

Clinical Evaluation of the Microscopic-Observation Drug-Susceptibility Assay for Detection of Tuberculosis

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Background. There is an urgent need for low-cost methods for rapid, accurate detection of *Mycobacterium tuberculosis* in clinical specimens. The microscopic-observation drug-susceptibility (MODS) assay is a relatively low-cost and simple liquid culture method that has been proposed for use in resource-limited environments.

Methods. This prospective study evaluated the performance of the MODS assay for detection of *M. tuberculosis* in persons undergoing evaluation for pulmonary tuberculosis in Brazil and Honduras. Respiratory specimens were evaluated using smear microscopy, culture on Löwenstein-Jensen medium, and culture using the MODS assay. A subset of specimens was also cultured using the Mycobacterial Growth Indicator Tube (MGIT) 960 automated system (Becton Dickinson). A study subject was considered to have tuberculosis if at least 1 culture on Löwenstein-Jensen medium was positive for *M. tuberculosis*.

Findings. A total of 1639 respiratory specimens obtained from 854 study subjects were analyzed. On a per-subject basis, MODS sensitivity was 97.5% (95% confidence interval [CI], 95.7–98.6), and specificity was 94.4% (95% CI, 93.1–95.2). Median times to detection were 21 days (interquartile range [IQR], 17–25 days) and 7 days (IQR, 5–10) for culture on Löwenstein-Jensen medium and for the MODS assay, respectively ($P < .01$). For 64 specimens cultured using the MGIT 960 automated system, median time to growth was similar for the MODS assay (7 days; IQR, 7–10 days) and the MGIT 960 automated system (8 days; IQR, 6–11.5 days; $P = .16$). The percentage of contaminated cultures was lower for the MODS assay than for culture on Löwenstein-Jensen medium (3.8% vs. 5.8%; $P < .01$).

Conclusions. The MODS assay is a relatively simple test whose good performance characteristics for detection of pulmonary tuberculosis may make it suitable for resource-limited environments.

There is an urgent need for low-cost methods for the diagnosis of tuberculosis (TB). Sputum smear microscopy detects only approximately one-half of all cases of culture-positive pulmonary TB [1]. Moreover, sputum smear microscopy has poor sensitivity in patients with TB who have HIV infection or AIDS, a group with high mortality from smear-negative TB [2–6]. Myco-

bacterial culture is more sensitive than smear microscopy, but methods involving solid media (e.g., Löwenstein-Jensen [LJ] medium) have the disadvantage of being slow, whereas the more rapid liquid culture methods generally have been considered to be too expensive for routine use in resource-limited environments [7]. The development of new tools for improved diagnosis of TB, including smear-negative TB, has been deemed to be a top priority by the World Health Organization [8, 9].

The microscopic-observation drug-susceptibility (MODS) assay is a relatively low-cost and simple liquid culture method [10–12]. The MODS assay uses enriched Middlebrook 7H-9 liquid medium and relies on microscopic detection of cording growth that is characteristic of *Mycobacterium tuberculosis*. Potential ad-

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vantages of the MODS assay are relatively rapid mycobacterial growth and reliance on microscopy skills similar to those used for smear microscopy. Caviedes et al. [10] originally showed that the MODS assay had 92% sensitivity for the detection of *M. tuberculosis* among 172 specimens. In a retrospective analysis of 1908 culture samples with positive results by either the MODS method or culture on LJ medium, the reported sensitivity of the MODS assay was 94% and that of culture on LJ medium was 87% [12].

We undertook a prospective study to further evaluate the MODS assay for detection of *M. tuberculosis* in persons undergoing evaluation for pulmonary TB. Our primary objective was to determine the diagnostic performance (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) of the MODS assay for detection of TB in patients with suspected pulmonary TB. Additional objectives of the study were to determine the diagnostic performance of the MODS assay for detection of *M. tuberculosis* in respiratory specimens and the time to *M. tuberculosis* growth.

