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Liquid vs. solid culture for tuberculosis: performance and cost in a resource-constrained setting

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SUMMARY

SETTING: National Health Laboratory Services tuberculosis (TB) laboratory, South Africa.

OBJECTIVES: To compare Mycobacterium Growth Indicator Tube (MGIT) with Löwenstein-Jensen (LJ) medium with regard to *Mycobacterium tuberculosis* yield, time to positive culture and contamination, and to assess MGIT cost-effectiveness.

DESIGN: Sputum from gold miners was cultured on MGIT and LJ. We estimated cost per culture, and, for smear-negative samples, incremental cost per additional *M. tuberculosis* gained with MGIT using a decision-tree model.

RESULTS: Among 1267 specimens, MGIT vs. LJ gave a higher yield of mycobacteria (29.7% vs. 22.8%), higher contamination (16.7% vs. 9.3%) and shorter time to positive culture (median 14 vs. 25 days for smear-negative specimens). Among smear-negative samples that were culture-positive on MGIT but negative/contaminated on LJ, 77.3% were non-tuberculous mycobacteria (NTM). Cost per culture on LJ, MGIT and MGIT+LJ was respectively US$12.35, US$16.62 and US$19.29. The incremental cost per additional *M. tuberculosis* identified by standard biochemical tests and microscopic cording was respectively US$504.08 and US$328.10 using MGIT vs. LJ, or US$160.80 and US$109.07 using MGIT+LJ vs. LJ alone.

CONCLUSION: MGIT gives higher yield and faster results at relatively high cost. The high proportion of NTM underscores the need for rapid speciation tests. Minimising contaminated cultures is key to cost-effectiveness.

KEY WORDS: *Mycobacterium tuberculosis*; LJ medium; MGIT; microscopic cording; anti-MPB64 assay

THE HUMAN immunodeficiency virus (HIV) epidemic has worsened the public health problem posed by tuberculosis (TB), partly by increasing TB incidence, especially in sub-Saharan Africa,[1] but also by making the diagnosis of TB more difficult. HIV-infected patients are more likely to have smear-negative TB,[2,3] although this may be in the context of disseminated disease, a high total bacillary burden and a high risk of mortality,[4] underlining the need for rapid diagnosis.

In low-income settings, TB diagnosis relies on sputum microscopy for acid-fast bacilli (AFB). The few facilities for culture generally use Löwenstein-Jensen (LJ) media, which can take months to give a result; wider use of LJ culture thus has limited potential to accelerate TB diagnosis.[5] Liquid media systems with early growth indicators, such as the Mycobacterial Growth Indicator Tube (MGIT), are more rapid and detect more mycobacterial isolates than LJ;[6–8] however, morphological examination of colonies alone can no longer be used for species identification, making other rapid methods more important.[9] The Capilia TB (anti-MPB64 monoclonal) assay (TAUNS, Numazu, Japan) uses monoclonal antibodies to detect a secreted mycobacterial protein, MPB64, which can differentiate *M. tuberculosis* complex from non-tuberculous mycobacteria (NTM)[10–12] and shows promise as an easy and rapid tool for identifying *M. tuberculosis* complex in liquid cultures.[13–15]

Liquid culture and molecular species identification tests have seldom been used in resource-constrained settings, largely because of cost, but these have the potential to reduce mortality by facilitating more rapid diagnosis of smear-negative TB. Economic evaluations of diagnostic strategies are needed to guide decisions on prioritising health care resources in TB control;[16] however, data on the cost-effectiveness of newer diagnostics are limited.

The aims of this study were to compare MGIT with LJ in the diagnosis of TB with respect to yield, time to positive culture and contamination rates in a high TB incidence and high HIV prevalence setting, and to evaluate microscopic cording and the anti-MPB64 assay in the identification of mycobacterial species. We also conducted a cost-effectiveness analysis comparing

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MGIT and MGIT+LJ with LJ alone, including standard biochemical assays, cording and anti-MPB64 assay in the diagnosis of smear-negative TB.

