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Multicenter Evaluation of Fully Automated BACTEC Mycobacteria Growth Indicator Tube 960 System for Susceptibility Testing of *Mycobacterium tuberculosis*

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The reliability of the BACTEC Mycobacteria Growth Indicator Tube (MGIT) 960 system for testing of *Mycobacterium tuberculosis* susceptibility to the three front-line drugs (isoniazid [INH], rifampin [RIF], and ethambutol [EMB]) plus streptomycin (STR) was compared to that of the BACTEC 460 TB system. The proportion method was used to resolve discrepant results by an independent arbiter. One hundred and ten strains were tested with an overall agreement of 93.5%. Discrepant results were obtained for seven strains (6.4%) with INH (resistant by BACTEC MGIT 960; susceptible by BACTEC 460 TB), for one strain (0.9%) with RIF (resistant by BACTEC MGIT 960; susceptible by BACTEC 460 TB), for seven strains (6.4%) with EMB (six resistant by BACTEC MGIT 960 and susceptible by BACTEC 460 TB; one susceptible by BACTEC MGIT 960 and resistant by BACTEC 460 TB), and for 19 strains (17.3%) with STR (resistant by BACTEC MGIT 960 and susceptible by BACTEC 460 TB). After resolution of discrepant results, the sensitivity of the BACTEC MGIT 960 system was 100% for all four drugs and specificity ranged from 89.8% for STR to 100% for RIF. Turnaround times were 4.6 to 11.7 days (median, 6.5 days) for BACTEC MGIT 960 and 4.0 to 10.0 days (median, 7.0 days) for BACTEC 460 TB. These data demonstrate that the fully automated and nonradiometric BACTEC MGIT 960 system is an accurate method for rapid susceptibility testing of *M. tuberculosis*.

Drug-resistant strains of *Mycobacterium tuberculosis*, though not a novel phenomenon, are emerging worldwide. According to the latest figures of the World Health Organization and the International Union against Tuberculosis and Lung Diseases, drug resistance, in particular acquired resistance, has poured additional fuel on the fire of global tuberculosis (TB) (18). Several outbreaks of multidrug-resistant TB (7) were characterized by delayed diagnoses, inadequate treatment regimens, high rates of mortality, and significant rates of transmission and have taught us two lessons: first, the days are definitely gone where full susceptibility of TB bacilli to front-line drugs can be taken for granted. Second, rapid detection of drug resistance is paramount, not only for effective treatment of TB patients but also for initiating adequate public health measures.

In the quest for new nonradiometric, culture-based strategies which allow both rapid detection of acid-fast bacilli and testing of susceptibility to antimicrobial agents, new liquid medium-based systems, such as the MB/BacT (Organon-Teknika, Durham, N.C.), ESP Culture System II (AccuMed International, Westlake, Ohio), MB Redox (Biotest, Dreieich, Germany), and the Mycobacteria Growth Indicator Tube 960 (MGIT 960, Becton Dickinson Microbiology Systems, Sparks, Md.), have become available. They all aim not only at recovering mycobacteria from clinical specimens but also at generating antimicrobial susceptibility testing (AST) data with a shorter turnaround time than that observed with the current "gold standard," the agar proportion method (11). The performance of a new system should be comparable with that of the BACTEC 460 TB system, with elimination of the two core problems associated with the old BACTEC 460 TB technology, i.e., the risk of needle punctures and disposal of radioactive waste. Preliminary studies utilizing those new systems report good overall agreement of AST results with those generated with established methods (1, 3–5, 8, 10, 12–13, 15).

Recent automation of the MGIT 960 technology was another step forward, as it allows continuous monitoring of positive fluorescence, which is based on bacterial growth. It is noninvasive and eliminates potential reading difficulties during visual judging of the tubes, apart from saving labor. The threshold algorithms help in determining the susceptibility automatically.

In this multicenter study we have evaluated the reproducibility and reliability of the BACTEC MGIT 960 instrument for testing of *M. tuberculosis* susceptibility to isoniazid (INH), rifampin (RIF) ethambutol (EMB), and streptomycin (STR) and have compared the results to those obtained by the radiometric procedure. Discordant results were resolved by testing the strains with the agar proportion method using Löwenstein-Jensen (LJ) medium (6). This was done by an additional site which thus acted as an independent arbiter. Last, in order to address safety, we performed drug susceptibility testing in plastic MGITs, in addition to the glass tubes.