METHODS

Study design, setting, and subjects. This prospective study was carried out at the National Thorax Institute (Tegucigalpa, Honduras) and the Federal University of Rio de Janeiro (Rio de Janeiro, Brazil). Subjects were recruited from outpatient clinics and inpatient wards. Study inclusion criteria were age ≥ 12 years, cough for ≥ 3 weeks, informed consent, and categorization by the treating clinician into 1 of the following categories: (1) new suspected pulmonary TB, (2) suspected treatment failure, (3) suspected relapse, or (4) treatment default [13]. Routinely collected clinical data were recorded on a study form. Respiratory specimens submitted for routine analysis were studied. Specimens were categorized as expectorated sputum samples, induced sputum samples, or secretions obtained by bronchial wash or bronchoalveolar lavage. A minimum of 1 and a maximum of 3 specimens per subject were included in the study.

All specimens were evaluated by Ziehl-Neelsen smear microscopy, culture on LJ medium, and the MODS assay. A subset of specimens at 1 site were also cultured using the Mycobacterial Growth Indicator Tube (MGIT) 960 automated system (Becton Dickinson) to compare the time to *M. tuberculosis* growth for the MODS and MGIT assays. Selection of specimens for MGIT evaluation was based solely on MGIT reagent availability; when reagents were available, consecutive specimens were tested using the MGIT 960 automated system.

A subject was considered to have TB if at least 1 culture on LJ medium was positive for *M. tuberculosis*. Subjects having ≥ 1 culture positive for *M. tuberculosis* by the MODS assay but no culture positive for *M. tuberculosis* on LJ medium underwent follow-up at 90 days after the initial specimen submission as

a means of discrepant analysis. The 90-day follow-up evaluation consisted of a review of interval treatment, symptoms, and diagnoses; a chest radiograph; and an additional sputum culture on LJ medium. A subject undergoing follow-up was considered to have TB if there was (1) a follow-up culture positive for *M. tuberculosis* on LJ medium; (2) a response to TB therapy (defined as a visible improvement on chest radiograph, diminished cough, and weight gain of $\geq 3\%$ of pretreatment weight in the absence of a plausible alternative diagnosis); or (3) death from TB. A panel of 3 TB experts who were not involved in the study reviewed the follow-up results and classified each individual as having TB or not having TB.

Informed consent was obtained from all subjects. This study was approved by Institutional Review Boards at Johns Hopkins University School of Medicine (Baltimore, MD), the University of Alabama at Birmingham (Birmingham), the Federal University of Rio de Janeiro, and the National Thorax Institute.

Decontamination of respiratory specimens. Specimens were digested and decontaminated using the *N*-acetyl-L-cysteine-sodium hydroxide method; the final sodium hydroxide concentration was 2% [14]. Pellets were resuspended in a final volume of 2 mL and used immediately for inoculation of culture media.

Smear microscopy. Ziehl-Neelsen staining was performed on concentrated specimens. Light microscopy was used to visualize acid-fast bacilli (AFB) [14].

MODS culture. MODS medium was prepared using Middlebrook 7H9 broth base (Becton Dickinson; 5.9 g per L), 0.31% glycerol, casein hydrolysate (Sigma; 1.25 g per L), 10% oleic albumin-dextrose-catalase (Becton Dickinson), and Panta (Becton Dickinson), as previously described [10]. Final antimicrobial concentrations were as follows: polymyxin B, 41 U/mL; amphotericin B, 4.1 $\mu\text{g/mL}$; nalidixic acid, 16.4 $\mu\text{g/mL}$; trimethoprim 4.1 $\mu\text{g/mL}$; and azlocillin, 4.1 $\mu\text{g/mL}$ (as for the MGIT 960 automated system). For each specimen, 1 mL of MODS medium was placed into 1 well of a sterile 24-well tissue culture plate (Costar), and then 200 μL of the decontaminated specimen was placed into the well. Specimens obtained from different subjects but processed on the same day were plated into different wells of the same plate, and the plate was placed within a gas-permeable plastic bag. Each plate had 1 negative control well that contained MODS medium. Plates were incubated at 37°C in 10% CO₂, and examined twice weekly for 8 weeks using $\times 40$ inverted microscopy. Wells were evaluated for growth and bacterial pellicle morphology. Growth was considered to be positive if pellicles were observed, negative if no pellicles were observed, or contaminated if fungal forms were present or if there was noncorded growth within 3 days after inoculation. Morphology was classified as positive if pellicles had a corded appearance or negative if pellicles did not have a corded appearance. A culture was considered to be positive

for *M. tuberculosis* if both growth and morphology were positive. The technologist performing the MODS assays was not aware of LJ or MGIT culture results.