The study was nested within a cluster randomised trial of community-wide isoniazid preventive treatment (IPT), 'Thibela TB' (meaning 'Prevent TB' in seSotho), in three South African gold mining companies.

METHODS

Study population

TB suspects were enrolled from routine mine health services participating in the Thibela TB study (limited to individuals with no previous history of TB); and from the Thibela TB study, at screening and prior to or during follow-up visits while taking IPT (regardless of TB history). Participants gave one on-the-spot sputum sample, after nebulisation if necessary.

Laboratory methods

All laboratory work was undertaken at the National Health Laboratory Services regional TB laboratory in Johannesburg, South Africa. Specimens were decontaminated using the sodium hydroxide-N-acetyl-L-cystein (NaOH-NALC) method and concentrated by centrifugation.[17] The pellet was resuspended in 1–2 ml of sterile phosphate buffer (pH 6.8), and an auramine-stained smear was examined under a fluorescence microscope; 0.5 ml of sediment was cultured using the BACTEC MGIT 960 system (BD Diagnostic Systems, Sparks, MD, USA); another 0.5 ml was inoculated onto an LJ slant. Positive cultures were confirmed by examining Ziehl-Neelsen (ZN) stained smears for AFB. Mycobacteria were identified using 1) standard biochemical tests (growth rate at 25°C and 37°C, pigment production, susceptibility to *p*-nitrobenzoic acid and biochemical tests, including 68°C heat stable catalase, nitrate reduction test and Tween 80 hydrolysis),[18] 2) the anti-MPB64 monoclonal antibody assay (TAUNS) following the manufacturer's instructions, and 3) by examining smears for microscopic serpentine cords of AFB.[19] A culture that was considered contaminated was only re-decontaminated and re-cultured if the ZN-stained smears were positive for AFB.

Statistical methods

Data were analysed using Stata version 10.0 (STATA, College Station, TX, USA). The time to positive culture was summarised using Kaplan-Meier curves, stratified by smear status and compared between culture methods using the Wilcoxon signed-ranks test.

Using standard biochemical testing as the gold standard, the sensitivity and specificity of microscopic cording and the anti-MPB64 assay in identifying *M. tuberculosis* were determined, stratified by smear status. The 95% confidence intervals (CIs) for sensitivity and specificity were calculated using the exact binomial method.

Cost analyses

Economic cost analyses from a provider perspective compared LJ alone to 1) MGIT alone and 2) MGIT+LJ, each in conjunction with anti-MPB64 assay or cording vs. standard biochemical assay. Cost per culture (based on all specimens) and per *M. tuberculosis* case identified were calculated from time of arrival of specimens to identification of mycobacterial species in the laboratory. Specimen collection, transport to the laboratory and return of results were costed, but the costs were excluded on the basis that they were study-specific and not generalisable.

All resources used in the steps required for culturing were measured using an ingredients-based approach. Infrastructure costs were obtained through capital audit and apportioned to the diagnostic process based on proportion of time and space used. Capital costs were annualised using a useful life of 20 years for buildings, 5 years for furniture and 6 years for equipment and a discount rate of 3%.[20] Use of laboratory, medical and other supplies was measured through detailed staff re-enactment of specimen processing. Staff time in laboratory was estimated by staff interview. Administrative staff time and supplies were included in the costing, but laboratory overhead costs (equipment maintenance, lighting, cleaning, water, etc.) were not available at the time of data collection and these were therefore estimated at 5% of all capital items at the laboratory.[21]

All costs were valued at current market prices and expressed in 2007 $US, using an exchange rate of US$1 = ZAR7.00 (as estimated for 30 June 2007, the end of the study period, using http://www.x-rates.com).

Cost-effectiveness

Cost-effectiveness analysis was restricted to smear-negative specimens. The incremental cost per additional positive culture and additional *M. tuberculosis* isolated using MGIT or MGIT+LJ vs. LJ alone, speciated by standard biochemical tests, anti-MPB64 assay or microscopic cording, was calculated using a decision tree model programmed in Excel 2003 (MicroSoft, Redmond, WA, USA). For the cost per additional *M. tuberculosis* case isolated, the same species identification method was used for the positive culture system (MGIT or MGIT+LJ) and the comparator LJ alone.

