Effectiveness and Cost of Rapid and Conventional Laboratory Methods for *Mycobacterium Tuberculosis* Screening

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SYNOPSIS

Objective. Because delay in the diagnosis of tuberculosis (TB) contributes to the spread of disease and the associated mortality risk, the authors examined the effectiveness and cost of recent advances in methods of diagnosing TB and testing for drug susceptibility, comparing these rapid methods to traditional approaches.

Methods. Decision analysis was used to compare newer rapid and older non-rapid methods for diagnosing TB and testing for drug susceptibility. The average time to diagnosis, average time to treatment, average mortality, and cost of caring for patients evaluated for TB were compared.

Results. Using a combination of solid medium and broth cultures, nucleic acid probes for identification, and radiometric broth drug susceptibility testing would lead to diagnosis on average 15 days faster and to appropriate therapy on average five days sooner than methods currently employed by many U.S. laboratories. The average mortality would drop by five patients per 1000 patients evaluated (31%) and the average cost per patient would drop by $272 (18%).

Conclusions. In this era of cost containment, it is important to incorporate test sensitivity and specificity when evaluating technologies. Tests with higher unit costs may lead to lower medical expenditures when diagnostic accuracy and speed are improved. U.S. laboratories should employ available rapid techniques for the diagnosis of TB.

Between 1985 and 1993, the United States experienced a tuberculosis (TB) epidemic, with 64,000 more cases than the number that would have been expected if the historical downward trend in TB case rates had continued.[1] Institutional outbreaks of drug-resistant TB contributed to this national epidemic.[2–4] Delay in diagnosing TB and in obtaining drug susceptibility results is believed to have contributed significantly to the number of people whose lives were lost during these outbreaks.[2] Delay in the diagnosis and adequate treatment of TB has contributed to community spread of both drug-susceptible and drug-resistant disease.[5–7]

Recent advances in techniques for culturing and identifying *Mycobacterium tuberculosis* (*M. tuberculosis*) can shorten from 6–8 weeks to 3–4 weeks the total time needed to *(a)* obtain a specimen and to *(b)* culture it, *(c)* identify it, and *(d)*

test it for drug susceptibility.[8] By decreasing time to diagnosis, these techniques may also help decrease the average time it takes to begin adequate treatment.

To establish the presence of mycobacteria in a sputum specimen, radiometric broth cultures are faster than conventional solid medium cultures. New, rapid nucleic acid amplification techniques applied directly to sputum specimens can confirm the presence of *M. tuberculosis* independently of cultures. New methods for mycobacterial species identification, which are faster than older biochemical testing methods, include high-performance liquid chromatography (HPLC), nucleic acid probes (DNA probes), and para-nitro-α-acetylamino-β-hydroxy-propiophenone (NAP). And radiometric broth methods can speed testing for drug susceptibility, replacing conventional solid media methods.

Though rapid testing technology exists, approximately 60% of community or hospital-based laboratories[9] and 23% of state laboratories[10] use traditional biochemical testing methods to identify *M. tuberculosis*, and the majority of both types of laboratories use solid media alone for drug susceptibility testing. In two separate studies, 70% of laboratories surveyed reported using non-rapid methods for culturing *M. tuberculosis*.[9,10]

With a change in diagnostic methods, laboratories could diagnose patients 38% faster, doctors could place patients on adequate therapy 70% sooner, and patients would have a 31% lower mortality.

In order to evaluate whether more laboratories should use rapid diagnostic methods for TB, we examined the effectiveness and cost of both rapid and non-rapid methods of diagnosing *M. tuberculosis* and testing for drug susceptibility. We analyzed the effectiveness of laboratory strategies from three perspectives: minimizing time to diagnosis, minimizing time to acceptable therapy, and minimizing mortality.

Methods

This study uses decision analysis to compare the effectiveness and cost of traditional and rapid methods for the culture, identification, and susceptibility testing of *M. tuberculosis*. We developed a decision model using DPL software (ADA Decision Systems, Menlo Park, CA). The underlying structure of the model is shown in the Figure and described in what follows.

