# Use of Microscopic-observation Drug Susceptibility Assay (MODS) among Drug-Resistant Tuberculosis Suspects in Harare, Zimbabwe

by
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# Introduction

- The WHO estimates a global prevalence of 650,000 cases of MDR-TB, contributing to 150,000 annual deaths.(1)
- Despite these staggering figures, only 6% of worldwide cases are detected.(2)
- DST for surveillance and patient management in high burden countries is urgently needed

1 WHO global report 2010

2 Who. Global TB control – epidemiology, strategy, financing. 2009

# Introduction

- MODS assay :
  - liquid culture-based diagnostic test based on characteristic cording of *Mtb.*
  - Accurate and inexpensive test.
  - Endorsed by the WHO for rapid screening of patients suspected of having MDR-TB.
- Despite calls for an expanded role for use of the MODS assay in high HIV-prevalence regions, data among HIV-infected TB and MDR-TB suspects remain limited.
- Recent review of global MDR-TB trends, only 18 of 46 countries from the WHO African Region had nationwide drug resistance data, and only five had reported data since 2002 (3)

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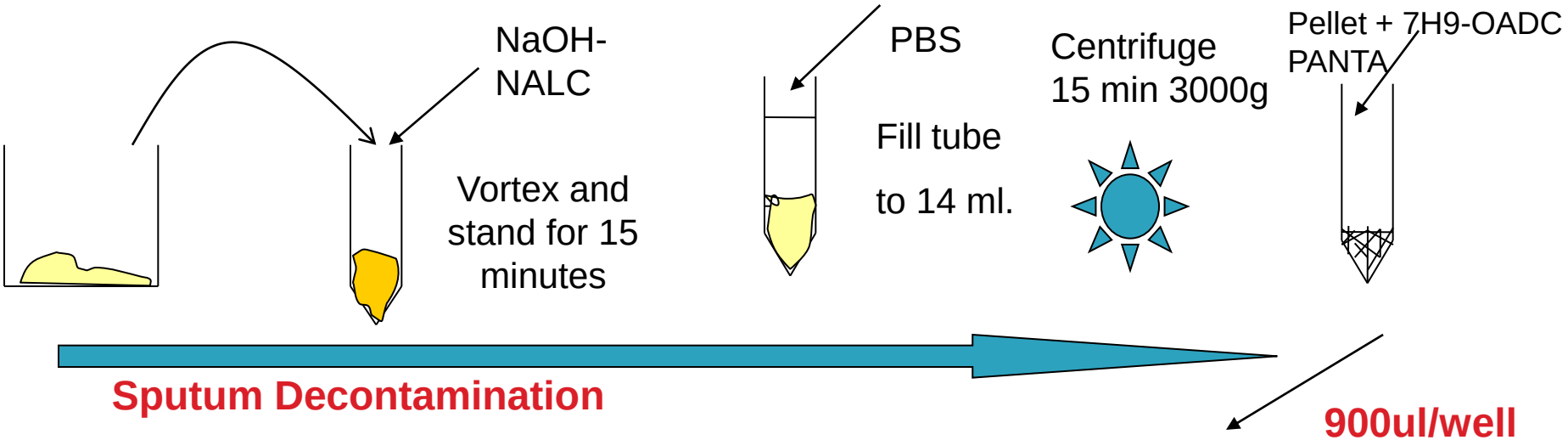
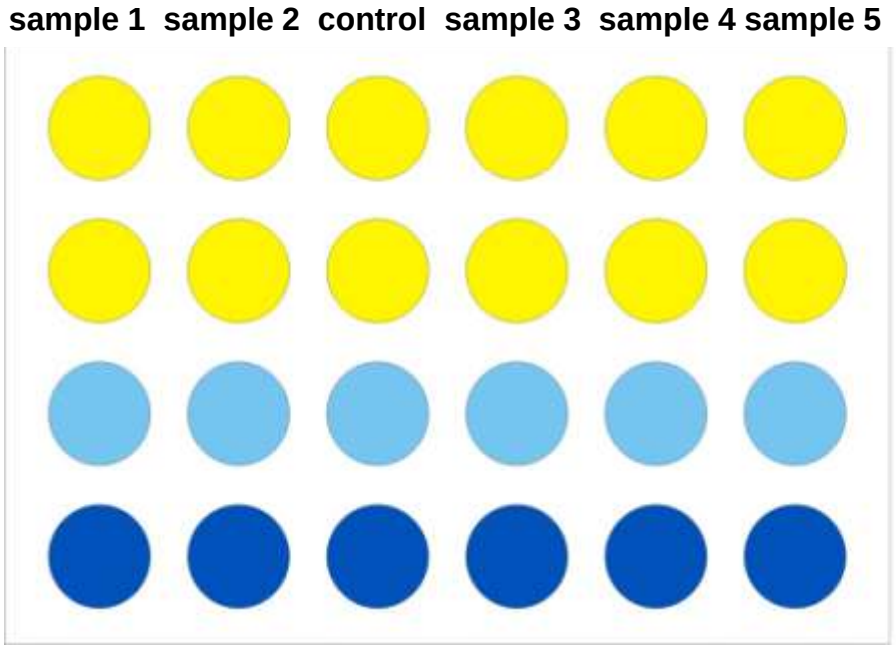
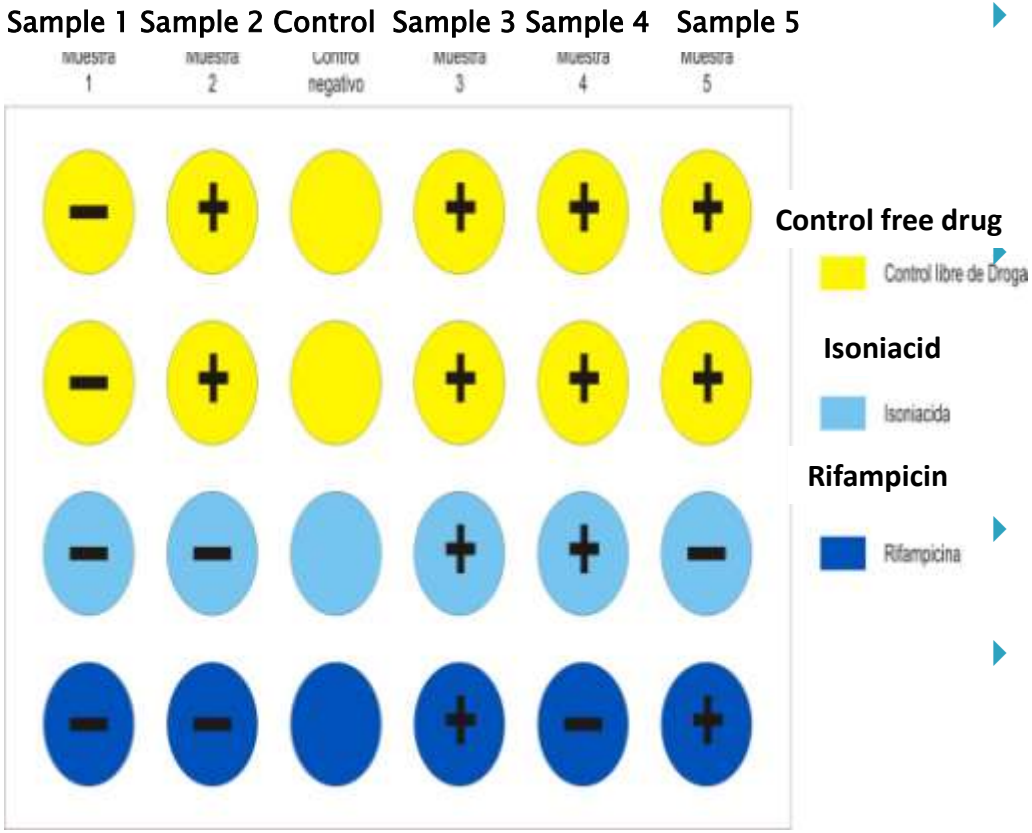
3 Wright A, et al Epidemiology of ant tuberculosis drug resistance 2002–07:


NaOH-
NALC
Vortex and
stand for 15
minutes
PBS
Fill tube
to 14 ml.
Centrifuge
15 min 3000g
Pellet + 7H9-OADC
PANTA
Sputum Decontamination
900ul/well


sample 1
sample 2
control
sample 3
sample 4
sample 5
Control free drug
Isoniacid
Rifampicin

# INTERPRETATION OF RESULTS




- Sample 1 is – ve;

  Negative
- Sample 2 is + ve;

  Sensitive
- Sample 3 is +ve; MDR
- Sample 4 is +ve;

  INH resistant
- Sample 5 is +ve;

  RIF resistant

# Study Question

- With limited data existing on use of the (MODS) assay
  - Can  MODS be used to diagnose MDR TB among Drug-Resistant Tuberculosis suspects in a high HIV prevalence setting?

# Objectives

- To estimate the diagnostic accuracy of the MODS assay for *M. tuberculosis* detection against MGIT and solid LJ among MDR-TB suspects in a high HIV-prevalence region.
- To assess accuracy of MODS DST against a reference standard absolute concentration method.
- To determine sensitivity and specificity of the MODS Assay for detection of resistance to isoniazid, rifampicin and ( MDR-TB)
- To dertemine median turn around time for MDR TB detection .

# Study Methodology

**Study Design**

- An operational research study carried out in the Biomedical Research and Training Institute (BRTI) TB Laboratory at the National Microbiology Reference Laboratory in Harare.

# Study Methodology

- **Study population**
  - (DR TB) suspect patients undergoing routine work-up and from participants of ongoing clinical studies.
    - six previously cultured MDR isolates included for assessment of DST accuracy.
- ***Inclusion Criteria***
  - DR TB suspects defined by :
    - ✓ history of prior treatment (> 1 month, classified according to WHO criteria (1)
    - ✓ contact to an individual with known or suspected drug-resistant TB. In addition
- ***Exclusion Criteria***
  - New TB diagnosis cases
  - Follow up of MDR TB treatment