Sensitivity analysis

The base-case scenario assumed that the MGIT system was used at 75% throughput (as was observed with MGIT systems used under routine conditions in the same laboratory), 5% overheads and 16% contamination rate of MGIT cultures (as observed). This

differed from the actual study conditions, where the MGIT system was used exclusively for study specimens and ran at 4% capacity. In a sensitivity analysis, we explored a low-cost scenario assuming an MGIT system throughput of 100% and a high-cost scenario assuming 50% throughput and overheads of 25%. For all cost-effectiveness estimates, we also explored the effect of reducing the proportion of MGIT cultures contaminated from 16% (as observed) to 4% (the best achieved in this laboratory using an alternative decontamination regimen [unpublished data]), assuming the proportion of specimens yielding *M. tuberculosis* was the same in contaminated and uncontaminated samples.

Ethical considerations

All participants who provided a sputum specimen gave written or witnessed verbal informed consent. The study was approved by the Research Ethics Committees of the University of KwaZulu-Natal and the London School of Hygiene & Tropical Medicine.

RESULTS

Participants

From July 2006 to June 2007, 1267 specimens (763 from routine mine health services and 504 from the Thibela TB study) had culture results available from both LJ and MGIT. Among the 1267 participants, 99.4% (n = 1260) were male, reflecting the sex distribution of this workforce, with a median age of 43 years (range 19–67, n = 1256); 51 (4.0%) were taking IPT at the time of enrolment and 35 (2.8%) had previously taken IPT; 1105 of the 1267 (87.2%) sputum specimens were smear-negative.

Table 1 Comparison of results of mycobacterial culture (*Mycobacterium tuberculosis* and non-tuberculous mycobacteria combined) on LJ medium vs. MGIT, stratified by smear status

	MGIT culture			
LJ culture	Positive	Negative	Contaminated	Total (column %)
Smear-positives				
Positive	138	1	5	144 (88.9)
Negative	5	2	1	8 (4.9)
Contaminated	8	2	0	10 (6.2)
Total (row %)	151 (93.2)	5 (3.1)	6 (3.7)	162 (100)
Smear-negatives				
Positive	116	12	17	145 (13.1)
Negative	100	632	120	852 (77.1)
Contaminated	9	30	69	108 (9.8)
Total (row %)	225 (20.4)	674 (61.0)	206 (18.6)	1105 (100)

LJ = Löwenstein-Jensen; MGIT = Mycobacterial Growth Indicator Tube.

Yield and contamination rates of cultures

Overall, 254 specimens were culture-positive for mycobacteria on both LJ and MGIT, and 634 were negative on both systems. The yield of mycobacteria was higher for MGIT (376/1267, 29.7%) compared to LJ (289/1267, 22.8%; $P < 0.001$). MGIT alone detected mycobacteria on culture in 122 specimens where LJ was either negative or contaminated, compared to 35 detected by LJ which were negative or contaminated on MGIT. Contamination rates were generally high, and were higher for MGIT (16.7%) than LJ (9.3%).

Among the 162 smear-positive samples, 151 (93.2%) were positive for mycobacteria on MGIT, 144 (88.9%) were positive on LJ and 138 (85.2%) were positive on both (Table 1).

