Cost-Effectiveness Analysis of Introduction of Rapid, Alternative Methods to Identify Multidrug-Resistant Tuberculosis in Middle-Income Countries

Carlos Acuna-Villaorduna,[1,5] Anna Vassall,[6] German Henostroza,[1,2] Carlos Seas,[1,2] Humberto Guerra,[1,2] Lucy Vasquez,[3] Nora Morcillo,[7] Juan Saravia,[4] Richard O'Brien,[8] Mark D. Perkins,[8] Jane Cunningham,[9] Luis Llanos-Zavalaga,[2] and Eduardo Gotuzzo[1,2]

[1]Instituto de Medicina Tropical Alexander Von Humboldt, [2]Universidad Peruana Cayetano Heredia, [3]Instituto Nacional de Salud, and [4]Direccion de Salud Lima Norte, Lima, Peru; [5]Internal Medicine Department, Washington Hospital Center, Washington, DC; [6]Royal Tropical Institute, Amsterdam, The Netherlands; [7]Antonio Cetrangolo Hospital, Buenos Aires, Argentina; and [8]Foundation for Innovative New Diagnostics and [9]Tropical Disease Research, World Health Organization, Geneva, Switzerland

Background. Resistance to commonly used antituberculosis drugs is emerging worldwide. Conventional drug-susceptibility testing (DST) methods are slow and demanding. Alternative, rapid DST methods would permit the early detection of drug resistance and, in turn, arrest tuberculosis transmission.

Methods. A cost-effectiveness analysis of 5 DST methods was performed in the context of a clinical trial that compared rapid with conventional DST methods. The methods under investigation were direct phage-replication assay (FASTPlaque-Response; Biotech), direct amplification and reverse hybridization of the *rpoB* gene (INNO-LiPA; Innogenetics), indirect colorimetric minimum inhibitory concentration assay (MTT; ICN Biomedicals), and direct proportion method on Löwenstein-Jensen medium. These were compared with the widely used indirect proportion method on Löwenstein-Jensen medium.

Results. All alternative DST methods were found to be cost-effective, compared with other health care interventions. DST methods also generate substantial cost savings in settings of high prevalence of multidrug-resistant tuberculosis. Excluding the effects of transmission, the direct proportion method on Löwenstein-Jensen medium was the most cost-effective alternative DST method for patient groups with prevalences of multidrug-resistant tuberculosis of 2%, 5%, 20%, and 50% (cost in US$2004, $94, $36, $8, and $2 per disability-adjusted life year, respectively).

Conclusion. Alternative, rapid methods for DST are cost-effective and should be considered for use by national tuberculosis programs in middle-income countries.

Resistance to commonly used antituberculosis drugs is emerging worldwide [1–3]. National tuberculosis (TB) control programs require effective strategies to rapidly detect and treat infection with resistant organisms. Guidelines on multidrug-resistant (MDR) TB treatment and affordable drugs are now available [4–9]. However, a consensus on the best strategy for detection of MDR TB in resource-poor settings remains elusive. Conventional drug-susceptibility testing (DST) methods are slow and cumbersome [10, 11]. This limits their availability and allows the transmission of MDR TB to proceed unchecked [12–15]. In contrast, alternative, rapid methods for assessment of in vitro antibiotic susceptibility would permit the prompt detection and treatment of MDR TB.

The indirect proportion method on Löwenstein-Jensen medium (IDLJ) is the most widely used DST method. However, it takes 8–12 weeks to yield results in good circumstances and up to 6 months in field conditions. Morbidity, mortality, and transmission of resistant strains during this period are critical concerns. Recently, several alternative methods for DST have been

Received 29 December 2007; accepted 9 March 2008; electronically published 7 July 2008.

Presented in part: 36th Union World Conference in Lung Health, Paris, France, October 2005 (abstract 1825-22).

Reprints or correspondence: Dr. Carlos Acuna-Villaorduna, Washington Hospital Center, Internal Medicine Dept., Rm. 2A38, 110 Irving St. NW, Washington, DC 20010-3017 (carlosvillaorduna@hotmail.com).

Clinical Infectious Diseases 2008; 47:487–95
© 2008 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2008/4704-0008$15.00
DOI: 10.1086/590010

Table 1. List of variables and assumptions used in cost-effectiveness analysis.