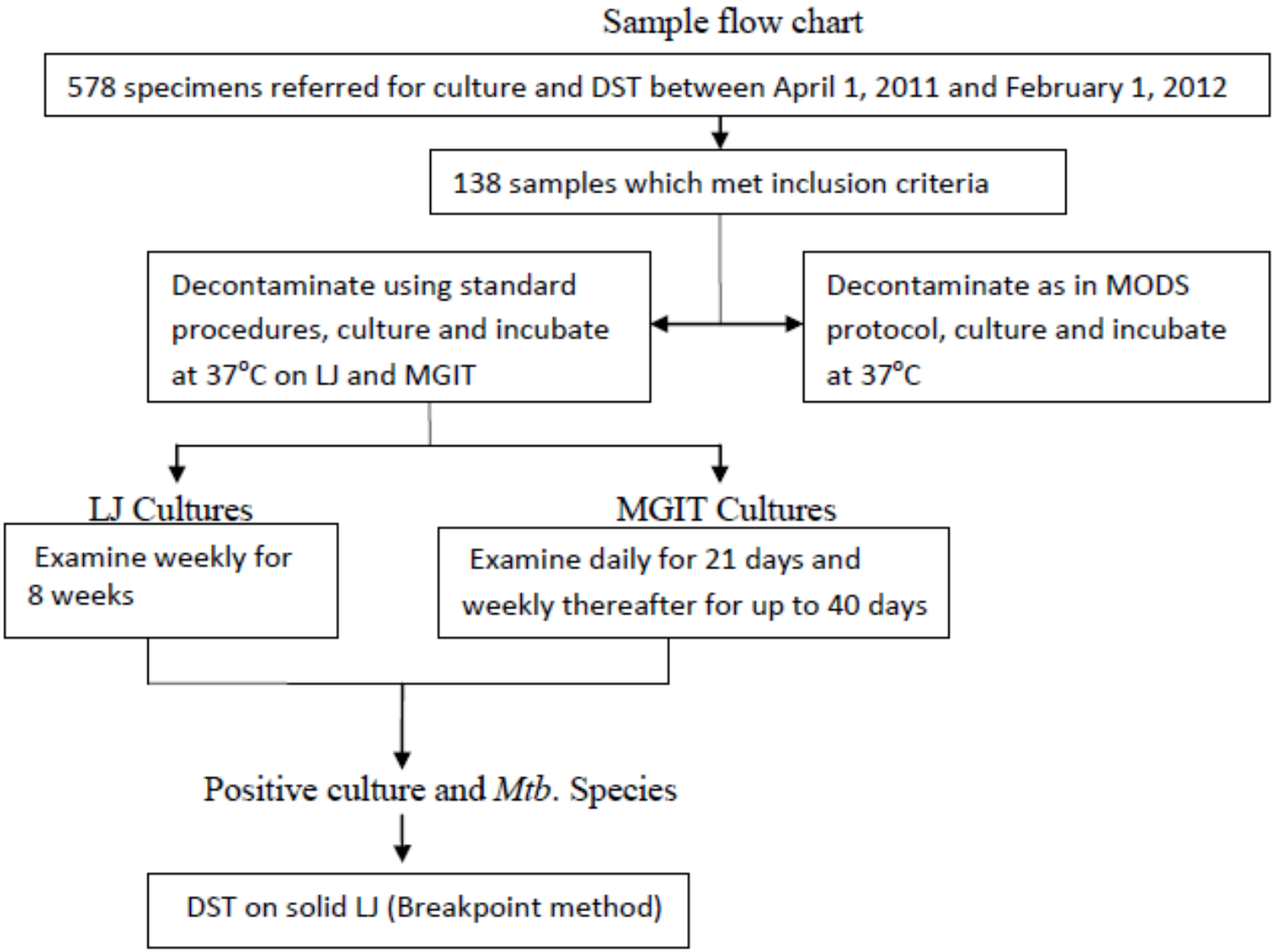