Among smear-negative samples, the yield of

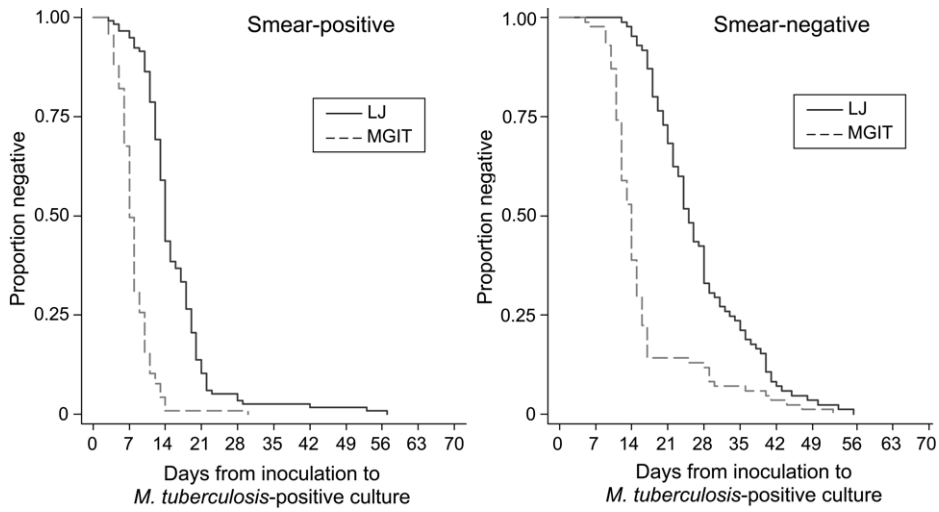

Figure Kaplan-Meier plots showing time to positive *Mycobacterium tuberculosis* culture for MGIT compared to LJ medium for smear-positive and smear-negative specimens. Smear-positives (n = 117): median (range) MGIT 7 (3–30) vs. LJ 14 (2–57). Smear-negatives (n = 85): median (range) MGIT 14 (5–53) vs. LJ 25 (12–57). MGIT = Mycobacterial Growth Indicator Tube; LJ = Löwenstein-Jensen.

Table 2 Organisms identified from positive mycobacterial cultures, stratified by smear status

	MGIT-positive *n* (column %)	LJ-positive *n* (column %)	Gain from MGIT* *n* (column %)
Smear-positives	123	120	8
M. tuberculosis	97 (78.9)	96 (80.0)	4 (50.0)
M. kansasii	17 (13.8)	14 (11.7)	3 (37.5)
M. avium complex	0	0	0
NTM (unspeciated)	9 (7.3)	10 (8.3)	1 (12.5)
Smear-negatives	189	125	88
M. tuberculosis	92 (48.7)	81 (64.8)	20 (22.7)
M. kansasii	19 (10.1)	14 (11.2)	9 (10.2)
M. avium complex	19 (10.1)	6 (4.8)	15 (17.1)
NTM (unspeciated)	59 (31.2)	24 (19.2)	44 (50.0)

*Additional organisms identified using MGIT where LJ was negative or contaminated.
LJ = Löwenstein-Jensen; MGIT = Mycobacterial Growth Indicator Tube; NTM = non-tuberculous mycobacteria.

mycobacteria was higher for MGIT (225/1105, 20.4%) compared to LJ (145/1105, 13.1%; Table 1). MGIT alone detected an additional 109 cultures positive for mycobacteria where LJ was either negative or contaminated, compared to the additional 29 positive cultures detected by LJ alone (Table 1).

Time to positive M. tuberculosis *culture*

Among all TB suspects, the yield of *M. tuberculosis* was slightly higher for MGIT (233/1266, 18.4%) than for LJ (215/1266, 17.0%; $P = 0.01$).

Among specimens positive on both MGIT and LJ, time to positive *M. tuberculosis* culture was shorter with MGIT both for smear-positive specimens (median 7 vs. 14 days, respectively; Wilcoxon signed-ranks test $P < 0.001$, $n = 117$, Figure) and for smear-negative specimens (median 14 vs. 25 days respectively, Wilcoxon signed-ranks test $P < 0.001$, $n = 85$).

Organism identification

Among smear-positive specimens, the majority of positive cultures were *M. tuberculosis* on both MGIT and LJ (78.9% and 80%, respectively); *M. kansasii* was the most common NTM identified (13.8% and 11.7% on MGIT and LJ, respectively; Table 2).

Among smear-negative specimens, fewer than half (48.7%) of the cultures positive on MGIT were *M. tuberculosis*, compared with 64.8% on LJ (Table 2). *M. kansasii* was identified in a similar proportion of positive cultures on MGIT and on LJ (10.1% vs. 11.2%). *M. avium* complex was identified in 10.1% of positive MGIT cultures vs. 4.8% LJ (Table 2). Among 88 mycobacterial isolates from smear-negative specimens 'gained' on MGIT (i.e., specimens that were culture-positive on MGIT but negative or contaminated on LJ), only 22.7% were *M. tuberculosis*, the majority being NTM (Table 2).