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MATERIALS AND METHODS

Evaluation sites. Susceptibility testing results were generated by two mycobacteriology laboratories, the Mycobacteriology Laboratory, University of Nantes, Nantes, France (center 1), and the Swiss National Center for Mycobacteria, Department of Medical Microbiology, University of Zurich, Zurich, Switzerland (center 2). A third laboratory, the National Reference Center for Mycobacteria, Research Center, Borstel, Germany (center 3), acted as an arbiter site for the resolution of discrepant results.

Strains. A total of 110 *M. tuberculosis* strains were evaluated in this study. A total of 64 strains were fresh clinical isolates grown in MGIT (41 and 23 from centers 1 and 2, respectively). Another 46 strains (44 from center 1 and 2 from center 2) were selected from the culture collections in Nantes and Zurich, respectively. These strains were grown on LJ medium prior to inoculation to the MGIT medium. Accuprobe culture confirmation kits (GenProbe, San Diego, Calif.) and biochemical methods were used for identification.

Preparation of inocula. For strains grown in the MGIT medium and incubated at 37°C in the BACTEC MGIT 960 instrument with ambient air, each culture was used for susceptibility testing within 1 to 5 days after the instrument flagged a positive signal. On days 1 and 2 following positivity, cell suspensions were used undiluted; on days 3 through 5, suspensions were diluted 1:5 with sterile saline. Tubes which had been positive for more than 5 days had first to be subcultured again into a new MGIT medium. As for strains initially grown on LJ medium and incubated at 37°C in ambient air, colonies no older than 14 days were suspended in 4 ml of Middlebrook 7H9 broth (adjusted to a McFarland standard of 0.5). One milliliter of this suspension was diluted with 4 ml of sterile saline (1:5 dilution). Growth control (GC) and drug-containing MGITs (see below) were inoculated with 0.5 ml.

MGIT GC. One hundred microliters of a positive MGIT 960 broth was pipetted into 10 ml of sterile saline to prepare a 1:100 dilution of the growth suspension for the GC tube. Half a milliliter of the diluted suspension was inoculated into an MGIT without drug.

Drug solutions. For drug susceptibility testing using the BACTEC MGIT 960 system, 4 ml of sterile distilled water was added to a lyophilized vial of the drug in question (stock solution). Part of the stock solution (0.1 ml) was added to an MGIT. The final critical concentrations were 0.1 μg/ml for INH, 1.0 μg/ml for RIF, 5.0 μg/ml for EMB, and 1.0 μg/ml for STR. For testing at the higher drug concentrations (0.4 μg/ml for INH, 7.5 μg/ml for EMB, and 4.0 μg/ml for STR), 2 ml of sterile distilled water was added to the lyophilized vial of the respective higher-concentration drug vial, and 0.1 ml was added to an MGIT. For drug susceptibility testing in the BACTEC 460 TB system, final drug concentrations were 0.1 μg/ml for INH, 2.0 μg/ml for RIF, 2.5 μg/ml for EMB, and 2.0 μg/ml for STR. Only those strains which showed a resistance to one or more drugs at the critical drug concentrations were tested at the higher concentrations in BACTEC 460 TB (0.4 μg/ml for INH, 7.5 μg/ml for EMB, and 6.0 μg/ml for STR).

Drug susceptibility testing. (i) BACTEC MGIT 960 system. BACTEC MGIT 960 drug susceptibility testing supplement (0.8 ml) (oleic acid-albumin-dextrose-catalase), 100 μl of the drug stock solution, and 0.5 ml of the suspension containing *M. tuberculosis* were added to an MGIT. The GC did not contain any drugs. Drug susceptibility testing sets were entered into the BACTEC MGIT 960 instrument and continuously monitored until a susceptible or resistant result was obtained. The drug susceptibility testing set results were reported by the instrument (determined by the software algorithms, once the GC became positive). Drug susceptibility testing was done in glass MGITs; center 2 used, in addition, plastic MGITs for 10 AST sets.

(ii) BACTEC 460 TB system. Half a milliliter of a positive MGIT 960 sample was inoculated into a 12B vial and was incubated till the growth index was ≥ 500. Drug susceptibility testing was done following the standard procedure (S. H. Siddiqi, product and procedure manual, revision D, for BACTEC 460 TB system, Becton Dickinson Microbiology Systems, Sparks, Md.). Organisms initially grown on solid medium were inoculated in 12B vials and were tested as soon as the growth index was ≥ 500.