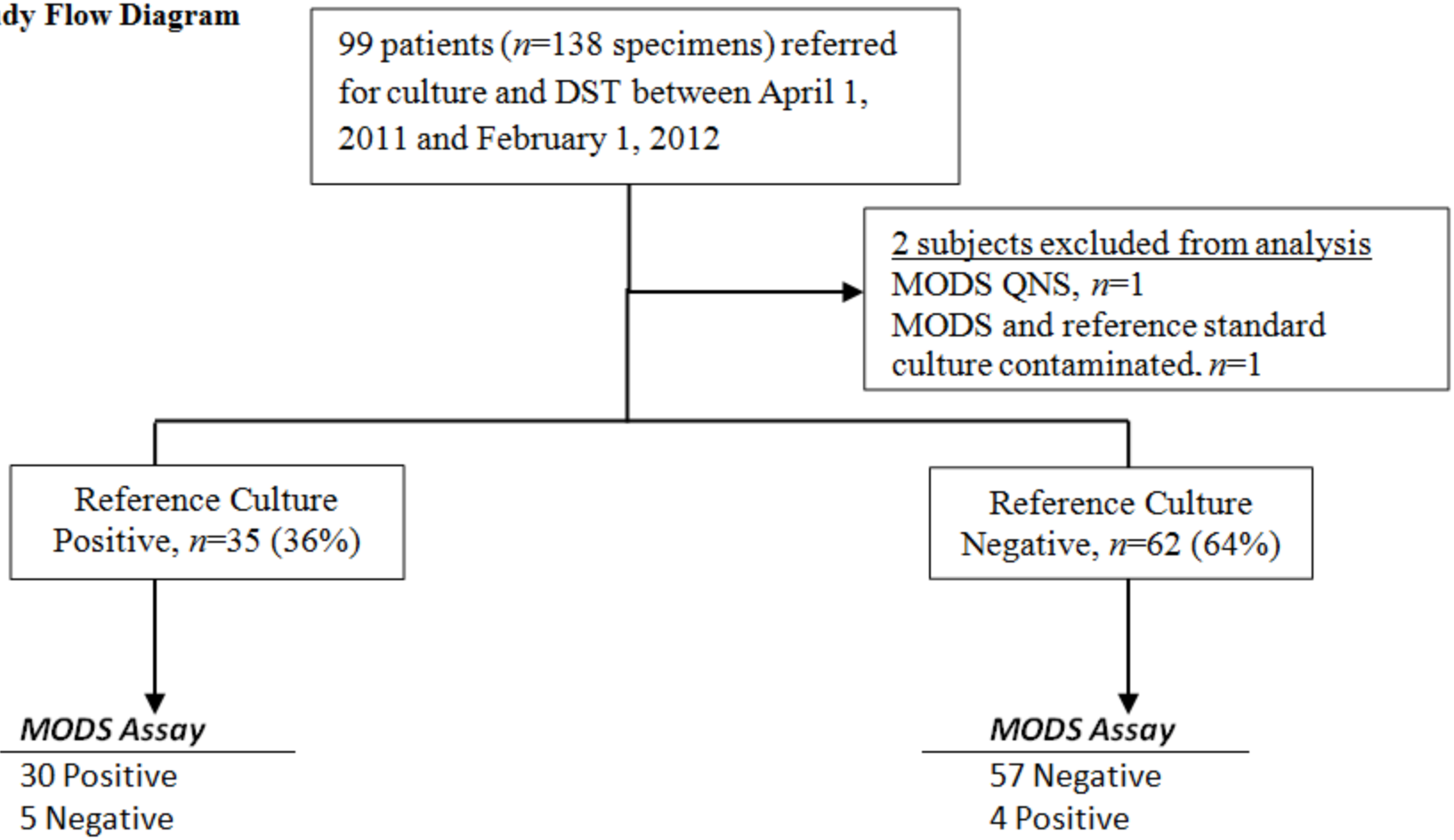