Variable	Base-case estimate	Source
Variables related to costs		
Cost of MDR TB treatment	$2895	[31]
Daily cost of SCC (intensive phase)	$0.92	[27]
Daily cost of SCC (continuation phase)	$0.17	[27]
Duration of intensive phase, days	60	[27]
Duration of continuation phase, days	120	[27]
Wastage of buildings, equipments, and staff, %	20	Observations, records
Wastage of medical supplies, %	5	Observations, records
Exchange rate of soles to US$1	3.5	WHO-CHOICE[b]
Discount rate, %	3	[33, 34]
Length of time to change from first-line to MDR TB treatment after diagnosis, days	7	Data from NTPs
Variables related to effectiveness		
Sensitivity for Rif resistance only; for multidrug resistance[c]		
FASTPlaque-Response	93.6; 92.8	Clinical trial
INNO-LiPA	92.5; 92.8	Clinical trial
DLJ	93.5; 93.5	Clinical trial
MTT assay	84.3; 83.5	Clinical trial
IDLJ	98; 98	Assumption
Specificity for Rif resistance; multidrug resistance[c]		
FASTPlaque-Response	96.8; 95.3	Clinical trial
INNO-LiPA	99.3; 98.1	Clinical trial
DLJ	99.0; 98.5	Clinical trial
MTT assay	99.2; 97.8	Clinical trial
IDLJ	98; 98	Assumption
Speed of diagnosis, days		
FASTPlaque-Response	2	Clinical trial
INNO-LiPA	2	Clinical trial
DLJ	40	Clinical trial
MTT assay	35	Clinical trial
IDLJ	70	Clinical trial
Rate of contamination and/or indeterminate results, %		
FASTPlaque-Response	24.6	
INNO-LiPA	0.7	
DLJ	6.1	
MTT assay	8.9	
IDLJ	6.4	
Variables related to impact of diagnosis on transmission		
Rate of infected patients who developed active MDR TB after 2 years, %	8	[45]
Probability of infection after exposure to a patient with MDR TB[a]	$\frac{e^{\log\ \text{odds}}}{1+e^{\log\ \text{odds}}}$	[29]
Average no. of close contacts per patient	6	Clinical trial
Average no. of contact hours per day of household contacts	8	Assumption
Death rate per month for patients with MDR TB who received first-line treatment, %	2	Assumption
Length of time that patient with MDR TB continued first-line treatment without diagnosis, months	5	Clinical trial
Cure rate among patients with MDR TB treated with second-line standardized treatment, %	50	[32]
Variables related to calculation of DALYs		
Age at illness, mean years	31	Clinical trial
Life expectancy, years	70	Census data
Discount rate for assessment of costs and health gains in the future, %	3	[33, 34]

NOTE. DALY, disability-adjusted life year; DLJ, direct proportion method on Löwenstein-Jensen medium; IDLJ, indirect proportion method on Löwenstein-Jensen medium; MDR, multidrug resistant; NTP, national tuberculosis (TB) control program; Rif, rifampicin; SCC, short-course chemotherapy; WHO, World Health Organization.

[a] This model estimates the probability of being infected with TB after having contact for a specific amount of time with a patient who has smear-positive TB. We assumed that 8% of infected people will develop active TB in the future. Log odds were calculated assuming that the hypothetical contact was exposed for 8 h daily to a 30-year-old patient with smear-positive pulmonary TB with cavitations on chest radiograph.

[b] WHO-CHOICE Web site at http://www.who.int/choice/en.

[c] Resistance to Rif and isoniazid.

Table 2. Unit cost per test.

Test, method	Sputum collection	Decontamination	Preparation of LJ medium	Testing related							Average cost per patient
				Overhead	Capital	Staff	Medical supplies	Subtotal	Contamination adjustment	Subtotal	
Detection of Rif resistance											
IDLJ	5.74	11.43	4.33	4.00	6.27	3.45	0.54	14.26	1.27	15.53	37.03
FASTPlaque-Response	5.74	11.43	0.00	3.17	1.62	6.27	8.41	19.38	4.77	24.15	41.32
INNO-LiPA	5.74	11.43	0.00	2.54	1.46	5.51	84.46	93.96	0.66	94.62	111.79
DLJ	5.74	11.43	2.17	0.92	1.76	2.12	0.52	5.32	0.32	5.64	24.98
MTT assay	5.74	11.43	0.54	2.79	2.33	3.27	3.58	11.97	0.77	12.74	30.45
Detection of multidrug resistance											
IDLJ	5.74	11.43	5.42	4.48	6.20	4.83	0.54	16.05	1.43	17.48	40.07
FASTPlaque-Response	5.74	11.43	0.00	3.17	1.62	6.18	8.41	19.38	4.77	24.15	41.32
INNO-LiPA	5.74	11.43	0.00	2.54	1.46	5.51	84.46	93.96	0.66	94.62	111.79
DLJ	5.74	11.43	4.33	2.19	2.78	2.95	0.52	8.44	0.52	8.96	30.46
MTT assay	5.74	11.43	0.54	3.42	2.73	4.75	5.84	16.74	1.07	17.81	35.52

NOTE. Data are US$2004. DLJ, direct proportion method on Löwenstein-Jensen (LJ) medium; IDLJ, indirect proportion method on LJ medium; Rif, rifampicin.

developed, including colorimetric indicators for early detection of bacterial growth, molecular methods to detect resistance-associated mutations, and phage-replication assays. Several studies have evaluated the performance of these methods, with promising results [16–25]. However, there are no studies that estimate the cost and cost-effectiveness of implementing DST methods in low- or middle-income settings. Therefore, the question of whether DST methods are affordable and cost-effective in the context of the severe resource constraints faced by developing countries remains unanswered.

Peru is a middle-income country [26] with an incidence of pulmonary TB of 178 cases per 100,000 inhabitants. Currently, MDR TB testing is limited to the IDLJ method for those at high risk for MDR TB and those who experience treatment failure after 5 months of treatment [27]. Recently, several alternative methods for detection of MDR TB have been evaluated in a large trial. These included a commercially available line-probe assay (INNO-LiPA; Innogenetics) that detects mutations in the *rpoB* "hotspot" gene region, which is responsible for >90% of rifampicin resistance [16, 17]; a phage-based assay (FASTPlaque-Response; Biotech) that detects live *Mycobacterium tuberculosis* in a plaque assay on a lawn of rapidly growing detector cells [18, 19]; a noncommercial colorimetric assay (MTT; ICN Biomedicals) that uses tetrazolium salt, 3-(4,5-dimethylthiazolyl-2)-2,5-diphenyltetrazolium bromide, which is a general indicator of cellular growth and viability whose oxidized yellow form becomes purple after reduction to formazan by the dehydrogenases of live bacterial cells [20–22]; and the direct proportion method on Löwenstein-Jensen medium (DLJ), whereby sputum is inoculated directly on Löwenstein-Jensen slants with and without antibiotics after being decontaminated and diagnosis is based on the proportion of mycobacteria growing in a drug-containing Löwenstein-Jensen slant, compared with the growth of the strain in a drug-free slant [25].

