- MGIT recovery rate:
  - 92% (SS+)
  - 94% (SS-)
- LJ recovery rate:
  - 82% (SS+)
  - 41% (SS-)
- MGIT contamination
  - 8%
- LJ contamination
  - 2%

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Time to Detection

	All Specimens	AFB+	AFB-
LJ	28 (22-38) (n=739)	27 (21-36) (n=539)	35 (28-42) (n=200)
MGIT	9 (6-14) (n=1252)	7 (5-10) (n=729)	14 (8-19) (n=523)

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DST Data (Samara)

Drug, MGIT Concentration	Number concordant (n=202)	Percent concordant
Isoniazid (H), 0.1 µg/ml	197	98
Rifampicin (R), 1.0 µg/ml	198	98
Ethambutol (E), 5.0 µg/ml	193	96
Streptomycin (S), 1.0 µg/ml	185	92

- The median time to DST result from positive culture was 9 days (range 6-12) with MGIT and 21 days (range 18-21) with LJ

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Implementation Issues – Lessons Learned

- **Biosafety**
  - Aerosol-producing procedures
  - Biosafety level (BSL) 2+ and 3 facilities and practices
- **Procurement, Shipping, Customs**
  - Delays of up to ~3 months in instrument and consumables ordering, shipment, customs clearance, and delivery
  - Reagents and supplies should be ordered with ample lead-time

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Implementation Issues – Lessons Learned

- **Inventory Management and Shelf-life**
  - Certain reagents have short shelf-lives (~6 months)
  - Closely monitor inventory and expiration dates

- **Electrical Supply and Back-up Power**
  - The MGIT 960 requires constant electricity
  - Back-up electrical power is necessary to maintain constant incubator temperature and prevent data loss

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Implementation Issues – Lessons Learned

- **Training**
  - Both on-site and off-site MGIT culture and DST training
  - Consistent access to external technical assistance are important
- **Technical Support and Maintenance**
  - Expectations and capabilities for services should be clarified with suppliers
  - Maintenance and service contracts are essential

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Implementation Issues – Lessons Learned

- **Contamination**
  - Initial contamination can exceed 20%
  - ≤10% over time with experience, meticulous technique, QA/QC procedures, and step-wise adjustments to SOPs

- **Species identification**
  - Should be performed on all positive liquid cultures
  - Methods should be rapid (e.g., Capilia or molecular assays)

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Conclusions

- Implementation of MGIT culture and DST is feasible in lower income settings
- FIND Demonstration Projects have found increased rate of mycobacterial detection and decreased time to detection
- Increased cost is being addressed

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Recommendations

- Documentation of need
- Financial support
- Infrastructure
- Human resources and training
- Supply logistics
- Customer support
- Specimen collection and transport
- Recording and reporting
- Phased implementation
- Species identification
- QMS and SOPs

Next Steps

- Data collection through mid-2008
- STAG TB 2008:
  - DST performance
  - Cost-effectiveness
  - Patient impact

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