Prevalence estimates. Patients evaluated for TB by laboratory examination of sputum specimens may have drug-sensitive TB (DSTB), multidrug-resistant TB (DRTB), mycobacterial infections other than *M. tuberculosis* (MOTT), or no mycobacterial infections. In many clinical laboratories, *M. tuberculosis* is not present in the large majority of sputum samples evaluated for TB. We based our estimates of the proportion of sputa in which mycobacteria would be present on reports of clinical laboratory studies.[11-13] We based our estimates of the percentages of mycobacterial infections due to *M. tuberculosis*[14] and *M. tuberculosis* infections due to multidrug-resistant organisms[15] on U.S. survey data. Using these data, we estimated that 14% of patients evaluated in the United States have *M. tuberculosis* (0.68 [proportion of sputum mycobacteria that are *M. tuberculosis*[14]] × 0.21 [proportion of sputa with mycobacteria present[11]]). In order to simulate the range of TB epidemiology across the United States, we varied this value between 1% ($0.22^{14} \times 0.054^{13}$) and 26% ($0.88^{14} \times 0.30$) in the sensitivity analyses conducted for the present study.

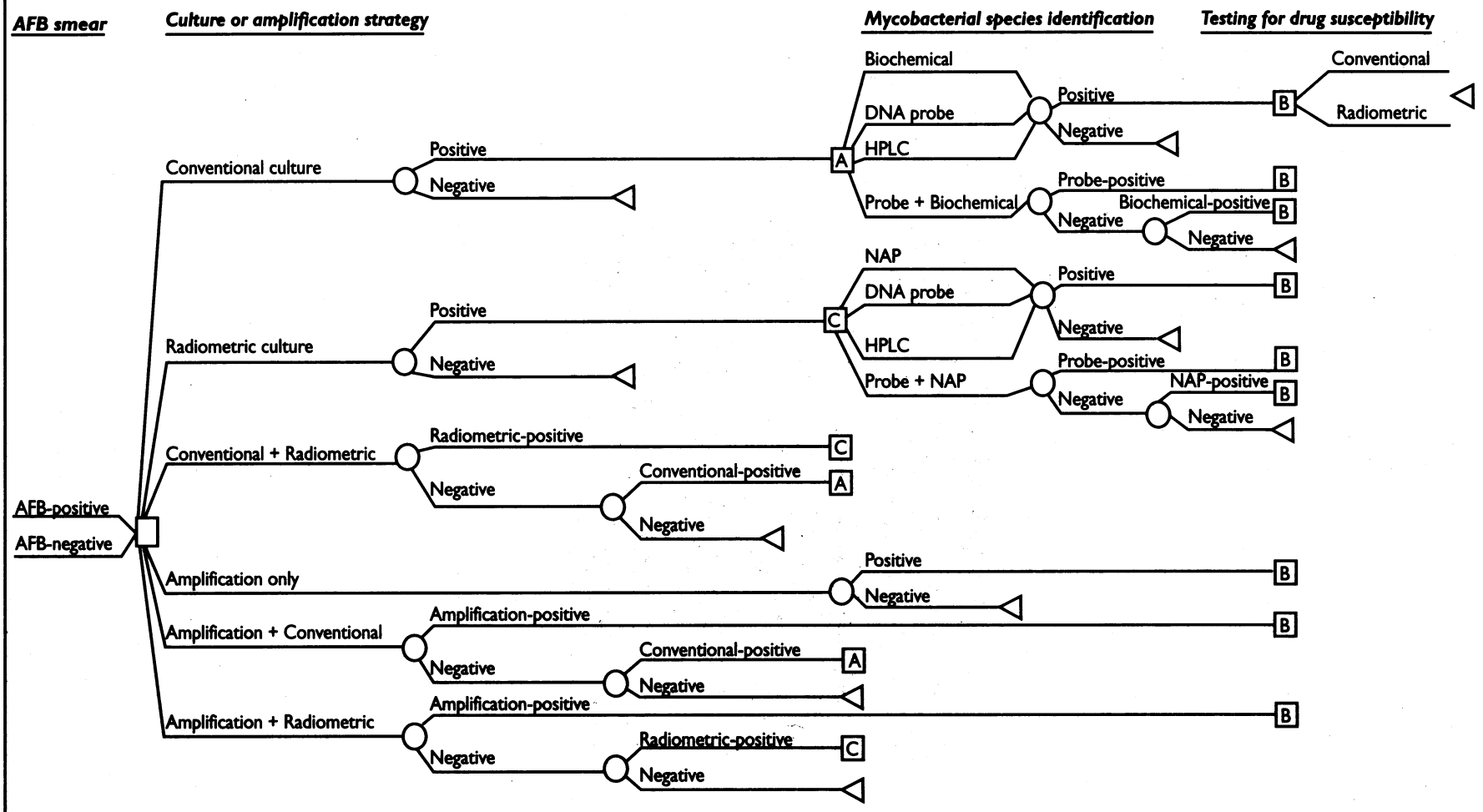
Identifying the presence of mycobacteria. The model assumes that every specimen receives a smear for acid-fast bacilli (AFB). The initial decision point in the model is the choice of culture or amplification method(s) for all specimens. In our model, we included six options: three culture methods and three strategies employing rapid amplification technology alone or in combination with culture methods.