We report the costs and cost-effectiveness of introducing these methods in Peru for patient groups with different prevalences of MDR TB. Our results can be used by other national TB control programs in middle-income countries to help assess whether alternative DST methods could rationally be adopted and to estimate the financial impact of doing so.

METHODS

Data on the cost and performance of DST methods were collected from a phase 3 clinical trial conducted in Lima Norte, Peru. This region, 1 of 5 health care jurisdictions in Lima, has a population of 3.3 million inhabitants. The prevalence of MDR TB is 2% among new patients with smear-positive TB and is 50% among those who experience treatment failure [27]. From May 2004 through September 2005, all adults newly diagnosed with smear-positive pulmonary TB from all 37 health care centers in Lima Norte were identified. After informed consent was obtained, at least 1 sample containing 5 mL of sputum was obtained from each patient and was sent for decontamination and DST (3 samples had been taken previously to establish smear-positive TB). IDLJ, INNO-LiPA, MTT, and DLJ were performed at the National Institute of Health laboratory in Lima. FASTPlaque-Response was performed at the Alexander von Humboldt Tropical Medicine Institute laboratory in Lima.

Cost and cost-effectiveness estimates were calculated for patient groups with 2%, 5%, 20%, and 50% prevalence of MDR TB. These rates correspond to those most commonly found in global surveillance of TB drug resistance by the World Health Organization [28]. Costs and health outcomes for each method were calculated and compared with a "do-nothing" scenario in which MDR TB treatment is provided but DST is not available. In this scenario, clinical diagnosis of MDR TB is made on the basis of failure of first-line treatment. It was assumed that patients who experienced failure of first-line treatment would be

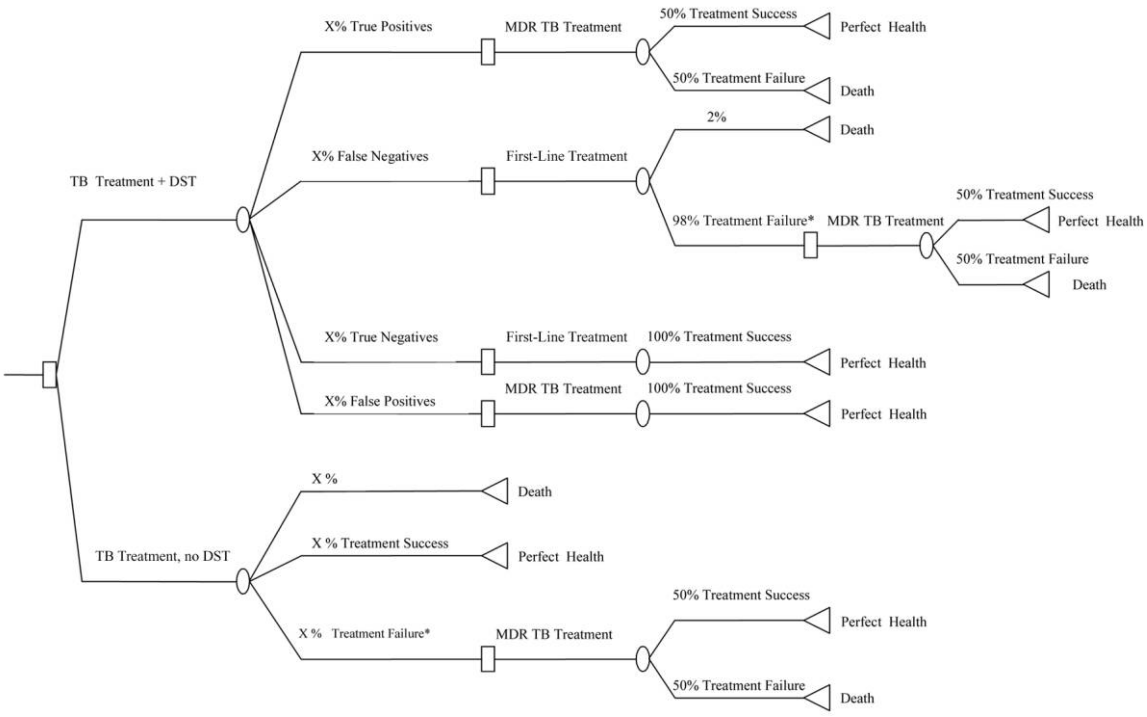

Figure 1. Patient pathways for drug-susceptibility testing (DST) methods, compared with clinical diagnosis of multidrug-resistant (MDR) tuberculosis (TB). X values are determined by prevalence of MDR TB. *Treatment failure is defined as the persistence of positive smear results after 5 months of first-line treatment.

switched to a standardized MDR TB treatment regimen at 5 months and that 2% of patients would die while waiting for MDR TB treatment. In contrast, it was assumed that a patient with DST results positive for MDR TB would be switched to MDR TB treatment within 7 days. Patient pathways for DST and for clinically defined MDR TB are shown in figure 1.

The first step in our analysis was to calculate the average cost per case detected for each DST method. This cost includes the unit costs of tests, the cost savings from the reduced duration of first-line treatment that results from increased diagnostic speed, and the costs of mistakenly treating false-positive cases. The cost of false-positive cases was calculated assuming that the corresponding patients would receive a full course of MDR TB treatment.