Culture on LJ medium. Slants were prepared from a powder base (Becton Dickinson), and 200 μ L of each decontaminated specimen was inoculated onto each of 2 slants. Slants were incubated at 37°C in ambient CO₂ and were examined visually twice weekly for 8 weeks. A culture was considered to be contaminated if growth was smear negative for AFB. For cultures positive for AFB, biochemical tests (nitrate reduction, niacin accumulation, and 68°C catalase production) were performed for species designation [14]. For an individual subject, species designation was performed on the first positive culture on LJ medium; if the culture was positive for *M. tuberculosis*, then subsequent positive cultures were considered to be positive for *M. tuberculosis* if the morphological characteristics and time to growth were typical for *M. tuberculosis*.

Culture using the MGIT 960 automated system. Culture was performed according to the manufacturer's instructions for the MGIT 960 automated system (Becton Dickinson). Inoculation volume was 0.5 mL per tube.

Quality assurance testing. Each new batch of medium for each of the assay types (MODS, LJ, and MGIT) was tested for sterility and for growth of *M. tuberculosis* using an aliquot of an archived reference strain. Each new batch of medium for the MODS assay was tested for the ability to support corded growth using *M. tuberculosis* as a positive control and *Mycobacterium avium* as a negative control.

Analyses. Approximately 215 cases of TB were calculated to be necessary to be 99% confident that the true sensitivity of the MODS assay was within 3% of the estimated 97% sensitivity. Assuming that ~25% of patients with suspected TB would have results positive for *M. tuberculosis* by culture on LJ medium, the sample size was 860 patients with suspected pulmonary TB. The primary analysis of MODS sensitivity, specificity, PPV, and NPV was performed on a per-subject basis. A secondary analysis was performed on a per-specimen basis to determine concordance of MODS results with those of the companion culture on LJ medium. A MODS culture with corded growth was considered to be falsely positive if the companion LJ culture grew a mycobacterium identified as "not *M. tuberculosis*." Comparison of median times to growth was by paired Student's *t* test. The McNemar test was used for comparing paired proportions, and the χ^2 test was used for comparing nonpaired proportions. A *P* value of <.05 was considered to be statistically significant.

RESULTS

Study subjects and specimens. A total of 1658 specimens were collected from 863 subjects. Figure 1 shows a flow diagram of study subjects. Nine subjects had no cultures performed on LJ

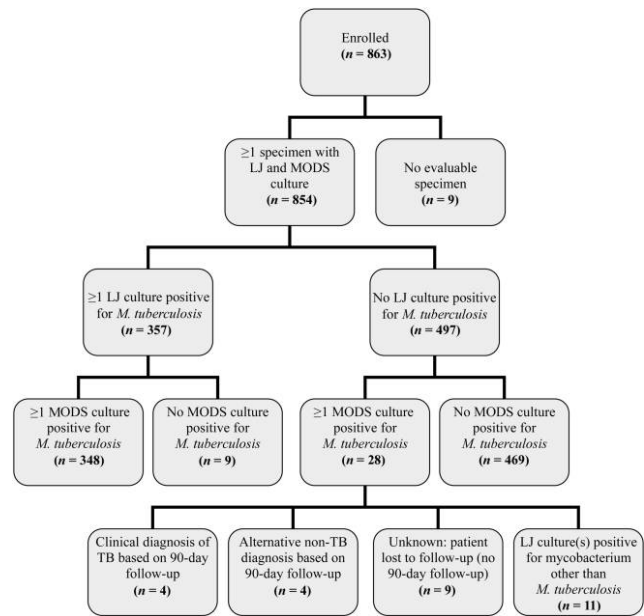


Figure 1. Flow diagram for study subjects. LJ, Löwenstein-Jensen medium; *M. tuberculosis*, *Mycobacterium tuberculosis*; MODS, microscopic-observation drug-susceptibility assay; TB, tuberculosis.

medium; these 9 subjects and their specimens were excluded from the analysis. Data was analyzed for 854 subjects and 1639 specimens tested by both the MODS assay and culture on LJ medium.