Species identification results, comparing microscopic cording and the anti-MPB64 assay with standard biochemical tests as the gold standard, were available for 341 specimens (Table 3). Among the 213 smear-negative specimens, the sensitivity and specificity of microscopic cording were respectively 99.0% and 99.1% (Table 3). One smear-negative isolate showing typical cording morphology was identified as NTM and another isolate with no cording was identified as *M. tuberculosis* complex, using standard biochemical tests. Two smear-positive isolates showing typical cording morphology were identified as NTM and one isolate with no cording was positive for *M. tuberculosis*, using standard biochemical tests.

The sensitivity and specificity of the anti-MPB64 assay among smear-negatives was respectively 99.0% and 99.1% (Table 3). Using standard biochemical tests, one smear-negative isolate that was negative with the anti-MPB64 assay was identified as *M. tuberculosis* complex, while another that was positive for *M. tuberculosis* complex using the anti-MPB64 assay was identified as *M. kansasii*. Two smear-positive isolates identified as *M. tuberculosis* complex using the anti-MPB64 assay were identified as *M. kansasii* and unspeciated NTM using standard biochemical tests.

The four isolates that were discrepant in comparing the anti-MPB64 assay with standard biochemical tests were also discrepant on cording compared with standard biochemical tests.

Costs of culture and organism identification

Costs were calculated over the 12-month study period for all 1275 cultures (Table 4). Transport costs

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.

were calculated at US$11.72 per culture, but were excluded from the final calculation of a public sector laboratory cost per culture because they were private sector provider costs. In the base-case scenario, average cost per LJ, MGIT and MGIT+LJ conducted was respectively US$12.35, US$16.62 and US$19.29 (Table 5). The capital cost component was similar for LJ and MGIT, at respectively 12% and 18%. At the laboratory level, staff and medical consumables were the highest cost drivers for LJ and MGIT, respectively.

The cost of organism identification per positive culture on MGIT in the base-case scenario was US$35.94 using standard biochemical tests, US$15.49 for anti-MPB64 assay and US$2.28 for cording.

Table 4 Items and costs included in the calculation of mycobacterial culture costs (containing unit and unit costs, all in $US)

	Cost per culture (N = 1275)					
	LJ		MGIT		MGIT+LJ	
	US$	%	US$	%	US$	%
Capital costs						
Buildings	0.52	4	0.52	3	0.52	3
Furniture	0.45	4	0.35	2	0.45	2
Medical equipment	0.45	4	2.03	12	2.05	11
Non-medical equipment	0.09	1	0.09	1	0.09	0
Subtotal	1.50	12	2.99	18	3.10	16
Recurrent costs						
Staff costs, culture	6.44	52	6.53	39	7.60	39
Staff costs, non culture	1.82	15	1.73	10	1.93	10
Medical supplies	2.29	19	5.02	30	6.28	33
Non-medical supplies	0.22	2	0.21	1	0.23	1
Overheads	0.08	1	0.15	1	0.15	1
Subtotal	10.85	88	13.63	82	16.20	84
Total culture costs	12.35	100	16.62	100	19.29	100

LJ = Löwenstein-Jensen medium; MGIT = Mycobacterial Growth Indicator Tube.

Cost-effectiveness of MGIT vs. LJ

Subsequent analysis was restricted to 1113 smear-negative specimens (1105 included in the laboratory analysis plus eight for which laboratory data were incomplete). In the base-case scenario, the cost per additional *M. tuberculosis* case identified with standard biochemical tests was US$504.08 for MGIT and US$160.80 for MGIT+LJ vs. LJ alone (Table 5); this decreased to respectively US$397.67 and US$129.53 if the anti-MPB64 assay was used for identification, and further decreased to respectively US$328.10 and US$109.07 with microscopic cording.