Unit costs of tests for each DST method were measured using standard methods [29, 30]. Costs were calculated for each test by using a health care services perspective. Costs were measured for IDLJ and all alternative DST methods for detection of resistance to rifampicin and, when appropriate, resistance to rifampicin and isoniazid (i.e., multidrug resistance). All costs were measured from the time of sputum collection until the time of test results. We included all indirect (overhead) and direct (including buildings, equipment, training, transportation, supplies, salaries, and utilities) inputs. Test costs were calculated using the "ingredients" approach. This multiplies the quantity of inputs used by their price. There were 2 exceptions: the cost of sputum collection, which was taken from Suárez et al. [31], and overhead and quality-control costs, which were calculated by allocating the total expenditures to each test on the basis of staff time (e.g., management and/or supervision costs) or, when relevant, building space (e.g., utilities costs).

The quantity of inputs used (e.g., staff time and supplies) was measured by a mixture of observations and recording by laboratory technicians. This was done at the midpoint of the trial. Quantities were based on 20 observations per test method and were verified by examination of protocols, expenditures, and laboratory records. This measurement did not include staff time between tests, the wastage of supplies, and unused equipment capacity. Data on these items were collected through a mixture of observations, interviews, and examination of laboratory records. Costs were then calculated assuming 80% usage of staff and equipment and 5% wastage of medical supplies. Costs of contamination and invalid tests were also included.

Costs are presented using international prices (US$2004). Prices of inputs vary considerably by country, and there are no standard international prices available for many laboratory supplies. We sourced prices from catalogs and Web sites, reviewed by the World Health Organization. The cost of delivering the goods to Lima was included. Local prices were converted to international prices with an exchange rate of 3.5 soles to $1.

Table 3. Average cost per case detected, excluding the effects of transmission.

Test, method	Unit cost for 1000 patients	Total cost[a] for 1000 patients, by prevalence of Rif resistance				Average cost per case detected, by prevalence of MDR TB			
		50%	20%	5%	2%	50%	20%	5%	2%
Detection of Rif resistance									
IDLJ	37,034	60,241	81,766	92,528	94,681	123	417	1889	4833
FASTPlaque-Response	41,276	60,026	105,000	127,488	131,985	129	564	2737	7084
INNO-LiPA	111,788	94,059	116,686	128,000	130,262	205	635	2786	7088
DLJ	24,980	27,609	43,422	51,329	52,911	59	233	1103	2843
MTT assay	30,446	34,404	45,811	51,514	52,655	85	281	1266	3235
Detection of multidrug resistance									
IDLJ	40,067	63,274	84,799	95,561	97,714	129	433	1950	4886
FASTPlaque-Response	41,276	83,349	141,985	171,303	177,166	181	770	3714	9603
INNO-LiPA	111,788	111,384	144,550	161,134	164,450	242	784	3494	8914
DLJ	30,462	40,447	60,675	70,789	72,811	87	326	1522	3913
MTT assay	35,521	60,452	84,317	96,250	98,636	151	525	2399	6146

NOTE. Data are US$2004. DLJ, direct proportion method on Löwenstein-Jensen medium; IDLJ, indirect proportion method on Löwenstein-Jensen medium; MDR, multidrug resistant; Rif, rifampicin; TB, tuberculosis.

[a] Cost includes unit costs, cost savings from the reduced duration of first-line treatment, and cost of unnecessarily treating false-positive cases.

The second step was to estimate the average cost per case detected, including the future cost savings associated with the reduced transmission of MDR TB that results from improved diagnostic speed. Estimates of the period of infectiousness assume that DST would occur at 0 months for all patient groups, that patients would remain infectious for the first 2 months of treatment, and that patients with false-negative results would remain infectious for the entire period. The model presented by Bailey et al. [32] was used to estimate the probability of infection and the secondary cases averted during the period of infectiousness. This model excludes further (tertiary) cases generated by secondary cases. Cost savings were calculated by multiplying the number of secondary cases by costs of MDR TB treatment. These future savings were discounted at an annual rate of 3%, as recommended by the Panel on Cost-Effectiveness in Health and Medicine [33–34].

The third step was to estimate the average cost per disability-adjusted life year (DALY) for each test. Estimates of health outcomes and DALYs were based on the deaths averted from early case detection and the corresponding reduced transmission. For those who received treatment, no direct health benefit was assumed for early initiation of treatment, because evidence of this is scanty. Deaths averted from secondary cases were calculated assuming that 30% remain untreated, in line with national case-detection rates. Age at onset of MDR TB, treatment cure rates, and life expectancy were sourced from clinical trial data, data from national TB control programs, and international life tables. As with cost savings from reduced transmission, DALYs calculated exclude the benefits of prevention of further tertiary cases generated by secondary cases.

Data analysis was conducted using Excel (Microsoft). A full list of assumptions, variables, and their sources is presented in table 1. It should be noted that, although IDLJ is widely used as the gold standard for DST in developing countries, there is little evidence to support this use. Therefore, the cost-effectiveness of IDLJ was calculated assuming 98% specificity and 98% sensitivity. A spreadsheet containing all estimates and data analysis can be obtained on request.