Culture methods. Although other culture methods exist, we chose three traditional culture strategies that are used in state laboratories according to a recent survey[10]: conventional solid media culture, radiometric broth culture, or a combination of conventional and radiometric cultures. When solid media and radiometric cultures are used, both culture methods must have no growth to be classified as negative.

Amplification methods. M. tuberculosis may also be identified directly from clinical specimens using nucleic acid amplification, a new and faster technology that can be used in place of traditional culture methods (conventional or radiometric cultures or a combination of the two).[12,16,17] Currently, two diagnostic kits using nucleic acid amplification are approved by the Food and Drug Administration for clinical use in AFB-smear-positive specimens.

Combining culture and non-culture methods. The combinations of conventional culture and direct amplification or radiometric culture and direct amplification were also included as options in the model. For the strategies that combine direct amplification and culture, only specimens

Decision tree for the assessment of sputum specimens obtained from patients suspected of having tuberculosis



AFB = acid-fast bacilli
HPLC = high-performance liquid chromatography
Amplification: direct amplification with a nucleic acid probe

Biochemical = biochemical testing
Radiometric: radiometric broth culture
NAP = para-nitro-α-acetylamino-β-hydroxy-propiophenone

Conventional: solid media culture
DNA probe = nucleic acid probe

The squares represent decision nodes, the circles represent chance nodes, and the triangles represent endpoints. *AFB smear*: each sputum specimen is smeared on a slide, stained, and examined for the presence of acid-fast bacilli. *Culture or amplification strategy*: each sputum specimen is assigned to a culture or amplification strategy and tested accordingly; amplification-positive specimens proceed to drug susceptibility testing. *Mycobacterial species identification*: each culture-positive specimen is tested to determine if *M. tuberculosis* is present. *Testing for drug susceptibility*: each culture-positive or amplification-positive specimen is tested using solid media or radiometric culture methods to determine to which drugs the organism is sensitive.

that are both amplification-negative and culture-negative are reported as negative for *M. tuberculosis*.

Mycobacterial species identification. The model assumes that culture-positive specimens are submitted for mycobacterial species identification. The currently available identification methods include biochemical testing, high-performance liquid chromatography (HPLC), nucleic acid probes (DNA probes), and para-nitro-α-acetylamino-β-hydroxypropiophenone (NAP). HPLC, DNA probes, and NAP require less time on average than biochemical testing for the species identification of *M. tuberculosis* from positive cultures. Almost half of all state and public health laboratories use a combination of methods to identify *M. tuberculosis*.[10] Therefore, we also modeled species identification using selected combinations of these methods.

Testing for drug sensitivity. The next step is that specimens identified as infected with *M. tuberculosis* are submitted for drug susceptibility testing. Either solid media or radiometric broth testing may be performed; specimens are reported as drug-sensitive or drug-resistant. In our model, treatment is assumed to be adjusted as necessary to agree with drug susceptibility results. The model assumes that patients with false drug sensitivity test results receive 90 days of therapy for drug-sensitive TB before drug resistance is detected.[7]

Treatment regimens. For the treatment, mortality, and cost analyses, we assume that all AFB-smear-positive or direct-amplification-positive patients are started on a standard treatment for *M. tuberculosis* pending culture results. (Solid medium or radiometric cultures are currently used alone, in combination, or with amplification; no laboratories employ amplification alone.) The exception is in parts of the country with high rates of multidrug-resistant tubercle bacilli, such as New York City, where we assume that patients are initially started on a treatment regimen for possible multiple drug resistance. We further assume that treatment is deferred in people whose sputa are AFB-smear-negative or direct-amplification-negative until *M. tuberculosis* is identified. The standard regimen consists initially of isoniazid, rifampin, pyrazinamide, and ethambutol.[7] A quinolone is added in the initial multidrug-resistance regimen.[18]

Mortality. The model takes into account the risk of mortality from transmission of TB in susceptible contacts of patients when patients are inadequately diagnosed or treated. The additional mortality attributable to the transmission of TB is calculated by multiplying the probability of infectious cases causing secondary cases[19] by the mortality risk of treated TB.