Sensitivity analyses

In the low-cost scenario (assuming the MGIT system ran at 100% of maximum capacity), the cost per MGIT

Table 5 Cost (in $US) per culture, per *M. tuberculosis* isolate identified using different methods, and cost-effectiveness ratios for MGIT vs. LJ medium: base-case scenario and sensitivity analyses

	MGIT contamination rate 16%			MGIT contamination rate 4%		
	Base case*	Low†	High‡	Base case*	Low†	High‡
Cost per culture						
LJ	12.35	12.15	13.04	NA	NA	NA
MGIT	16.62	16.53	18.66	NA	NA	NA
MGIT+LJ	19.29	18.99	21.65	NA	NA	NA
Cost per *M. tuberculosis* identified						
LJ						
Standard biochemical tests	202.41	199.87	211.36	NA	NA	NA
Anti-MPB64 assay	172.28	169.76	180.76	NA	NA	NA
Microscopic cording	151.53	149.01	160.00	NA	NA	NA
MGIT						
Standard biochemical tests	243.92	242.65	265.61	215.30	214.20	233.50
Anti-MPB64 assay	203.59	202.36	224.89	174.50	173.44	192.25
Microscopic cording	176.06	174.83	197.34	147.05	145.99	164.79
MGIT+LJ						
Standard biochemical tests	184.50	182.36	200.91	168.98	167.08	183.52
Anti-MPB64 assay	153.78	151.66	169.89	138.93	137.04	153.23
Microscopic cording	133.15	131.03	149.25	118.29	116.40	132.58
Cost per additional *M. tuberculosis* identified (LJ alone as comparator)						
MGIT						
Standard biochemical tests	504.08	478.24	605.53	248.06	237.43	289.73
Anti-MPB64 assay	397.67	371.89	498.45	180.06	169.48	221.11
Microscopic cording	328.10	302.33	428.87	135.79	125.20	176.82
MGIT+LJ						
Standard biochemical tests	160.80	159.19	187.08	135.19	133.94	155.38
Anti-MPB64 assay	129.53	127.94	155.64	105.22	103.97	125.40
Microscopic cording	109.07	107.48	135.18	84.68	83.43	104.86

*Base-case scenario: MGIT system throughput of 75% and 5% overheads.
†Low-cost scenario: MGIT system throughput of 100%.
‡High-cost scenario: MGIT system throughput of 50% and overheads of 25%.
MGIT = Mycobacterial Growth Indicator Tube; LJ = Löwenstein-Jensen medium; NA = not applicable.

culture decreased from US$16.62 to US$16.53 (Table 5). Costs per additional *M. tuberculosis* confirmed with cording were likewise altered from US$328.10 to US$302.33 for MGIT and US$109.07 to US$107.48 for MGIT+LJ vs. LJ alone.

In a high-cost scenario (50% throughput on MGIT and overheads increased to 25%), the cost per culture for LJ, MGIT and MGIT+LJ increased from respectively US$12.35 to US$13.04, US$16.62 to US$18.66 and US$19.29 to US$21.65. The cost per additional *M. tuberculosis* case confirmed with cording changed from respectively US$328.10 to US$428.87 and US$109.07 to US$135.18 for MGIT and MGIT+LJ.

In scenarios assuming a reduction in contamination rates from 16% to 4% of MGIT cultures (assuming 75% throughput and 5% overheads), the cost per additional *M. tuberculosis* case identified for 1) MGIT alone and 2) MGIT+LJ using standard biochemical tests, anti-MPB64 assay and cording was respectively US$248.06 and US$135.19; US$180.06 and US$105.22; and US$135.79 and US$84.68 (Table 5).

Changes in discount rates (from 3% to 6%) did not show significant changes in cost per culture and cost-effectiveness ratios (data not shown).