Sensitivity analysis was performed to test the robustness of our results. Results were subjected to 1-way, 2-way, and multiway analyses. The effects of changes in prices ($\pm 10\%$), sensitivities ($\pm 2\%$), specificities ($\pm 2\%$), and our efficiency assumptions ($\pm 5\%$) were among the variables tested. Finally, we ran a Monte Carlo simulation involving 10,000 iterations for most variables in our model, including the sensitivities and specificities of tests, period of infectiousness, wastage, self-cure rate, hours of daily contact, number of contacts per patient, and percentage of patients with latent TB who developed active TB. We used @Risk software, version 3.5 (Palisade), to determine the means and upper and lower bounds (95% CI) of the main output of interest (i.e., average cost per DALY gained).

RESULTS

During the study period, 1120 patients with smear-positive pulmonary TB were enrolled. Of these, 278 were excluded: 35 because of inability to produce sputum and 243 because the sample obtained was later found to be smear negative. A total of 842 patients had confirmed cases of smear-positive and culture-positive pulmonary TB. DST results were available from IDLJ for 804 (95.5%) of the specimens, from FASTPlaque-Response for 607 (72.1%), from INNO-LiPA for 797 (94.7%),

Table 4. Average cost per case detected, including the effects of transmission.

Test, method	Total cost[a] for 1000 patients, by prevalence of Rif resistance				Average cost per case detected, by prevalence of MDR TB			
	50%	20%	5%	2%	50%	20%	5%	2%
Detection of Rif resistance								
IDLJ	−327,321	−73,259	53,772	79,178	−668	−374	1098	4041
FASTPlaque-Response	−369,360	−66,754	84,549	114,810	−793	−358	1815	6162
INNO-LiPA	−334,473	−54,727	85,146	113,121	−728	−298	1853	6155
DLJ	−382,584	−120,655	10,310	36,503	−822	−648	222	1962
MTT assay	−365,343	−114,088	11,540	36,665	−898	−701	284	2253
Detection of multidrug resistance								
IDLJ	−324,287	−70,226	56,805	82,211	−662	−358	1159	4111
FASTPlaque-Response	−345,420	−29,523	128,426	159,991	−749	−160	2785	8672
INNO-LiPA	−317,385	−26,957	118,257	147,309	−688	−146	2564	7985
DLJ	−369,745	−103,402	29,769	56,404	−795	−556	640	3031
MTT assay	−337,908	−75,027	56,414	82,646	−842	−468	1406	5150

NOTE. Data are US$2004. DLJ, direct proportion method on Löwenstein-Jensen medium; IDLJ, indirect proportion method on Löwenstein-Jensen medium; MDR, multidrug resistant; Rif, rifampicin; TB, tuberculosis.

[a] Cost includes unit costs, cost savings from the reduced duration of first-line treatment, and cost of treating false-positive cases.

from DLJ for 739 (87.8%), and from MTT for 799 (94.9%). FASTPlaque-Response displayed high levels of contamination and indeterminate results. Table 1 shows diagnostic performances, speed of diagnosis, and contamination rates.

Unit costs for each DST method are presented in table 2. The unit cost for all tests, aside from INNO-LiPA, was $25–$42. DLJ had the lowest unit cost ($30.46 to test for MDR TB). INNO-LiPA had the highest unit cost ($111.79 to test for MDR TB). Medical supplies (i.e., kit costs) are the major determinant of costs for the commercial tests. The noncommercial tests (DLJ, IDLJ, and MTT) are more time intensive and, therefore, had a high proportion of overhead and capital costs. Staff costs are high for INNO-LiPA and FASTPlaque-Response because of the time and expertise required. Unit costs for tests of multidrug resistance are slightly higher than those for tests of rifampicin resistance.

The cost of testing for 1000 patients and the average cost per case detected for each DST method, excluding savings from reduced transmission, are presented in table 3. DLJ had the lowest cost per case detected for all prevalence groups ($3913, $1522, $326, and $87 per MDR TB case detected in groups with prevalence of 2%, 5%, 20%, and 50%, respectively). IDLJ ranked second ($4886, $1950, $433, and $129 per MDR TB case detected, respectively), and MTT ranked third ($6146, $2399, $525, and $151 per MDR TB case detected, respectively).

Table 4 presents the cost of testing for 1000 patients and the average cost per case detected for each DST method, including savings from reduced transmission. All tests were cost saving in patient groups with >20% prevalence of MDR TB. For the group with 50% prevalence of MDR TB, all methods generated near-equivalent savings (~$700 saved per MDR TB case detected). DLJ was the lowest-cost option for the groups with 2% and 5% prevalence of MDR TB ($3031 and $640 per case detected, respectively). IDLJ was the second-lowest-cost option for these groups ($4111 and $1159 per case detected, respectively).

Table 5 presents the average cost per DALY for each DST method. Including the cost savings from reduced transmission, DLJ had the lowest cost per DALY gained for the group with a 2% prevalence of MDR TB ($41 per DALY gained), and MTT had the second lowest cost per DALY gained ($95 per DALY gained). One-way sensitivity analysis showed that our results were robust for all variables tested. The 95% CIs generated by the Monte Carlo analysis showed a significant degree of uncertainty that will affect the cost-effectiveness ranking of different DST methods, particularly for patient groups with a high prevalence of MDR TB.

DISCUSSION

MDR TB testing is not routinely performed in developing countries, which raises concern about the transmission of resistant strains from unidentified cases. Our study demonstrates that MDR TB testing among patients with smear-positive TB, with IDLJ or other methods, is cost-effective, even in settings with a moderate prevalence of drug resistance.