The mortality analyses require estimates of the relative risk of death from standard and multidrug-resistant therapy. To create a baseline mortality risk for multidrug-resistant therapy, we multiplied the ratio of serious side effects among people receiving therapies for drug-resistant[20] and drug-sensitive[21] TB by the baseline mortality risk for drug-sensitive therapy. This ratio may overestimate the mortality risk from therapy for multidrug-resistant organisms because we drew our estimates of the prevalence of side effects from a study that included a referral population given a variety of combinations of anti-tuberculous agents.[22]

Comparing effectiveness. The effectiveness of the various laboratory strategies was measured in terms of minimizing time to correct diagnosis, minimizing time to acceptable treatment, or minimizing mortality. Minimizing the time to diagnosis is often assumed to be a proxy for minimizing time to effective treatment or minimizing mortality. However, the fastest test is not always the best test for reducing morbidity and mortality; in evaluating laboratory technologies, the accuracy of diagnostic information must be considered.

Time to acceptable therapy was estimated by allowing for treatment choices at three points at which decisions about therapy are likely to be made or changed: after acid-fast smear results are available, after culture and identification results or amplification results are available, and after drug susceptibility results. We defined acceptable therapy based on the following assumptions: *(a)* Patients with multidrug-resistant disease on standard treatment are not receiving adequate therapy. *(b)* Treating patients who are not infected with *M. tuberculosis* is not acceptable therapy. *(c)* Therapy for patients with multidrug-resistant TB ("multidrug-resistant therapy") *is* acceptable for patients with drug-sensitive disease.

To evaluate how best to minimize mortality, the model incorporates an average baseline mortality risk[22,23] and mortality risks for: drug toxicity,[24] treated drug-sensitive TB,[21] treated multidrug-resistant TB,[20] and untreated TB[25] (see Table 1). To calculate overall mortality for a given laboratory strategy, the mortality rates for people with untreated TB, those with treated TB, and those receiving treatment without having TB are multiplied by the time spent, if any, in each of these states. Laboratory strategies that reduce the time to treatment while avoiding treating patients unnecessarily are associated with lower overall mortalities.

Comparing costs. To compare the overall average cost of each laboratory strategy, we included the costs of diagnostic tests,[26] any anti-TB therapy given,[26] treatment for drug-induced hepatitis,[23,27] treatment costs of secondary transmission (transmission of TB to susceptible contacts of infected patients when patients are inadequately diagnosed or treated), and the additional costs of anti-tuberculous treatment caused by delays in therapy or misdiagnosis.[28] (Data on the costs of laboratory tests were obtained from the National Jewish Center for Immunology and Respiratory Medicine in Denver and from the Massachusetts state public health laboratory.)

The drugs used for the treatment of multidrug-resistant TB vary with resistance patterns.[18] To estimate the drug

Table 1. Probabilities, time values, and costs used in the analyses, showing baseline U.S. values and values for HIV-infected population