Reproducibility testing. Prior to testing clinical strains, a blinded panel of 10 strains of *M. tuberculosis* were sent to each center for reproducibility testing with the BACTEC MGIT 960 system by Becton Dickinson. Expected results had been generated by Becton Dickinson with the reference method (BACTEC 460 TB system). Center 1 tested the 10 strains in duplicate at three cycles (thus, six replicates per strain). Center 2 did reproducibility testing in triplicate at three cycles (thus, nine replicates per strain). Center 3 tested the 10 strains in duplicate (thus, two replicates per strain).

Quality control. Reference strains of *M. tuberculosis* (ATCC 27294 and ATCC 35822) were used as a batch quality control on a weekly basis.

TABLE 1. Reproducibility testing

Drug (concn in μg/ml)	No. of tests performed[a]	No. of results agreeing with reference method (BACTEC 460 TB)	Agreement (%)
INH (0.1)	170	170	100
INH (0.4)	170	165	97.1
RIF (1.0)	170	169	99.4
EMB (5.0)	170	170	100
EMB (7.5)	167	166	99.4
STR (1.0)	170	169	99.4
STR (4.0)	170	170	100
Total of tests	1,187	1,179	99.3

[a] Center 1, 10 strains in duplicate at three different times (thus, six replicates per strain); center 2, 10 strains in triplicate at three different times (thus, nine replicates per strain); and center 3, 10 strains in triplicate (thus, two replicates per strain).

Resolution of discrepant results. Strains for which results from BACTEC MGIT 960 and BACTEC 460 TB were discordant were sent to center 3 for independent resolution of discrepant results by applying the proportion method on LJ slants according to the German Deutsches Institut für Normung standard (6). The bacterial suspension was adjusted to that of a McFarland no. 1. A 10^{-2} dilution of the bacterial suspension was then plated on LJ medium containing the desired concentrations of the drugs (INH, 0.25 and 1 mg/liter; RIF, 16 and 32 mg/liter; EMB, 1 and 2 mg/liter; and STR, 4 and 8 mg/liter). The slants were incubated at 37°C by normal atmosphere. Performance parameters (sensitivity, specificity, positive predictive value, and negative predictive value) were determined after resolution of discrepant results.

Statistical analysis. The McNemar chi-square test was used for comparing the BACTEC MGIT 960 with the BACTEC 460 TB method. A significance value of $P = 0.05$ was used.

RESULTS

Overall results of reproducibility testing of the BACTEC MGIT 960 system with 10 *M. tuberculosis* strains (1,187 single susceptibility tests) are presented in Table 1. Full agreement of results was found in 1,179 tests (99.3%).

One hundred and ten clinical strains of *M. tuberculosis* were tested for susceptibility to the four anti-TB drugs at the critical (low) concentration. The strains resistant at the critical concentrations were tested at the higher concentrations of INH ($n = 29$), EMB ($n = 17$), and STR ($n = 34$) (Table 2). INH results agreed for 106 of 110 strains tested at the critical concentration (96.4% agreement) and for 26 of 29 at the higher

TABLE 2. Drug susceptibility results of clinical strains of *M. tuberculosis* as determined by BACTEC MGIT 960 and BACTEC 460 TB system[a]

Drug (concn in μg/ml)	No. of tests	No. of results that were:				Agreement (%)
		S by both tests	R by MGIT 960; S by 460 TB	S by MGIT 960; R by 460 TB	R by both tests	
INH (0.1)	110	81	4		25	96.4
INH (0.4)	29	5	3		21	89.7
RIF (1.0)	110	92	1		17	99.1
EMB (5.0)	110	93	3	1	13	96.4
EMB (7.5)	17	7	3		7	82.4
STR (1.0)	110	76	9		25	91.8
STR (4.0)	34	12	10		12	70.6
Total of tests	520	366	33	1	120	93.5

[a] S, susceptible; R, resistant.

TABLE 3. Resolution of discrepant results by proportion method on solid LJ medium[a]

Drug (concn in μg/ml)	Initial results for:		Resolved results[b] for:		
	R by MGIT 960; S by 460 TB	S by MGIT 960; R by 460 TB	R by MGIT 960 and PM (true resistant)	S by MGIT 960 and PM (true susceptible)	R by MGIT 960; S by PM (false-resistant ME)
INH (0.1)	4		1		3
INH (0.4)	3		1		2
RIF (1.0)	1		1		0
EMB (5.0)	3	1	0	1	3
EMB (7.5)	3		1		2
STR (1.0)	9		1		8
STR (4.0)	10		6		4
Total of tests	33	1	11	1	22

[a] S, susceptible; R, resistant; PM, proportion method.
[b] Arbiter results based on the proportion method.

concentration (89.7% agreement). RIF results agreed for 109 of 110 strains tested (99.1% agreement). EMB results agreed for 106 of 110 strains tested at the critical concentration (96.4% agreement) and for 14 of 17 at the higher concentration (82.4% agreement). STR results obtained by the two methods agreed for 101 of 110 strains at the critical concentration (91.8% agreement) and for 24 of 34 at the higher concentration (70.6% agreement).