All the DST methods studied are cost-effective when the average cost per DALY (excluding effects of transmission) is compared with a benchmark of gross national income. For example, the cost-effectiveness of using the least cost-effective alternative, FASTPlaque-Response, in groups with 2% prevalence of MDR TB ($272 per DALY gained) compares favorably

Table 5. Costs per disability-adjusted life year (DALY) gained.

Test, method	Average cost per DALY, excluding savings from reduced transmission (95% CI[a]), by prevalence of Rif resistance				Average cost per DALY, including savings from reduced transmission (95% CI[a]), by prevalence of MDR TB			
	50%	20%	5%	2%	50%	20%	5%	2%
Detection of Rif resistance								
IDLJ	6 (3–8)	18 (13–27)	85 (60–124)	219 (154–317)	CS	CS	22 (0–62)	156 (88–251)
FASTPlaque-Response	4 (1–8)	16 (5–32)	80 (23–152)	206 (62–394)	CS	CS	36 (0–106)	163 (20–344)
INNO-LiPA	5 (3–10)	17 (6–32)	76 (23–145)	192 (56–371)	CS	CS	33 (0–98)	150 (14–321)
DLJ	2 (0–6)	7 (0–23)	33 (0–107)	85 (0–277)	CS	CS	CS	32 (0–221)
MTT assay	3 (0–7)	10 (0–24)	45 (0–115)	115 (0–297)	CS	CS	CS	67 (0–247)
Detection of multidrug resistance								
IDLJ	6 (4–9)	20 (14–28)	89 (62–128)	227 (160–328)	CS	CS	25 (0–66)	163 (93–261)
FASTPlaque-Response	5 (2–9)	22 (9–39)	105 (45–188)	272 (117–486)	CS	CS	63 (2–139)	230 (77–436)
INNO-LiPA	6 (3–11)	21 (9–37)	93 (36–166)	237 (91–427)	CS	CS	50 (0–119)	194 (50–378)
DLJ	2 (0–6)	8 (0–23)	36 (0–110)	94 (0–284)	CS	CS	CS	41 (0–231)
MTT assay	4 (0–8)	12 (0–28)	57 (0–130)	144 (0–335)	CS	CS	8 (0–81)	95 (0–282)

NOTE. Data are US$2004. CS, cost savings (i.e., the costs from reduced treatment in the future outweigh the present costs of drug-susceptibility testing); DLJ, direct proportion method on Löwenstein-Jensen medium; IDLJ, indirect proportion method on Löwenstein-Jensen medium; MDR, multidrug resistant; Rif, rifampicin; TB, tuberculosis.

[a] The 95% CIs were generated by Monte Carlo analysis.

with that of providing antiretroviral therapy to patients with TB who are coinfected with HIV ($462 per DALY gained) [35] and that of providing individualized treatment for patients with MDR TB that is not responding to standardized second-line therapy ($368 per DALY gained) [31]. Strikingly, introducing an inexpensive and moderately rapid method such as MTT for populations with high prevalence of MDR TB had cost-effectiveness comparable to that of implementing the directly observed treatment–short course (DOTS) strategy in developing countries ($12 vs. $15 per DALY gained) [36].

Our calculation of cost-effectiveness underestimates both the health benefits and cost savings from early diagnosis. We assumed no benefit for timely treatment, nor benefits for reduced transmission from secondary cases. However, all DST methods yielded cost savings, compared with clinically defined drug resistance, in settings of high-prevalence of MDR TB. DST methods generate substantial savings in diagnostic time that translate into substantial cost savings when transmission is considered, even in a model that includes only household contacts and secondary cases. MDR TB treatment costs have a substantial impact on our estimates of treatment savings. Treatment and hospitalization costs are comparatively low in Peru ($2895 for MDR TB treatment and $75 for first-line treatment) [31]. Thus, the cost savings associated with the reduction of transmission that results from rapid diagnosis may be higher in other settings, particularly where ambulatory care is not well established [37].

Because of high levels of uncertainty found by the Monte Carlo analysis and taking into account that our data are generated from a single clinical trial, our study is only suggestive of the relative cost-effectiveness ranking of different tests. Nevertheless, we found that test costs and costs of false-positive cases substantially affect the cost-effectiveness of DST. DLJ performs well in both aspects, and therefore, DLJ emerged as the most cost-effective DST method. For groups with a higher prevalence of MDR TB, the speed of diagnosis becomes more important; although DLJ still performs well, the difference in cost per DALY between alternative DST methods is reduced.

Our study assumed an accuracy for IDLJ of 98%, as is commonly found for proficiency testing. Under this assumption, our calculations showed that IDLJ may not always be the most cost-effective option for any patient group. In addition, the real-life performance of indirect methods may be much slower than that observed in a clinical trial. DLJ is cheaper than and as effective as IDLJ, it yields results 4 weeks earlier, and it can be implemented in most laboratories. Our study showed that MTT is also lower in cost and is faster than IDLJ, although, in practice, it may lead to emergence of resistance because of its low sensitivity.

The selection of DST method is dependent not solely on cost-effectiveness but also on feasibility. A high TB burden and lack of infrastructure represent significant obstacles to implementing DST methods in developing countries [38]. Therefore, their implementation must be accompanied by a national commitment to improve culture-performing laboratories. Introduction of INNO-LiPA remains a challenge because of the cost and complexity of performing this assay based on standard PCR of processed DNA-extracted sputum. However, DLJ, MTT,

and FASTPlaque-Response can be adopted in most laboratories that currently perform conventional culture on Löwenstein-Jensen medium. More research is therefore required to examine further the feasibility, costs, and effectiveness of these methods in other settings.