Definition	*Base*	*Range*	*HIV+*
The probability that a specimen with *M. tuberculosis* is acid-fast bacilli (AFB) smear-positive	0.67[11]	0.531[34]–0.757[35]	0.233[36]
The sensitivity of conventional culture in AFB-smear-positive specimens with *M. tuberculosis*	0.913[37]	0.727[38]–0.961[39]	1.0[36]
The sensitivity of conventional culture in AFB smear-negative specimens with *M. tuberculosis*	0.75[37]	0.525[40]–0.917[13]	0.5[36]
The error rate in a laboratory, such as from contamination of culture plates with mycobacteria from other specimens.[a]	0.0023[41]	0–0.0256[42]	
The sensitivity of radiometric culture in AFB-smear-positive specimens with *M. tuberculosis*	0.978[37]	0.882[39]–1.0[11]	0.882[36]
The sensitivity of radiometric culture in AFB smear-negative specimens with *M. tuberculosis*	0.875[37]	0.724[11]–1.0[43]	0.667[36]
The sensitivity of direct amplification with probe in AFB-smear-positive specimens with *M. tuberculosis*	1.0[44,45]	0.953[34]–1.0	
The sensitivity of direct amplification with probe in AFB-smear-negative specimens with *M. tuberculosis*	0.70[45,46]	0.635[34]–0.921[47]	
The sensitivity of biochemical tests for the identification of *M. tuberculosis*	1.0[48]	0.9977 –1.0	
Sensitivity of the para-nitro-α-acetylamino-β-hydroxypropiophenone test (NAP) to identify *M. tuberculosis*	0.993[48]	0.972[48]–1.0[38]	
The sensitivity of the nucleic acid probe for the identification of *M. tuberculosis*	1.0[49]	0.83[50]–1.0	
The sensitivity of high-performance liquid chromatography (HPLC) for identification of *M. tuberculosis*	0.983[51]	0.885–1.0[52]	
The sensitivity of conventional drug susceptibility testing for drug-sensitive TB specimens (DSTB).[b]	1.0[48]	0.996[53]–1.0	
The sensitivity of conventional drug susceptibility testing for drug-resistant TB specimens (DRTB)	0.885[48]	0.797–0.971[53]	
The sensitivity of radiometric susceptibility testing for DSTB specimens	0.987[48]	0.888–0.991[53]	
The sensitivity of radiometric susceptibility testing for DRTB specimens	1.0[48]	0.987[53]–1.0	
Average time to conventional culture isolation of mycobacteria	AFB+ = 22.3 days AFB- = 31.8 days[40]	16.5[54]–27.3 days[43] 20.5–32.1 days	
Average time to radiometric culture isolation of mycobacteria	AFB+ = 9.3 days AFB- = 16.8 days[40]	7.3[54]–13.1 days[55] 11.3–21.8 days	
Average duration of NAP identification test	AFB+ = 5 days AFB- = 5.7 days[40]	4[56]–5.7 days	
Average duration of biochemical tests for identification	AFB+ = 11.3 days AFB- = 20.9 days[40]	11.3–28 days[53]	
Average time from initiation of conventional susceptibility testing to report	19.1 days[53]	13.7[53]–28 days[53]	
Average time from initiation of radiometric susceptibility testing to report	6.1 days[37]	4.2[53]–6.9 days[53]	
Time before a false negative *M. tuberculosis* infection is diagnosed properly	180 days	0–270 days	
Time before a false negative DRTB case is diagnosed correctly	90 days	0–270 days	
Time before a false positive *M. tuberculosis* case is diagnosed correctly	60 days	0–270 days	
Average duration of therapy for drug-sensitive TB; two months of three/four-drug therapy and four months of two-drug therapy	180 days		

Table 1 (continued).

Definition	*Base*	*Range*	*HIV+*
Average duration of therapy for multidrug-resistant TB.	548 days	456–730 days[18]	
The annual mortality risk arising from the toxicity of standard therapy for DSTB.	0.0009[c]	0.002–0.032[32]	
The annual mortality risk arising from the toxicity of therapy for multidrug-resistant TB.	0.002[d]	0.0009–0.002	0.032[32]
The average cost of smear and conventional culture.	$21.85	$5.20[e]–$38.50[26]	
The average cost of smear and radiometric culture.[f]	$28.50	$13.00[e]–$44.00[26]	
The average cost of the cultures for radiometric broth and solid medium combined (assuming that both methods are initiated simultaneously for all specimens).	$33.10	$17.20[e]–$49.00[26]	
The average cost of biochemical identification tests.	$25.00	$4.00[e]–$45.00[57]	
The average cost of the NAP test.	$5.00[26]		
The average cost of the probe identification test.	$25.00	$8.25[e]–$41.50[26]	
The average cost of the HPLC test.	$25.00	$3.17[51]–$25.00	
The average estimated cost of direct amplification.[g]	$30.00	$11.00[34]–$50.00[h]	
The average cost of conventional susceptibility testing for 10 drugs.	$47.50	$35.00[i]–$60.00[26]	
The average cost of radiometric susceptibility testing for 4 drugs.	$77.50	$40.00[i]–$115.00[26]	
The estimated daily cost of treatment for DSTB, excluding cost of drugs.[j]	$35.00[27] adjusted	$0.66[26]	
The estimated daily cost of treatment for DRTB, excluding cost of drugs.	$35.00		
The daily cost of the initial multidrug-resistant therapy, estimated from wholesale costs of the constituent drugs.	$14.80[26]	$14.80–$18.44[k]	
The daily cost of the initial standard drug therapy, estimated from wholesale costs of the constituent drugs	$9.44[26]		
The estimated daily cost of the four-month, two-drug therapy for drug-sensitive TB.	$0.95[26]		

[a]This value is used for all identification tests on specimens with mycobacterial infections other than *M. tuberculosis* and for specimens with no mycobacteria present that are sent for culture.

[b]Susceptibility test sensitivity is a combined value from tests with isoniazid and rifampin.

[c]L. Geiter, Centers for Disease Control and Prevention, personal communication. Unpublished data from USPHS Trial 21.