Demographic and clinical characteristics of the 854 subjects are shown in table 1. Mean age (\pm SD) was 44 (\pm 16) years (range, 12–91 years). Among HIV-infected individuals, median and mean CD4⁺ T lymphocyte counts were 42 and 115 cells/mm³, respectively (range, 5–740 cells/mm³). Among 1639 specimens that were collected and evaluated, 1353 (82.5%) were expectorated sputum samples, 237 (14.5%) were induced sputum samples, and 49 (3.0%) were bronchoalveolar lavage or bronchial wash samples. Mean and median numbers of specimens per subject were 1.9 and 2, respectively.

Per-subject diagnostic performance of the MODS assay. Among 854 subjects, 357 (41.8%) received a final diagnosis of TB (figure 1 and table 2). As shown in table 3, the sensitivity, specificity, PPV, and NPV of the MODS assay were 97.5% (95% CI, 95.7%–98.6%), 94.4% (95% CI, 93.1%–95.2%), 92.6% (95% CI, 90.9%–93.6%), and 98.1% (95% CI, 96.8%–98.9%), respectively.

Twenty-eight subjects were eligible for 90-day follow-up evaluation, because each had \geq 1 MODS result positive for *M. tuberculosis*, but no initial culture on LJ medium positive for *M. tuberculosis*. Among these 28 subjects, 4 received a diagnosis of TB on the basis of 90-day follow-up evaluation results (all 4 subjects had a response to TB therapy), 4 received an alternative, non-TB diagnosis, and 11 received a diagnosis of non-

Table 1. Characteristics of study subjects.

Variable	No. of subjects	No. (%) of subjects, by final diagnosis received	
		TB	No TB
Study site			
Honduras	295	114 (38.6)	181 (61.4)
Brazil	559	243 (43.5)	316 (56.5)
Sex			
Male	491	226 (46.0)	265 (54.0)
Female	363	131 (36.1)	232 (63.9)
HIV infection status			
Positive	102	32 (31.4)	70 (68.6)
Negative	297	171 (57.6)	126 (42.4)
Unknown	455	154 (33.8)	301 (66.2)
Type of TB case suspected			
New suspected case	528	205 (38.8)	323 (61.2)
Suspected TB treatment failure	109	78 (71.6)	31 (28.4)
Suspected TB after treatment default	43	23 (53.5)	20 (46.5)
Suspected TB relapse	174	51 (29.3)	123 (70.7)
Total number of specimens from subject			
1	363	124 (34.2)	239 (65.8)
2	197	73 (37.1)	124 (62.9)
3	294	160 (54.4)	134 (45.6)

NOTE. TB, tuberculosis.

tuberculous mycobacteria (NTM) infection on the basis of the results of biochemical tests performed on isolates with a positive culture on LJ medium. A definitive diagnosis could not be established for 9 (32%) of 28 subjects, because they were lost to follow-up; for analysis purposes, they were considered not to have TB.

Among 357 patients with TB, 274 had at least 1 smear result positive for AFB, and the remaining 83 were smear negative (smear sensitivity, 76.8%; 95% CI, 74.1%–78.9%). The MODS assay detected 75 of these 83 smear-negative TB cases (90.4%). On a per-subject basis, smear specificity, PPV, and NPV were 94.0% (95% CI, 92.0%–95.5%), 90.1% (95% CI, 87.0%–92.7%), and 84.9% (95% CI, 83.2%–86.3%), respectively.

Per-specimen concordance of AFB smear, the MODS assay, and culture on LJ medium. Among 1639 specimens, 589 (35.9%) had smear results positive for AFB, 728 (44.4%) were positive for *M. tuberculosis* by the MODS assay, and 681 (41.5%) were positive for *M. tuberculosis* by culture on LJ medium (table 2). Per-specimen concordance for smear and culture on LJ medium was 87.0% (95% CI, 85.4%–88.3%); for the MODS assay and culture on LJ medium, the per-specimen concordance was 94.2% (95% CI, 93.1%–95.1%) (table 3). Among 71 specimens that were negative for *M. tuberculosis* by culture on LJ medium but positive for *M. tuberculosis* by the MODS assay, the LJ medium was contaminated in 29 (40.8%), grew a NTM in 20 (28.2%), and showed no growth in 22

(31.0%). Among 24 specimens that were positive for *M. tuberculosis* by culture on LJ medium but negative for *M. tuberculosis* by the MODS assay, the MODS culture medium was contaminated in 10 (41.7%) and showed no growth in 14 (58.3%).