It should also be noted that, although INNO-LiPA and FASTPlaque-Response appear to be the least cost-effective of the methods studied, their high kit costs had a substantial impact on our results. If national TB control programs were to have access to concessional prices or less expensive versions, this would considerably increase their affordability and cost-effectiveness. Furthermore, a test that is the most cost-effective but not the most effective method should not necessarily be prioritized. The question for policy makers is whether the extra cost (~$90,000 for FASTPlaque-Response and INNO-LiPA) is justified by the ~600 DALYs generated (~20 deaths averted), compared with other uses for their funds.

We present results for different prevalence groups, to assist the generalization of our findings to other settings. Our results are applicable to countries where prevalence of HIV infection is low and ambulatory treatment is available. Effectiveness in terms of DALYs may be higher in countries with a high prevalence of HIV infection, because of a greater number of deaths averted, and in which rapid tests might have a substantial impact on treatment outcomes [39, 40]. In addition, rapid tests may prevent the emergence of extensively drug-resistant TB in settings where quality-assured treatment (i.e., the DOTS strategy) is not provided.

In conclusion, MDR TB has emerged as a major public health threat worldwide. The establishment of the DOTS-Plus and the Green Light Committee has greatly improved the availability of treatment, but delays in the diagnosis of MDR TB remain a major obstacle to its control (L. Castagnini, J. Cunningham, and E. Gotuzzo, unpublished data) [41–44]. Our results indicate that several DST methods are cost-effective, and additional trials should be considered by national TB control programs. However, the feasibility of implementing rapid DST methods and the health benefits that might accrue from their use require further study. Additional data are needed from other populations and settings, particularly those in which HIV infection is prevalent. If interest and effort continue in this area of research, this will positively influence MDR TB policy, patient care, and, ultimately, TB control.

Acknowledgments

We thank Andrew Ramsay for his painstaking work in reviewing all the input required for each test.

Financial support. World Health Organization through its Tropical Disease Research program.

Potential conflicts of interest. R.O. works for the Foundation for Innovative New Diagnostics (FIND), which has a contractual agreement with Biotech, the manufacturer of the FASTPlaque-Response tuberculosis test, that calls for FIND to undertake evaluation and demonstration studies of the test. In turn, Biotech is to provide the test at the lowest possible price to the public health care sector in developing countries. All other authors: no conflicts.

References

1. Pablos-Méndez A, Raviglione MC, Laszlo A, et al. Global surveillance for antituberculosis-drug resistance, 1994–1997. N Engl J Med **1998**; 338:1641–9.
2. Espinal MA, Laszlo A, Simonsen L, et al. Global trends in resistance to antituberculosis drugs. N Engl J Med **2001**; 344:1294–303.
3. Heifets LB, Cangelosi GA. Drug susceptibility testing of *Mycobacterium tuberculosis:* a neglected problem at the turn of the century. Int J Tuberc Lung Dis **1999**; 3:564–81.
4. Globe M, Iseman MD, Madsen LA, et al. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. N Engl J Med **1993**; 328:527–32.
5. Narita M, Alonso P, Lauzardo M, et al. Treatment experience of multidrug-resistant tuberculosis in Florida, 1994–1997. Chest **2001**; 120: 343–8.
6. Tahaoglu K, Torun T, Sevim T, et al. The treatment of multidrug-resistant tuberculosis in Turkey. N Engl J Med **2001**; 345:170–4.
7. Burgos M, Gonzalez LC, Paz EA, et al. Treatment of multidrug-resistant tuberculosis in San Francisco: an outpatient-based approach. Clin Infect Dis **2005**; 40:968–75.
8. Chan ED, Laurel V, Strand MJ, et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med **2004**; 169:1103–9.
9. Mitnick C, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med **2003**; 348:119–28.
10. Heifets LB. Drug susceptibility test in the management of chemotherapy of tuberculosis. In: Heifets LB, ed. Drug susceptibility in the chemotherapy of mycobacterial infections. Boca Raton: CRC Press, **1991**:89–121.
11. Heifets LB. Drug susceptibility tests in mycobacteriology. Clin Lab Med **1996**; 16:641–56.
12. Pathania VS, Trnka L, Krejbich F, et al. A cost-benefit analysis of BCG revaccination in the Czech Republic. Vaccine **1999**; 17:1926–35.
13. Burgos M, DeRiemer K, Small PM, et al. Effects on drug resistance on the generation of secondary cases of tuberculosis. J Infect Dis **2003**; 188:1878–84.
14. Borgdorff MW, van der Werf MJ, de Haas PEW, et al. Tuberculosis elimination in The Netherlands. Emerg Infect Dis **2005**; 11:597–602.
15. Bastian I, Portaels F. Multidrug-resistant tuberculosis. Dordrecht, The Netherlands: Kluwer Academic Publishers, **2000**:253–66.
16. Viveiros M, Leandro C, Rodrigues L, et al. Direct application of the INNO-LiPA Rif.TB line-probe assay for rapid identification of *Mycobacterium tuberculosis* complex strains and detection of rifampin resistance in 360 smear-positive respiratory specimens from an area of high incidence of multidrug-resistant tuberculosis. J Clin Microbiol **2005**; 43:4880–4.
17. Jureen P, Werngren J, Hoffner S. Evaluation of the line probe assay (LiPA) for rapid detection of rifampicin resistance in *Mycobacterium tuberculosis.* Tuberculosis **2004**; 84:311–6.
18. Albert H, Trollip A, Seaman T, Mole RJ. Simple, phage-based (FASTPlaque) technology to determine rifampicin resistance of *Mycobacterium tuberculosis* directly from sputum. Int J Tuberc Lung Dis **2004**; 8:1114–9.
19. Butt T, Ahmad RN, Afzal RK, Mahmood A, Anwar M. Rapid detection of rifampicin susceptibility of *Mycobacterium tuberculosis* in sputum specimens by mycobacteriophage assay. J Pak Med Assoc **2004**; 54: 379–82.
20. Martin A, Morcillo N, Lemus D, et al. Multicenter study of MTT and resazurin assays for testing susceptibility to first-line anti-tuberculosis drugs. Int J Tuberc Lung Dis **2005**; 9:901–6.
21. Montoro E, Lemus D, Echemendia M, Martin A, Portaels F, Palomino