DISCUSSION

The World Health Organization now recommends expanded use of liquid culture systems in resource-constrained settings;[22] our data are among the first to document how these systems perform in a routine laboratory in such a setting. The higher yield and shorter time to positive culture with MGIT, particularly among smear-negative specimens, were expected and consistent with other work.[7,8,23–25] Less expected was the high yield of NTM, accounting for three quarters of mycobacterial isolates from specimens positive on MGIT but not on LJ. The proportion of NTM in our study was higher than reported from similar studies in Taiwan, Thailand and Zambia.[7,8,26] *M. kansasii* was relatively common among gold miners in South Africa both before[27–29] and after the introduction of MGIT culture systems,[30] but was more common in individuals with a previous history of TB or silicosis. More recently, among children with suspected TB in the Western Cape of South Africa investigated with induced sputum and gastric lavage specimens cultured on MGIT, one third of positive mycobacterial cultures were NTM, primarily *M. avium* complex and *M. gastri*;[31] 95% of these children were symptomatic (reflecting selection criteria). The clinical significance of the NTM isolates in our study is currently under investigation.

The high frequency of NTM underlines the importance of simple, rapid tests for species identification in combination with liquid culture media. Microscopic cording and the anti-MPB64 assay both performed very well when compared with standard biochemical tests, consistent with previous studies,[14,15,19] but our results go further to show that these tests (particularly microscopic cording) were both less labour intensive and cheaper, making them particularly suitable for resource-constrained settings.

A limitation in the use of MGIT is the relatively high proportion of cultures contaminated, reported at 5.5%–15% in high-income settings[6,7,23–24] and at 29.3% in Zambia.[8] This generally improves with experience of the system,[32] but our data illustrate the financial benefits of optimising the decontamination protocol to improve costs and cost-effectiveness. The cost per additional *M. tuberculosis* detected using MGIT vs. LJ was substantially lower when contamination was reduced from 16% to 4%.

Our costs per culture were lower than estimates from a similar study in Zambia,[33] where base-case throughput was substantially lower and overhead costs, which included transport and all resources not directly involved in performing the culture, were substantially higher. Comparable costs (i.e., excluding transport) in our study were slightly higher than estimates from Brazil;[34] this may be due to the assumption of available infrastructure capacity with no additional cost used in the Brazil study. The culture processing costs in our study (medical consumables, medical equipment and staff time used in performing cultures) accounted for respectively 74% and 82% of our total cost per culture for LJ and MGIT. We found improved cost-effectiveness, particularly in the scenario with high MGIT contamination, if both MGIT and LJ were used vs. MGIT alone, because having two cultures reduced the probability of a 'contaminated' result.

MGIT costs were also sensitive to throughput, with estimated costs for maximum throughput reflecting the costs that would be expected under operational conditions in a large routine laboratory. However, even assuming maximal throughput, the cost per additional *M. tuberculosis* case detected was substantial, raising questions about how MGIT technology should be prioritised in resource-constrained settings. Our data suggest that minimising the MGIT contamination rate is key to maximising cost-effectiveness.

Further work will follow up treatment outcomes based on earlier diagnosis to provide a cost-effectiveness analysis using cost per life year gained as a final health outcome, to provide better guidance for resource allocation across differing prevention and treatment strategies.[35]

The high prevalence of *M. kansasii* among our study population of gold miners is unlikely to be generalisable to community TB clinics, and this is a limitation of our study; in addition, we do not yet have data on the clinical significance of the NTM isolates.

CONCLUSIONS

In a routine laboratory setting in South Africa, the higher yield of MGIT compared to LJ has to be balanced against the higher proportion of NTM cultured. MGIT costs are high, and sensitive to throughput and particularly to contamination rates. Microscopic cording and the anti-MPB64 assay both performed very well compared with standard biochemical tests for organism identification; both, particularly cording, were less expensive. The clinical significance of the NTM, and the health outcome gains from earlier diagnosis, will be determined in future work.

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RÉSUMÉ

CONTEXTE : Laboratoire de tuberculose des Services du Laboratoire National de la Santé, Afrique du Sud.

OBJECTIFS : Comparer la technique du Mycobacterium Growth Indicator Tube (MGIT) avec les milieux de Löwenstein-Jensen (LJ) concernant le rendement en *Mycobacterium tuberculosis*, la durée avant une culture positive ainsi que le taux de contamination pour évaluer le rapport coût-efficacité de MGIT.