Comparison of BACTEC MGIT 960 with BACTEC 460 TB yielded 27 strains with discordant results: 22 strains with one, 3 strains with two and 2 strains with three discrepant results, amounting to 34 (6.5%) discrepant results out of a total of 520 tests (Table 2). Of those, 33 were resistant according to BACTEC MGIT 960 but susceptible according to BACTEC 460 TB (INH [$n = 7$], RIF [$n = 1$], EMB [$n = 6$], and STR [$n = 19$]). One strain was susceptible to EMB with the former but was resistant with the latter system (Table 2).

False-resistant ($n = 22$) results after resolution of discrepant results by the independent arbiter site (center 3) are presented in Table 3. There were no false-susceptible results. The results of the MGIT 960 system agreed with the results generated by the proportion method in 36%, while 22 results remained discordant. The accuracy of the MGIT 960 system compared to that of the 460 TB system is presented in Table 4. Sensitivity (i.e., the ability to detect true resistance) was 100% for all four drugs at both concentrations. Specificity (i.e., the ability to detect true susceptibility) ranged from 90.5 to 100% at the critical concentrations and from 89.8 to 98% at the higher concentrations.

TABLE 4. Accuracy of BACTEC MGIT 960 compared with that of BACTEC 460 TB system after resolution of discrepancies[a]

Drug (concn in μg/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
INH (0.1)	100	96.4	89.7	100
INH (0.4)	100	97.7	91.7	100
RIF (1.0)	100	100	100	100
EMB (5.0)	100	96.9	81.3	100
EMB (7.5)	100	98.0	80	100
STR (1.0)	100	90.5	76.5	100
STR (4.0)	100	89.8	81.2	100

[a] PPV, positive predictive value; NPV, negative predictive value.

TABLE 5. Time required for drug susceptibility testing of *M. tuberculosis*

No. of strains	Time (days) required for:			
	MGIT 960		460 TB	
	Median	Range	Median	Range
85[a]	6.3	4.6–11.7	7.0	4.0–10.0
25	7.1	5.7–10.9	5.0	5.0–7.0
110	6.5	4.6–11.7	7.0	4.0–10.0

[a] Eighty-five strains were from center 1; 25 from center 2; and 110 from centers 1 and 2.

Turnaround times for AST ranged from 4.6 to 11.7 days (median, 6.5 days) for BACTEC MGIT 960 and from 4.0 to 10.0 days (median, 7.0 days) for BACTEC 460 TB (Table 5). There was no significant difference between center 1 and center 2 for BACTEC MGIT 960. Turnaround times for resistant strains ranged from 5.0 to 10.9 days (median, 6.3 days) for BACTEC MGIT 960 and from 5.0 to 10.0 days (median, 7.0 days) for BACTEC 460 TB.

DISCUSSION

The purpose of this multicenter study was to evaluate the reliability of the newly introduced BACTEC MGIT 960 system for testing the susceptibility of *M. tuberculosis* to the three front-line drugs (INH, RIF, and EMB) and STR. We have compared the results to those obtained by the radiometric BACTEC 460 TB system. Most previous evaluations of newer AST systems have not included reproducibility testing (3, 4). In this study, excellent agreement was obtained for all four drugs at both concentrations and, thus, assured quality of the results.

Initial susceptibility testing yielded an overall agreement of 93.5%. There was a very good correlation for each of the drugs at the critical concentrations. After the 34 discrepant cases were retested by an independent arbiter site utilizing the proportion method, there were 22 major errors (ME) but no very ME (VME) by the BACTEC MGIT 960.