[d]Estimated by comparing the ratio of side effects from drug-resistant and drug-sensitive therapies and multiplying by the mortality risk from drug-sensitive treatment.

[e]Irene George. Massachusetts State Laboratory, Mycobacteriology Lab, personal communication, 1994.

[f]The estimate from Denver subtracts an estimated $5.00 from the cost of NAP, which this facility includes in the charge for radiometric broth cultures.

[g]The base and high values are for the direct amplification and probe, the low value for a polymerase chain reaction technique.

[h]Dick Geisler, Director of Sales, Gen-Probe, personal communication, 1994.

[i]George, Irene. Massachusetts State Laboratory, Mycobacteriology Lab. Personal communication. 1994.

[j]The estimate is derived from assumptions in Snider[25] adjusted for a six-month treatment regimen and with costs adjusted to 1994 dollars using the U.S. Statistical Indices for Health Costs.[58] This total treatment cost was then divided by the 180 days of treatment to derive the daily cost.

[k]The base cost includes the daily cost for ofloxacin; the high cost includes the daily cost for ciprofloxacin. Both costs were obtained from Brigham & Women's Hospital, Boston.

HIV+ = HIV-positive
AFB+ = acid-fast bacilli smear-positive
AFB- = acid-fast bacilli smear-negative

costs for multidrug-resistant therapy, we extrapolated the daily cost of the five initial drugs over the duration of treatment. The drug costs of individualized treatment plans may differ. Cost estimates are taken from published literature and from cost estimates derived by U.S. health care institutions (see Table 1).

Sensitivity analyses. We conducted sensitivity analyses varying all key variables such as test performances, costs, delays related to false positives and false negatives, mortality rates, and the effect of mortality from drug toxicity (Table 1).

Because the epidemiology of mycobacterial infections has likely changed since the most recently available U.S. surveys were done, we performed sensitivity analyses varying the percentages of mycobacterial infections due to *M. tuberculosis* and *M. tuberculosis* infections due to multidrug-resistant bacilli. The range of non-tuberculous mycobacterial infections (12%–78%) and multidrug-resistant TB (0.01%–14%) used reflect geographic areas with low rates of all mycobacterial infections, regions with high rates of mycobacterial infections other than *M. tuberculosis* and low rates of *M. tuberculosis*, areas with high rates of *M. tuberculosis* and low rates of other mycobacterial infections, and areas with high rates of all mycobacterial infections.[14]

HIV/AIDS. Because people infected with HIV may respond differently to both TB infections and therapy, all analyses were repeated using data taken from studies of HIV-infected people, both those meeting the definition of AIDS and those not meeting the definition. HIV-infected people are more likely to have multidrug-resistant TB,[29] clinical disease from non-tuberculous mycobacteria, and higher mortalities from TB[30,31] than non-HIV-infected people. These differences may alter optimal choice of diagnostic strategy.

All HIV-infected patients with positive AFB smears or positive direct amplification results are assumed to be started on presumptive treatment for multidrug-resistant TB pending culture results. People with negative AFB smears or negative direct amplifications are not started on therapy unless *M. tuberculosis* is identified after culture. No data exist on the relative risk of mortality from drug toxicity due to standard and multidrug-resistant anti-tuberculous treatment in HIV-infected people. In this analysis, the mortality among HIV-infected patients associated with drug toxicity from treatment for DSTB and DRTB are assumed to be equal to each other at 3.2 per 1000 people treated; this estimate was extrapolated from a retrospective analysis of TB treatment experience at San Francisco General Hospital.[32]

Results

Rapid diagnostic methods significantly decrease time to diagnosis, time to appropriate therapy, and mortality in addition to decreasing total health care costs. Although direct nucleic acid amplification of sputum leads to the fastest diagnosis, it also has a lower sensitivity for *M. tuberculosis* in smear-negative patients than other methods. Thus the model shows that the use of radiometric broth and solid medium cultures minimizes time to appropriate therapy, mortality, and costs. (See Table 2.)

Table 2. Optimal laboratory strategies for the diagnosis of tuberculosis in the United States

	Goal			
	Minimize time to diagnosis	*Minimize time to acceptable treatment*	*Minimize mortality*	*Minimize cost*
Culture method.....	Direct amplification	Solid media and radiometric broth cultures	Solid media and radiometric broth cultures	Solid media and radiometric broth cultures
Identification method...	Nucleic acid probe	Nucleic acid probe	Nucleic acid probe	Nucleic acid probe
Susceptibility testing....	Radiometric broth	Radiometric broth	Radiometric broth	Solid medium
Time/mortality/cost and percent reduction compared with solid media for culture and drug susceptibility testing and biochemical testing for identification of *M. tuberculosis*	6.1 days (84% reduction in time)	2.0 days (70% reduction in time)	11.5/1000 (31% reduction in mortality	$1277 (18% reduction in cost)

NOTE: These results assume that all acid-fast bacillus (AFB) smear-positive patients are started on empiric standard anti-tuberculous therapy and that AFB smear-negative patients are treated if *M. tuberculosis* is identified.