Species identification. A total of 681 specimens had mycobacterial growth by both culture on LJ medium and the MODS assay. Among these 681 specimens, growth on LJ medium was identified as *M. tuberculosis* for 657 and was not *M. tuberculosis* for 24. For all 657 specimens in which *M. tuberculosis* was identified by culture on LJ medium, the corresponding MODS culture had *M. tuberculosis* identified on the basis of visual detection of corded growth (concordance, 100%; 95% CI, 99.7%–100.0%). However, among the 24 specimens in

Table 2. Comparison of the microscopic-observation drug-susceptibility (MODS) assay with culture on Löwenstein-Jensen (LJ) medium for detection of tuberculosis.

MODS assay diagnosis	Culture on LJ medium			
	Per study subject		Per specimen	
	TB	Not TB	TB	Not TB
TB	348	28	657	71
Not TB	9	469	24	887

NOTE. TB, tuberculosis.

Table 3. Performance characteristics of the microscopic-observation drug-susceptibility assay for detection of tuberculosis.

Variable	Per study subject	Per specimen
Sensitivity	97.5 (95.7–98.6)	96.5 (95.1–97.5)
Specificity	94.4 (93.1–95.2)	92.6 (91.6–93.3)
Positive predictive value	92.6 (90.9–93.6)	90.2 (89.0–91.2)
Negative predictive value	98.1 (96.8–98.9)	97.4 (96.4–98.1)
Concordance	NA	94.2 (93.1–95.1)

NOTE. Data are % (95% CI). NA, not applicable.

which the mycobacterium grown on LJ medium was identified as not being *M. tuberculosis*, the corresponding MODS culture grew a mycobacterium that was designated as not *M. tuberculosis* for only 4 specimens and as *M. tuberculosis* for 20 specimens (concordance, 16.7%; 95% CI, 8.7%–16.7%). According to per-subject analysis, 17 individuals (2.0%) had ≥ 1 cultures on LJ medium positive for a NTM and no cultures on LJ medium positive for *M. tuberculosis*. For 11 (65%) of those 17 individuals, growth on medium for the MODS assay was incorrectly identified as *M. tuberculosis*.

Culture contamination. The proportion of contaminated cultures was lower for MODS cultures (62 [3.8%] of 1639 samples) than for cultures grown on LJ medium (95 [5.8%] of 1639 samples; $P \leq .01$). The percentage of contaminated MODS cultures was not significantly different between study sites (4.4% for Honduras vs. 3.4% for Brazil; $P = .30$). The proportion of contaminated cultures on LJ medium was 53 (8.0%) of 662 cultures for Honduras and 42 (4.3%) of 977 for Brazil ($P = .002$). During MODS testing, none of the negative control wells showed mycobacterial growth.

Time to growth. Figure 2 shows median times to growth for 657 specimens that were positive for *M. tuberculosis* by both culture grown on LJ medium and the MODS assay. Median times to growth were 21 days (interquartile range [IQR], 17–25 days) and 7 days (IQR, 5–10 days) for cultures grown on LJ medium and for the MODS assay, respectively ($P < .01$). Median times for growth using the MODS assay were the same (7 days) for the 2 study sites. Among these 657 culture-positive samples, cultures grown on LJ medium detected 16.6% of positive samples within 2 weeks, whereas the MODS assay detected 90.4% of positive samples within 2 weeks ($P < .01$). The MGIT 960 automated system was used to test a subset of specimens at 1 site. For 64 specimens that were culture positive for *M. tuberculosis* by culture on LJ medium, the MODS assay, and MGIT testing, the median time to growth was similar for the MODS and MGIT assays (7 days [IQR, 7–10 days] vs. 8 days [IQR, 6–11.5 days; $P = .16$]; the median time to growth on LJ medium was 24.5 days (IQR, 20–27.5 days).