JC. Comparative evaluation of the nitrate reduction assay, the MTT test, and the reazurin microtitre assay for drug susceptibility testing of clinical isolates of *Mycobacterium tuberculosis.* J Antimicrob Chemother **2005**; 55:500–5.
22. Foongladda S, Roengsanthia D, Arjrattanakool W, Chuchottaworn C, Chaiprasert A, Franzblau SG. Rapid and simple MTT method for rifampicin and isoniazid susceptibility testing of *Mycobacterium tuberculosis.* Int J Tuberc Lung Dis **2002**; 6:1118–22.
23. Lemus D, Martin A, Montoro E, Portaels F, Palomino JC. Rapid alternative methods for detection of rifampicin resistance in *Mycobacterium tuberculosis.* J Antimicrob Chemother **2004**; 54:130–3.
24. Traore H, Fissette K, Bastian I, Devleeschouwer M, Portlaes F. Detection of rifampicin resistance in *Mycobacterium tuberculosis* isolates from diverse countries by a commercial line probe assay as an initial indicator of multidrug resistance. Int J Tuberc Lung Dis **2000**; 4:481–4.
25. Vasquez L, Ascencios L, Quispe N, et al. Evaluation of direct susceptibility testing on Löwenstein-Jensen medium for detection of MDR-TB in smear positive patients in Lima, Peru [abstract PS 1803-21]. In: Program and abstracts of the 36th Union World Conference on Lung Health of the International Union against Tuberculosis and Lung Disease Congress (Paris). **2005**.
26. World Bank Group: GenderStats. Available at: http://devdata.worldbank.org. Accessed 27 June 2008.
27. Programa Nacional de Control de la Tuberculosis. Actualización de la doctrina, normas y procedimientos para el control de la tuberculosis en el Perú. Lima, Peru: Ministerio de Salud, **2001**.
28. Aziz MA, Wright A, Laszlo A, et al. Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. Lancet **2006**; 368:2142–54.
29. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford, UK: Oxford University Press, **1997**.
30. Tan-Torres Edejer T, Baltussen R, Adam T, et al. Making choices in health: WHO guide to cost-effectiveness analysis. Geneva: World Health Organization, **2003**.
31. Suárez PG, Floyd K, Portocarrero J, et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. Lancet **2002**; 359: 1980–9.
32. Bailey W, Gerald L, Kimerling M, et al. Predictive model to identify positive tuberculosis skin test results during contact investigations. JAMA **2002**; 287:996–1002.
33. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations for reporting cost effectiveness analysis. JAMA **1996**; 276:1339–41.
34. Siegel JE, Weinstein MC, Russell LB, et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA **1996**; 276: 1253–8.
35. Currie C, Floyd K, Williams, et al. Cost, affordability and cost-effectiveness of strategies to control tuberculosis in countries with high HIV prevalence. BMC Public Health **2005**; 5:130.
36. Baltussen R, Floyd K, Dye C. Cost-effectiveness analysis of strategies for tuberculosis control in developing countries. BMJ **2005**; 331:1364.
37. Rajbhandary SS, Marks SM, Bock NN. Cost of patients hospitalized for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis **2004**; 8: 1012–6.
38. Cunningham J, Perkins M. Diagnostics for tuberculosis: global demand and market potential. Geneva: World Health Organization, **2006**.
39. Moll A, Gandhi N, Pawinski R, et al. Identification of a multi-drug-resistant tuberculosis cluster as a cause of death among HIV-co-infected patients in rural South Africa [abstract 795]. In: Program and abstracts of the 13th Conference on Retroviruses and Opportunistic Infections (Denver). **2006**.
40. Fischl MA, Daikos GL, Uttamchandani RB, et al. Clinical presentation and outcome of patients with HIV infection and tuberculosis caused by multiple-drug-resistant bacilli. Ann Intern Med **1992**; 117:184–90.
41. Becerra MC, Freeman J, Bayona, et al. Using treatment failure under effective directly observed short-course chemotherapy programs to identify patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis **2000**; 4:108–14.
42. Okutan O, Kartaloglu Z, Cerraoglu K, et al. Delay of diagnosis in the Turkish servicemen with pulmonary tuberculosis. Mil Med **2005**; 170: 211–3.
43. Demissie M, Lindtjorn B, Berhane Y, et al. Patients and health service delay in the diagnosis of pulmonary tuberculosis in Ethiopia. BMC Public Health **2002**; 2:23.
44. Rodger A, Jaffar S, Paynter S, et al. Delay in the diagnosis of pulmonary tuberculosis, London, 1998–2000: analysis of surveillance data. BMJ **2003**; 326:909–10.
45. Small P, Fujiwara P. Management of tuberculosis in the United States. N Engl J Med **2001**; 345:189–200.