In the past few years, most of the studies comparing new systems with the agar proportion method or the BACTEC 460 TB system found discordant results (2–5, 15). When comparing the manual MGIT with the agar proportion method, Walters and Hanna (17) reported three VME of the manual MGIT among 117 strains of *M. tuberculosis* (two strains against INH and one against RIF). Similarly, in a large European multicenter study involving 441 strains of *M. tuberculosis*, Rüsch-Gerdes et al. (15) found 11 strains which yielded VME by the manual MGIT (one against INH, three against RIF, five against EMB, and two against STR) when it was compared to the BACTEC 460 TB system. Comparing the fully automated MB/BacT system with the agar proportion method, Diaz-Infantes et al. (5) reported five VME of 83 *M. tuberculosis* strains tested with the MB/BacT System (three strains with EMB and two with STR). By using the same system, Brunello and Fontana (4) found two VME out of 120 *M. tuberculosis* strains tested against INH, when it was compared with BACTEC 460 TB and the agar proportion method. Bergmann and Woods (3)

found three VME out of 20 *M. tuberculosis* strains tested with the ESP Culture System II (two strains against INH and one against STR) when it was compared with the proportion method. The absence of VME in our study indicates that the fully automated MGIT 960 system is reliable in detecting true-resistant strains. Nevertheless, additional studies are required to confirm our preliminary results.

False resistance, in turn, is considered an ME, as it indicates a drug to be not effective for treatment, even though in reality, the drug could be successfully used. In our study there were only four discordant results at the low concentration and three at the high concentration of INH. One strain was confirmed resistant by the arbiter at both concentrations. This strain was multidrug resistant and was missed by the BACTEC 460 TB system. The two discordant results at the higher concentration of INH were resistant at the critical concentration with both systems and should be considered low-level resistant strains.

Out of the 19 discrepancies observed with STR, seven were found true resistant by the arbiter and eight were false resistant at the critical concentration with the MGIT 960 system. Overall sensitivity for STR was 100%, and its specificity was the lowest of all drugs. There were seven VME of the BACTEC 460 TB when its results were compared to the arbiter results. Among the seven truly resistant strains, six showed a low level of resistance detected by both systems at the critical STR concentration. The moderately resistant strains were the one which gave the most discordant results. Such strains were not always detected by the BACTEC 460 TB system as described by Siddiqi et al. (16).

Among the primary drugs, EMB is considered a difficult drug to be tested that often yields less reproducible results. For the BACTEC 460 TB, Roberts et al. (14) observed a sensitivity value that did not exceed 66%, when it was compared with the proportion method. In 1994, a quality assurance program for drug susceptibility testing of *M. tuberculosis* was initiated by the World Health Organization in 16 laboratories across the world. The specificity values of EMB (mean, 98%) were significantly higher than its sensitivity values (mean, 66% [9]). As a consequence, the sensitivity of EMB leads to underreporting of drug resistance. With the MB/BacT System, Brunello and Fontana (4) found five ME of 120 strains and Diaz-Infantes et al. (5) found five ME of 83 strains in EMB testing. Rüsch-Gerdes et al. (15) found four ME with the manual MGIT. In our study, resolved results showed only three ME with the critical concentration and two ME at the high concentration of EMB in the BACTEC MGIT 960 system. A specificity of almost 97% at the critical concentration with 100% sensitivity indicates that EMB testing in the BACTEC MGIT 960 system is very reliable.

The absence of any false-susceptible results given by the BACTEC MGIT 960 (100% sensitivity) indicates the excellent ability of the system to detect true resistance. The overall specificity was excellent at the critical concentration for the front-line drugs and at the high concentration of INH and EMB. A lower specificity was observed for STR. In contrast, the BACTEC 460 TB failed to detect 11 true-resistant strains against STR, especially those harboring a low level of resistance. Plastic tubes were used without any influence on results (sensitivity, specificity, and time required for AST).

The median time for obtaining susceptibility results was 6.5 days, which is as rapid as that of the BACTEC 460 TB System (7.0 days) and slightly shorter than that observed by Brunello and Fontana (4) utilizing the MB/BacT system (8.5 days). Automation of the MGIT method has thus reduced the median time by two more days (time for manual MGIT, 8.8 days [15]). The shorter median time observed for the BACTEC 460 TB at center 2 (5.0 days) might be due to the daily testing schedule, whereas at center 1, drug susceptibility was not read daily (nonweekend protocol [Siddiqi, manual, Becton Dickinson]). There was no statistically significant difference in reporting time ($P > 0.05$) between susceptible and resistant strains.

In summary, our study demonstrates that the BACTEC MGIT 960 system is a reliable method for testing the susceptibility of *M. tuberculosis*. The overall excellent sensitivity suggests that the BACTEC MGIT 960 system is more efficient than the BACTEC 460 TB system in detecting true-resistant strains. Being as rapid as the results of BACTEC 460 TB, our results indicate that this system will easily replace the radiometric system.

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