Figure 3 shows time to growth (by the AFB smear status of the source specimen) for 657 specimens positive for *M. tuber-*

culosis by both culture on LJ medium and the MODS assay. For smear-negative specimens, median times to growth were 26 days for culture on LJ medium and 10 days for the MODS assay; culture on LJ medium detected 2.2% of these positive cultures within 2 weeks, whereas the MODS assay detected 73.1% of these positive cultures within 2 weeks ($P < .01$).

DISCUSSION

This multicenter trial, involving patients in countries with a high burden of TB, demonstrates that the sensitivity of the MODS assay was similar to that of culture on LJ medium for detection of *M. tuberculosis* in respiratory specimens, but the median time to growth and the percentage of contaminated cultures were significantly lower for the MODS assay than for culture on LJ medium. The MODS assay accurately identified

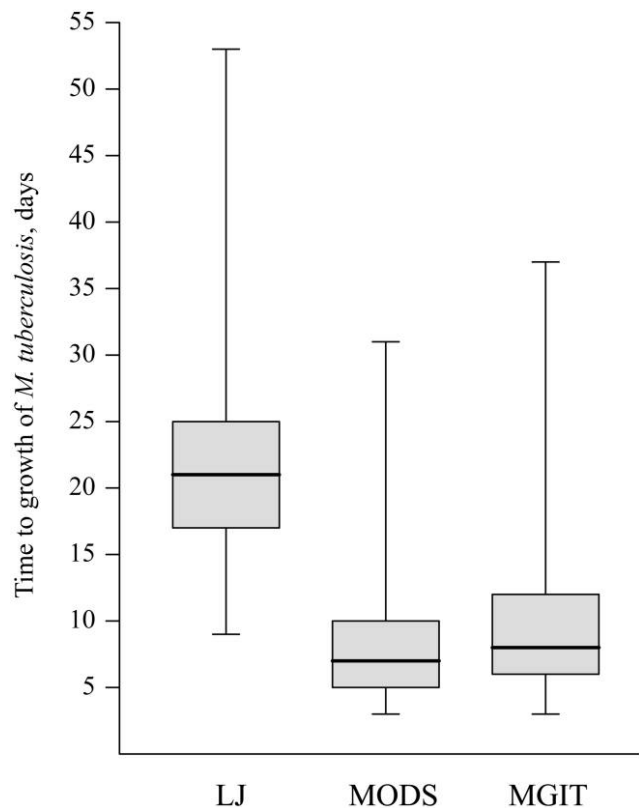


Figure 2. Box plot of median time to growth of *Mycobacterium tuberculosis* for each culture method. Box lengths indicate interquartile range, horizontal lines in each box represent the median of the distribution, and whiskers extend from the minimum value to the maximum value. For LJ and MODS, results for 657 specimens positive for *M. tuberculosis* by both LJ and MODS are shown ($P < .0001$). For MGIT, results for 64 specimens positive for *M. tuberculosis* by LJ, MODS, and MGIT are shown ($P = .16$ for comparison of MODS and MGIT). LJ, culture on Löwenstein-Jensen medium; MGIT, Mycobacterial Growth Indicator Tube 960 automatic system; MODS, microscopic-observation drug-susceptibility assay.

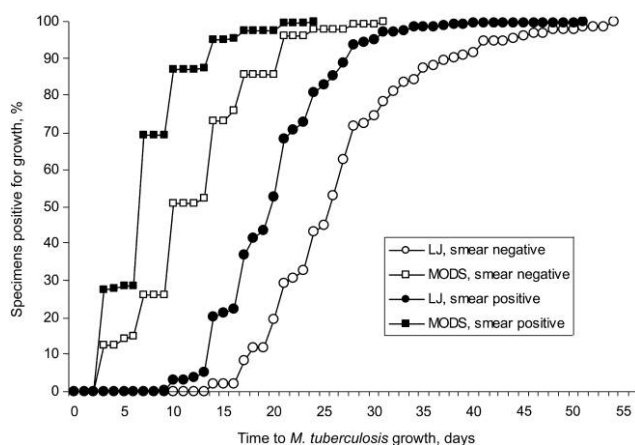


Figure 3. Time to growth of *Mycobacterium tuberculosis* for LJ and MODS, by acid-fast bacilli (AFB) smear microscopy status of the source respiratory specimen. Results are shown for 135 AFB smear-negative respiratory specimens and 522 AFB smear-positive respiratory specimens that were positive for *M. tuberculosis* by both LJ and MODS. LJ, culture on Löwenstein-Jensen medium; MODS, microscopic-observation drug-susceptibility assay.

patients with TB in approximately one-third of the time required for detection using culture on LJ medium.