SCHÉMA : On a cultivé sur MGIT et sur LJ l'expectoration provenant de mineurs d'or. Nous avons estimé, grâce à l'emploi d'un modèle d'arbre de décision, le coût par culture et, pour les échantillons à bacilloscopie négative des frottis, le coût supplémentaire par unité de *M. tuberculosis* supplémentaire obtenue par le MGIT.

RÉSULTATS : Sur 1267 échantillons, le rendement de MGIT a été plus élevé que celui de LJ en matière de mycobactéries (29,7% vs. 22,8%), le taux de contamination plus élevé (16,7% vs. 9,3%) et la durée avant une culture positive plus courte (médiane 14 jours vs. 25 jours pour les échantillons à bacilloscopie négative des frottis). Parmi les échantillons à bacilloscopie négative des frottis qui étaient positifs à la culture sur MGIT mais négatifs ou contaminés sur LJ, 77,3% étaient des mycobactéries non tuberculeuses (NTM). Les coûts par culture ont été respectivement de 12,35 US$ pour LJ, 16,62 US$ pour MGIT et 19,29 US$ pour MGIT+LJ. Le coût supplémentaire par unité de *M. tuberculosis* identifié par les tests biochimiques standard et la présence de torsades à l'examen microscopique a été respectivement de 504,08 US$ pour MGIT et 328,10 US$ pour LJ, ou encore de 160,80 US$ pour MGIT+LJ vs. 109,07 US$ pour LJ seul.

CONCLUSION : Le MGIT a consisté en un rendement plus élevé et donne une réponse plus rapide mais un coût relativement élevé. La proportion élevée de NTM souligne la nécessité de tests rapides de détermination de l'espèce ; la réduction du taux de cultures contaminées est essentielle en matière de rapport coût-efficacité.

RESUMEN

MARCO DE REFERENCIA: Un laboratorio de tuberculosis del Sistema Nacional de Salud de Sudáfrica.

OBJETIVOS: Comparar el rendimiento diagnóstico del sistema de cultivo con indicador de crecimiento de micobacterias en tubo (MGIT) con el medio Löwenstein-Jensen (LJ) en la detección de *Mycobacterium tuberculosis*, en relación con los resultados positivos, el lapso hasta obtener un cultivo positivo y la contaminación. Se evaluó además la rentabilidad del sistema MGIT.

MÉTODO: Se cultivaron muestras de esputo de trabajadores de minas de oro en el sistema MGIT y en LJ. Se evaluaron los costos por cultivo y por muestras con baciloscopia negativa y el incremento del costo por cada diagnóstico adicional de *M. tuberculosis* logrado con MGIT, aplicando un modelo de árbol de decisiones.

RESULTADOS: En las 1267 muestras analizadas, con MGIT se obtuvieron más resultados positivos que en LJ (29,7% contra 22,8%), se presentó mayor contaminación (16,7% contra 9,3%) y se precisó un lapso más corto hasta obtener un cultivo positivo (mediana de 14 días contra 25 días, en muestras con baciloscopia negativa). De las muestras con baciloscopia negativa y cultivo positivo en MGIT pero cultivo negativo o contaminado en LJ, 73% fueron micobacterias atípicas (NTM). El costo por cultivo en LJ fue US$ 12,35, en MGIT fue US$ 16,62 y usando ambos fue US$ 19,29. El costo adicional por cada *M. tuberculosis* detectado con los métodos bioquímicos corrientes fue US$ 504,08 y con la observación microscópica de la formación de cuerdas fue US$ 328,10 cuando se usó MGIT en comparación con LJ y de US$ 160,80 y US$ 109,07 cuando se usaron ambos medios, comparados con LJ solo.

CONCLUSIÓN: El sistema MGIT ofrece un mayor rendimiento y resultados más rápidos, con un costo relativamente alto. La gran proporción de NTM destaca la necesidad de pruebas rápidas de diagnóstico de las especies. Reducir al mínimo de la contaminación de los cultivos es un factor primordial en la rentabilidad de las pruebas.