Minimizing time to correct diagnosis. This model demonstrates that the average time to correct diagnosis of patients can be minimized by using direct nucleic acid amplification of sputum samples with probes for *M. tuberculosis* identification, and radiometric broth for drug susceptibility testing. In the United States, the average time to correct diagnosis using these methods would be 6.1 days. This represents an 84% reduction in time from 38.5 days, the average time to correct diagnosis with the strategy currently used in many laboratories (solid media cultures, biochemical testing for identification, and conventional drug susceptibility testing). These averages take into account the time necessary to do amplification in amplification-negative sputa and to do radiometric cultures for drug susceptibility testing in amplification-positive specimens.

Direct amplification techniques in combination with probes and radiometric drug susceptibility testing decrease the time to correct diagnosis by 82% to 91% across a range of *M. tuberculosis* rates seen in U.S. laboratories. A strategy employing direct amplification with probes and radiometric broth drug susceptibility testing also minimizes the average time to correct diagnosis for the HIV-infected population.

Minimizing time to adequate treatment. The diagnostic strategy that minimizes the average time to adequate therapy is to do both conventional and radiometric sputum cultures and to use probes for the identification of *M. tuberculosis* in positive cultures. For all patients identified as having *M. tuberculosis*, radiometric broth drug susceptibility testing is preferred to solid medium susceptibility testing.

By using this diagnostic strategy and providing presumptive therapy to AFB-smear-positive patients pending cultures results, the average time to acceptable therapy is 2.0 days, or 70% faster than the approach employing solid media cultures, biochemical testing, and solid media susceptibility testing (6.6 days).

With rapid diagnostic methods, patients can be placed on acceptable therapy sooner and complications and costs can be reduced.

This strategy is associated with the lowest average predicted time to adequate therapy, 69% to 77% lower than the time required by traditional methods, except in parts of the country with low rates of both *M. tuberculosis* and multiple drug resistance. In areas where *M. tuberculosis* comprises less than 33% of mycobacteria found in sputum samples and there is no multidrug-resistant TB, direct amplification and radiometric culture, probes, and radiometric drug susceptibility testing reduces the time to adequate treatment by 36% compared with solid media cultures, biochemical testing, and solid media susceptibility testing.

The optimal choice of culture and identification methods varied with the test sensitivity of probes and the time required to identify missed cases of TB. When the sensitivity of probes for the identification of *M. tuberculosis* decreases below 1.0, biochemical testing or a combination of probes and biochemical testing is recommended over probes alone. Direct amplification of sputum samples with radiometric cultures becomes the preferred culture strategy when the time for a missed diagnosis of TB drops from 180 days to 140 days or less.

Minimizing time to acceptable treatment in HIV-infected patients. Doing both conventional and radiometric cultures, using probes, and conducting radiometric susceptibility testing minimizes the average time to acceptable treatment in HIV-infected patients in addition to those who are not HIV-infected. The average time to acceptable treatment for HIV-infected people is 6.8 days, or 59% sooner than the 16.6 days required using solid media culture, biochemical testing for identification, and solid media drug susceptibility testing. Varying the proportion of mycobacterial isolates containing *M. tuberculosis* or the proportion of *M. tuberculosis* isolates containing multidrug-resistant organisms within the range observed in the United States did not change the recommended laboratory strategy for HIV-infected people.

Minimizing mortality. A diagnostic strategy of radiometric and conventional cultures, probes of positive cultures for *M. tuberculosis* identification, and radiometric drug susceptibility testing minimizes average mortality (Table 2). Average overall mortality is 31% lower with this strategy (11.5 per 1000) than with the use of solid media cultures, biochemical testing for identification, and solid media drug susceptibility testing (16.7 per 1000). The reduction in mortality using this recommended strategy would be 23% to 33% across the range of *M. tuberculosis* rates reported in U.S. laboratories. As in the treatment analysis, the preference of probes as the method for *M. tuberculosis* identification depends on the test's sensitivity.