In addition to having advantages over culture on LJ medium, the MODS assay has advantages over smear microscopy, which is the TB diagnostic test that is most widely used in developing countries. The MODS assay was more sensitive than smear microscopy in our study. Because smear-negative pulmonary TB can be transmissible and is associated with high mortality in HIV-infected persons, enhanced sensitivity would likely be beneficial from both public and individual health standpoints [15]. In addition, unlike smear microscopy, the MODS assay can be used for direct drug susceptibility testing [10–12].

The results from this study extend those of a smaller prospective study by Caviedes et al. [10] that evaluated 172 sputum specimens by the MODS assay, culture on LJ medium, testing with the MGIT 960 automated system, and a microagar 7H11 method; using as a reference standard the detection of *M. tuberculosis* by any culture method, the sensitivity of the MODS assay was 92%, with a median detection time of 9 days. In a more recent retrospective study, Moore et al. [12] analyzed their database of results for 5771 specimens. Using culture positivity by either method as a reference standard, sensitivities of the MODS assay and culture on LJ medium were 94% and 87%, respectively, with a median detection time of 8 days for the MODS assay.

One limitation of our study was that the 90-day follow-up evaluation could not be completed for 9 subjects. This diminished our ability to delineate whether the MODS assay result was a false positive or the LJ culture result was a false negative

in these individuals. These individuals were coded as not having TB cases, although clinical suspicion for TB was high. It is, therefore, possible that the true specificity and sensitivity of the MODS assay for diagnosis of TB are slightly higher than that demonstrated in our study. However, the maximum sensitivity of the MODS assay appears not to be substantially higher than that of culture on LJ medium. On the other hand, we cannot fully exclude the possibility of cross-contamination between the MODS wells. Because none of the negative control wells had positive results, it is unlikely that cross-contamination contributed to a substantial proportion of positive MODS assay cultures. Molecular fingerprinting of each *M. tuberculosis* isolate might have shed light on this issue but was not feasible in the context of this study.

An apparent shortcoming of the MODS assay is its relatively poor ability to discriminate *M. tuberculosis* from NTM. The clinical impact of this will depend on NTM prevalence among evaluated individuals. In our study, the ratio of subjects with NTM to subjects with TB was low, a scenario favorable to the MODS assay. Higher proportions of individuals with pulmonary NTM, relative to TB, would likely decrease the specificity and PPV of the MODS assay. Along these lines, the high PPV of the MODS assay for TB was among patients with a high pretest probability of TB (42% of our study subjects had TB). The PPV of the MODS assay might be lower if a lower proportion of evaluated subjects have TB.

In our study, the performance characteristics of the MODS assay were generally similar at the 2 study sites, indicating the feasibility of technology transfer to laboratories with the existing capacity to perform culture on LJ medium. However, the MODS assay is more challenging than smear microscopy, and implementation of MODS testing in a laboratory performing only smear microscopy would require augmentation of laboratory capacity. Potential challenges related to the MODS assay include CO₂ supplementation, the need for reagents and supplies that may not be readily accessible, the need for meticulous technique during inoculation and plate handling to prevent contamination, dependence on a motivated microscopist, and potential biohazards related to *M. tuberculosis* growing in liquid culture in plates requiring transport from incubator to microscope. However, some of the challenges may be overcome without complex or expensive measures. Modification of the current plate platform into a more secure platform (e.g., the use of a tight-fitting lid to reduce the possibility of spills) would be advantageous and is likely to be feasible. Furthermore, microscopy skills required for the MODS assay are generally similar to those required for smear microscopy, thereby potentially building on existing capacity in laboratories where smear microscopy is already performed.

The MODS assay holds promise as a relatively simple, rapid

method for diagnosis of pulmonary TB. Its low cost, relative to other liquid culture methods, may make it feasible for use in resource-limited countries [10].

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Potential conflicts of interest. All authors: no conflicts.

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