Sample flow chart
578 specimens referred for culture and DST between April 1, 2011 and February 1, 2012
138 samples which met inclusion criteria
Decontaminate using standard procedures, culture and incubate at 37°C on LJ and MGIT
Decontaminate as in MODS protocol, culture and incubate at 37°C
LJ Cultures
MGIT Cultures
Examine weekly for 8 weeks
Examine daily for 21 days and weekly thereafter for up to 40 days
Positive culture and Mtb. Species
DST on solid LJ (Breakpoint method)

**Figure1. Study Flow Diagram**



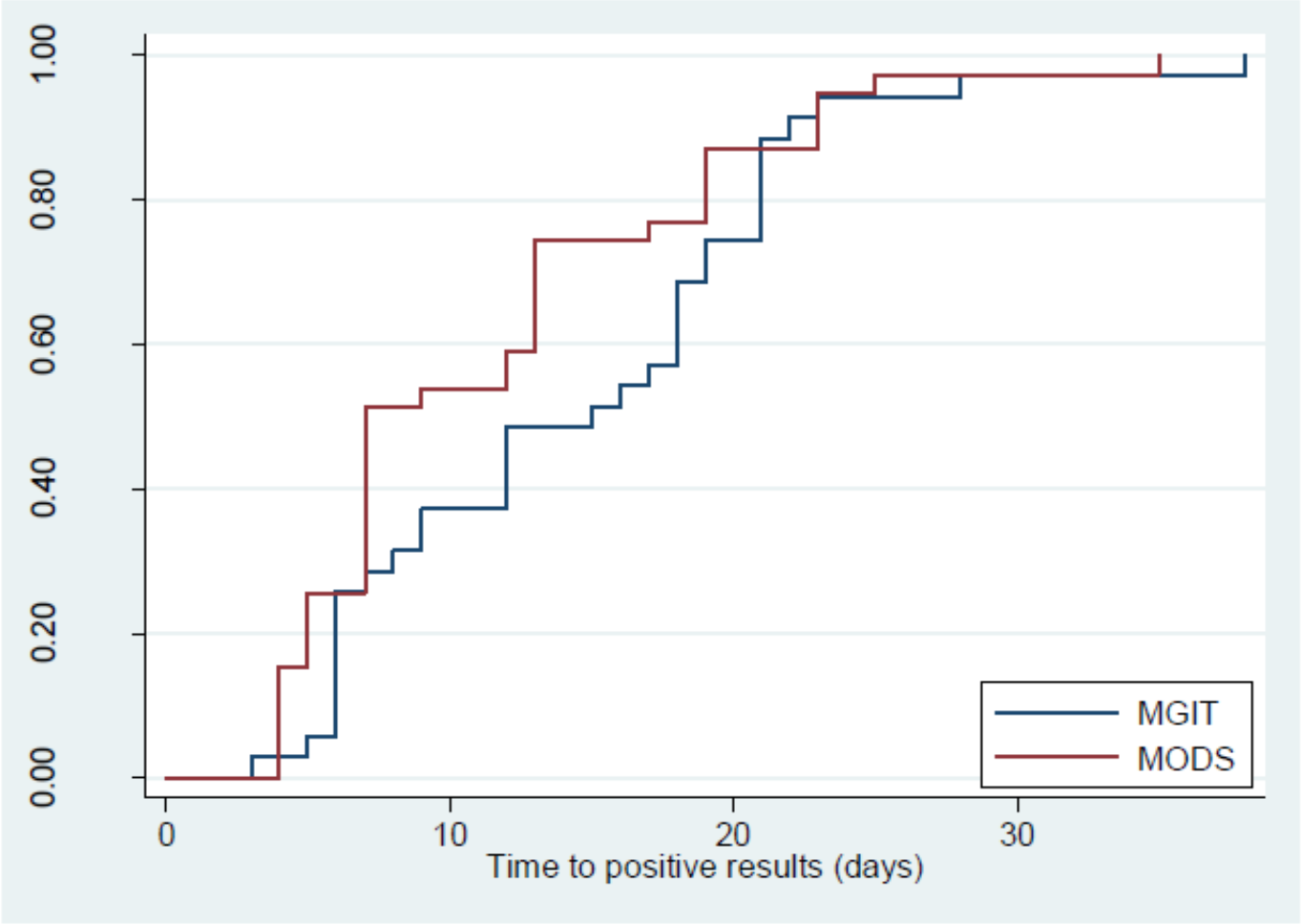

† One sample was reference standard negative and MODS contaminated, and thus excluded from speciticity calculation.

**Table 2.Comparison of the Microscopic-observation Drug-Susceptibility (MODS) Assay with Reference Standard Culture for Detection of *M. tuberculosis***

| MODS Assay | Reference Standard Culture |
|---|---|
| No. of samples positive for *M. tuberculosis* by reference standard method (%) | |
| **All directly inoculated samples (n=97)** | |
| Sensitivity, % (95% CI) | 86 (70-95) |
| Specificity, % (95% CI) | 93 (84-98) |
| Positive predictive value, % (95% CI) | 88 (73-97) |
| Negative predictive value, % (95% CI) | 92 (82-97) |
| **HIV-positive (n=39)*** | |
| Sensitivity, % (95% CI) | 85 (55-98) |
| Specificity, % (95% CI) | 92 (73-99) |
| Positive predictive value, % (95% CI) | 85 (55-98) |
| Negative predictive value, % (95% CI) | 92 (73-99) |
| **HIV-negative (n=20)*** | |
| Sensitivity, % (95% CI) | 86 (42-100) |
| Specificity, % (95% CI) | 100 (74-100) |
| Positive predictive value, % (95% CI) | 100 (54-100) |
| Negative predictive value, % (95% CI) | 93 (64-100) |