Minimizing mortality in HIV-infected patients. For HIV-infected people, average mortality is minimized by using both conventional and radiometric culture methods and probes or multiple identification methods. Radiometric drug susceptibility testing is preferred to solid medium susceptibility testing. Average mortality is 24% lower with these methods (421 per 1000) than with solid media culture methods, biochemical testing and solid media drug susceptibility testing (553 per 1000). These analyses assume that all HIV-infected people with AFB-positive smears are

started on empiric multidrug-resistant treatment pending culture results.

The recommended laboratory strategy for minimizing mortality does not change when the proportion of mycobacterial isolates containing *M. tuberculosis* or the proportion of *M. tuberculosis* isolates containing multidrug-resistant organisms are varied within observed ranges for the United States. The recommended strategy does not change when the annual mortality from HIV, from treated drug-sensitive TB, or from the toxicity of standard therapy are varied in sensitivity analyses.

Minimizing cost. Performing both conventional and radiometric cultures, using probes for identification, and conventional drug susceptibility testing with empiric standard therapy for AFB-smear-positive patients is associated with the lowest overall cost, $1277 per patient evaluated (Table 2). Using radiometric susceptibility testing instead of conventional susceptibility testing adds $2 to the cost per person evaluated. In contrast, the standard diagnostic strategy with solid media for culture, biochemical testing for *M. tuberculosis* identification of positive cultures, and solid media drug susceptibility testing costs $1551 per patient evaluated. Using both culture methods, probes for identification, and radiometric susceptibility testing, average overall costs are 18% lower (9% to 22% when *M.* tuberculosis rates are varied within observed ranges for the United States) than when conventional laboratory methods are used.

These results do not include costs associated with isolating AFB-smear-positive patients. As clinical data accumulate on the role of direct amplification in identifying AFB-smear-positive patients without TB and for discontinuing isolation sooner, the cost per patient evaluated of using this diagnostic method should be reassessed.

Minimizing cost in HIV-infected patients. The laboratory strategy of using both radiometric and solid medium cultures, probes, and radiometric susceptibility testing has the lowest cost per HIV-infected person evaluated. When these methods are combined with the treatment strategy of empiric multidrug-resistant anti-tuberculous chemotherapy in AFB-smear-positive HIV-infected people, the overall average cost is $2422 per person evaluated. The same treatment approach combined with solid media culture, biochemical testing, and solid media susceptibility testing costs $3093 per person evaluated. Thus the average cost per patient evaluated is 22% lower using the recommended laboratory methods.

Discussion

Many laboratories in the United States still use solid media cultures with biochemical testing for *M. tuberculosis* identification and solid media for drug susceptibility testing. Assuming that empiric anti-TB therapy consistent with the Centers for Disease Control and Prevention's TB treatment recommendations[7] is started in AFB-smear-positive people, we found that by changing the diagnostic methods used, laboratories could diagnose patients 38% faster, doctors could place patients on adequate therapy 70% sooner, and patients would have a 31% lower mortality. The associated medical costs would be 18% lower. The results represent overall averages for all patients evaluated for TB.

Tests with higher unit costs may lead to lower medical expenditures when diagnostic accuracy and speed are improved.

Using national or state data may obscure differences between states or within states. Even in states with low overall rates of TB, such as Kansas, certain counties report significant numbers of cases.[33] Though counties or cities with TB rates that vary substantially from the state average may benefit from individualized diagnostic and treatment strategies, the robustness of rapid methods over a range of TB conditions suggests that most laboratories and patients would benefit from using these methods for the diagnosis of *M. tuberculosis.*

For the HIV-infected population, time to adequate treatment, average mortality, and health care costs were all lowered by using both solid media and radiometric broth cultures, nucleic acid probe identification of positive cultures, and radiometric drug susceptibility testing instead of solid media cultures for diagnosis and drug susceptibility testing along with biochemical methods for *M. tuberculosis* identification. By incorporating rapid diagnostic methods, laboratories could diagnose HIV-infected patients 39% faster, doctors could place HIV-infected patients on adequate therapy 59% sooner, patients would have 24% lower mortality, and the associated medical costs would be 22% lower.

Rapid diagnostic methods may lead to savings in two ways: by increasing sensitivity and reducing the time to diagnosis. As a result, patients can be placed on acceptable therapy sooner and complications and costs can be reduced. In this era of cost containment, it is important to incorporate test sensitivity and specificity when evaluating technologies. Tests with higher unit costs may lead to lower medical expenditures when diagnostic accuracy and speed are improved.

The complete set of probabilities and costs used in these decision analyses are available from the authors by written request.

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