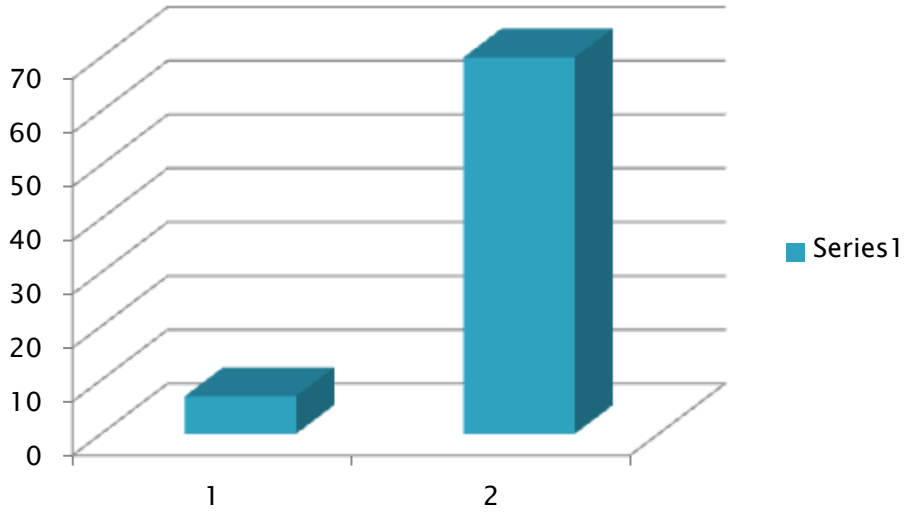
*Among persons with known HIV status (*n*=59/97 (61%)).

**Figure 2. Kaplan-Meier Plot of Time to *M. tuberculosis* Detection**




The median time to culture positivity was significantly shorter for MODS than manual MGIT (MODS 7 days [IQR 7–15 days] vs. MGIT12 days [IQR 6–16 days].

# Results (cont)




- Median TAT for MDR TB diagnosis for MODS was(7 d{IQR6-16 days}) was significantly shorter than for the absolute conc. method (70 d {IQR 49-96})

Table 3.Drug-Susceptibility Test Results from the MODS Assay

| | Isoniazid | Rifampin | Isoniazid + Rifampin (multidrug resistance) |
|---|---|---|---|
| No. of samples* | 31 | 31 | 31 |
| No. resistant (prevalence)† | 15/25 (60%) | 17/25 (68%) | 15/25 (60%) |
| Sensitivity, % (95% CI) | 96 (59-96) | 96 (79-100) | 96 (59-96) |
| Specificity, % (95% CI) | 89 (52-100) | 88 (47-100) | 89 (52-100) |
| Positive predictive value, % (95% CI) | 96 (77-100) | 96 (79-100) | 96 (77-100) |
| Negative predictive value, % (95% CI) | 89 (52-100) | 88 (47-100) | 89 (52-100) |

*Analysis limited to samples with positive microscopic-observation drug-susceptibility and reference standard culture.

†Among directly inoculated patient specimens.

sensitivity and specificity of the MODS assay for detection of resistance to isoniazid, rifampin, and MDR-TB on concurrent DST results,

# Conclusion

- In a high HIV-prevalence setting, MODS detected *M. tuberculosis* and *M. tuberculosis* drug resistance with high sensitivity and more rapid time to positivity compared with standard culture and DST methods.
- No detectable differences in diagnostic accuracy were noted for HIV-infected individuals
- Although debate continues with regards to the best scale-up option for DST in resource limited settings, (4)the short turnaround time, high accuracy, low cost, relative ease of operational implementation, and ability to discern both isoniazid and rifampicin resistance should make MODS a strong consideration.

4 Moore DA, Shah NS. Alternative methods of diagnosing drug resistance--what can they do for me? The ournal of infectious diseases. 2011 Nov 15;204 Suppl 4:S1110-9.

# Conclusion (cont)

- Studies focused on patient-important outcomes, along with population-based sampling methods to generate valid estimates of the prevalence and incidence of MDR-TB in modern-era Zimbabwe, are urgently needed.
- Prompt treatment of patients with MDR-TB and screening of their contacts will be essential to prevent further spread of drug-resistant *M. tuberculosis*;

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Thank you.